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(54) **TREATMENT OF A DISEASE OF THE
GASTROINTESTINAL TRACT WITH AN
IL-12/IL-23 INHIBITOR RELEASED USING
AN INGESTIBLE DEVICE**

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62/545,188, filed on Aug. 14, 2017, provisional ap-
plication No. 62/583,797, filed on Nov. 9, 2017.

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Publication Classification

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(51) **Int. Cl.**
C07K 16/24 (2006.01)
A61M 31/00 (2006.01)
A61P 1/00 (2006.01)

(21) Appl. No.: **16/465,632**

(52) **U.S. Cl.**
CPC **C07K 16/244** (2013.01); **A61K 2039/505**
(2013.01); **A61P 1/00** (2018.01); **A61M**
31/002 (2013.01)

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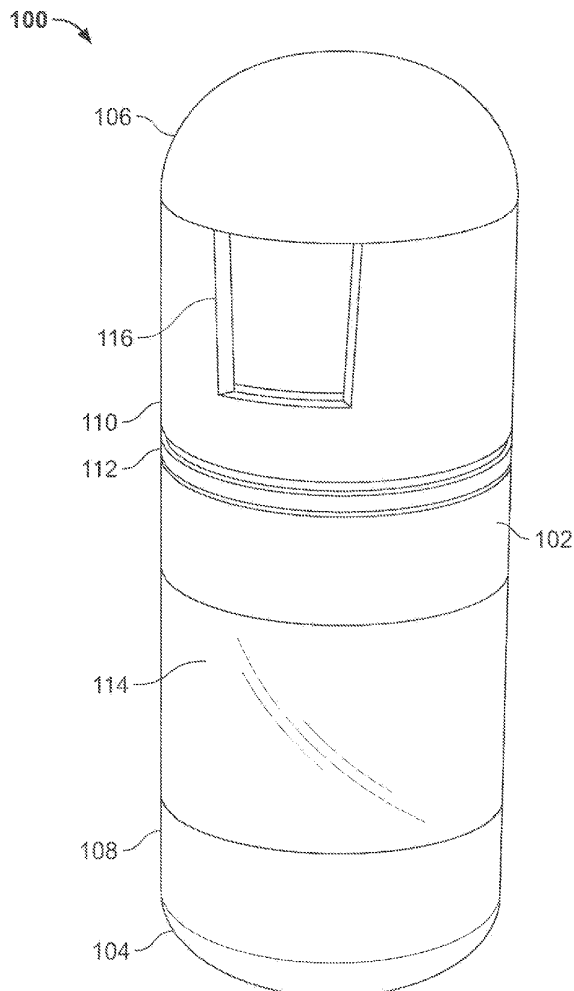
(57) **ABSTRACT**

Related U.S. Application Data

This disclosure features methods and compositions for treat-
ing diseases of the gastrointestinal tract with an IL-12/IL-23
inhibitor.

Specification includes a Sequence Listing.

(60) Provisional application No. 62/434,348, filed on Dec.
14, 2016, provisional application No. 62/478,744,



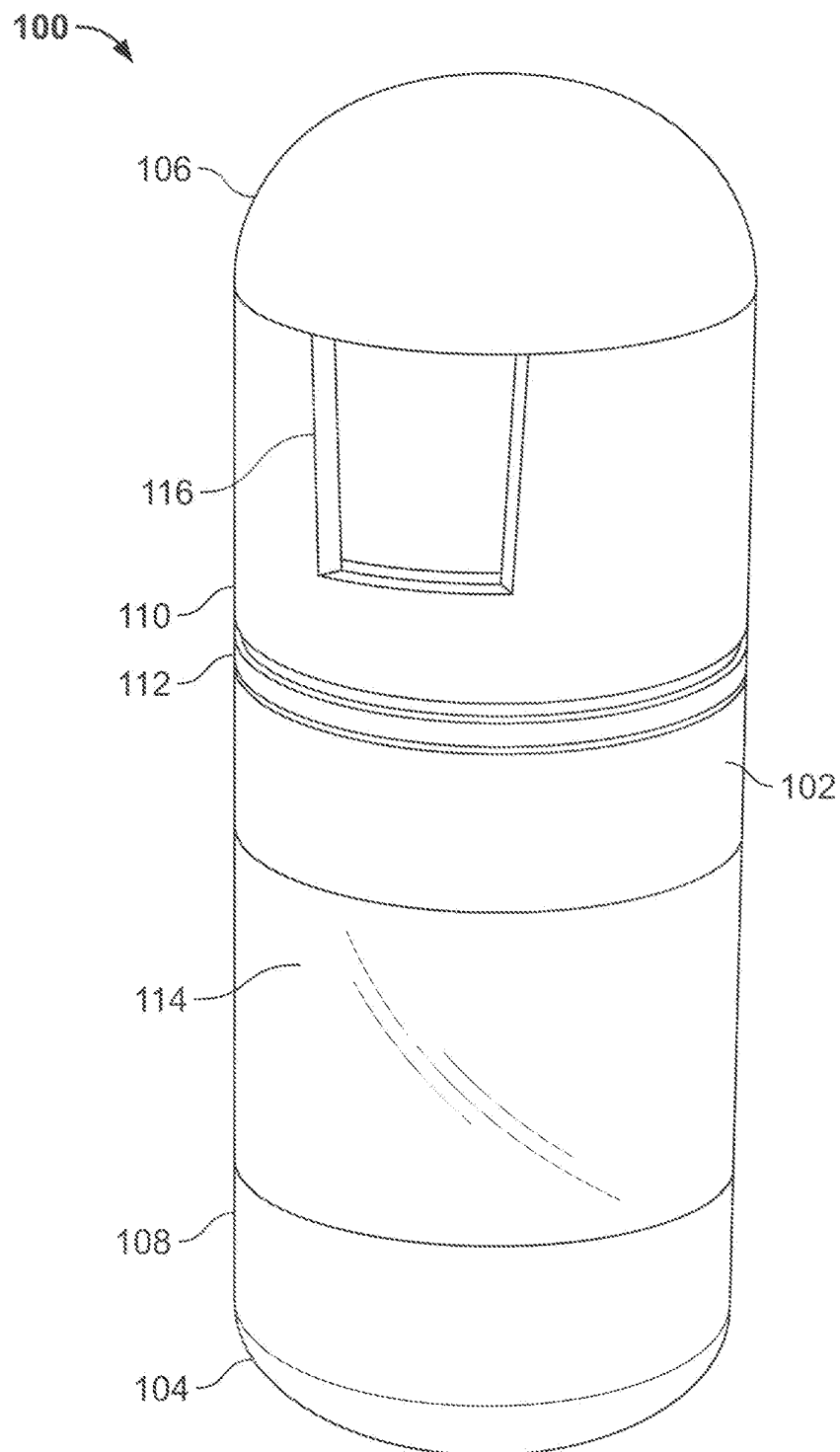


FIG. 1

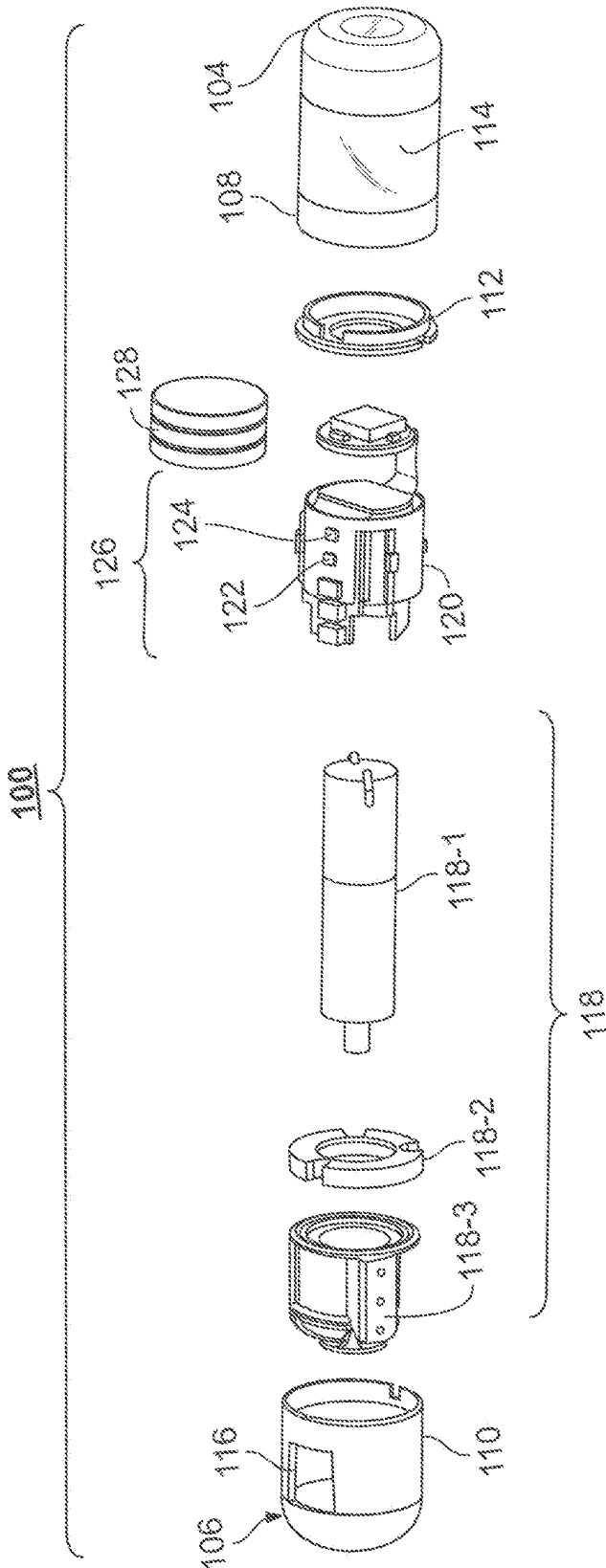


FIG. 2

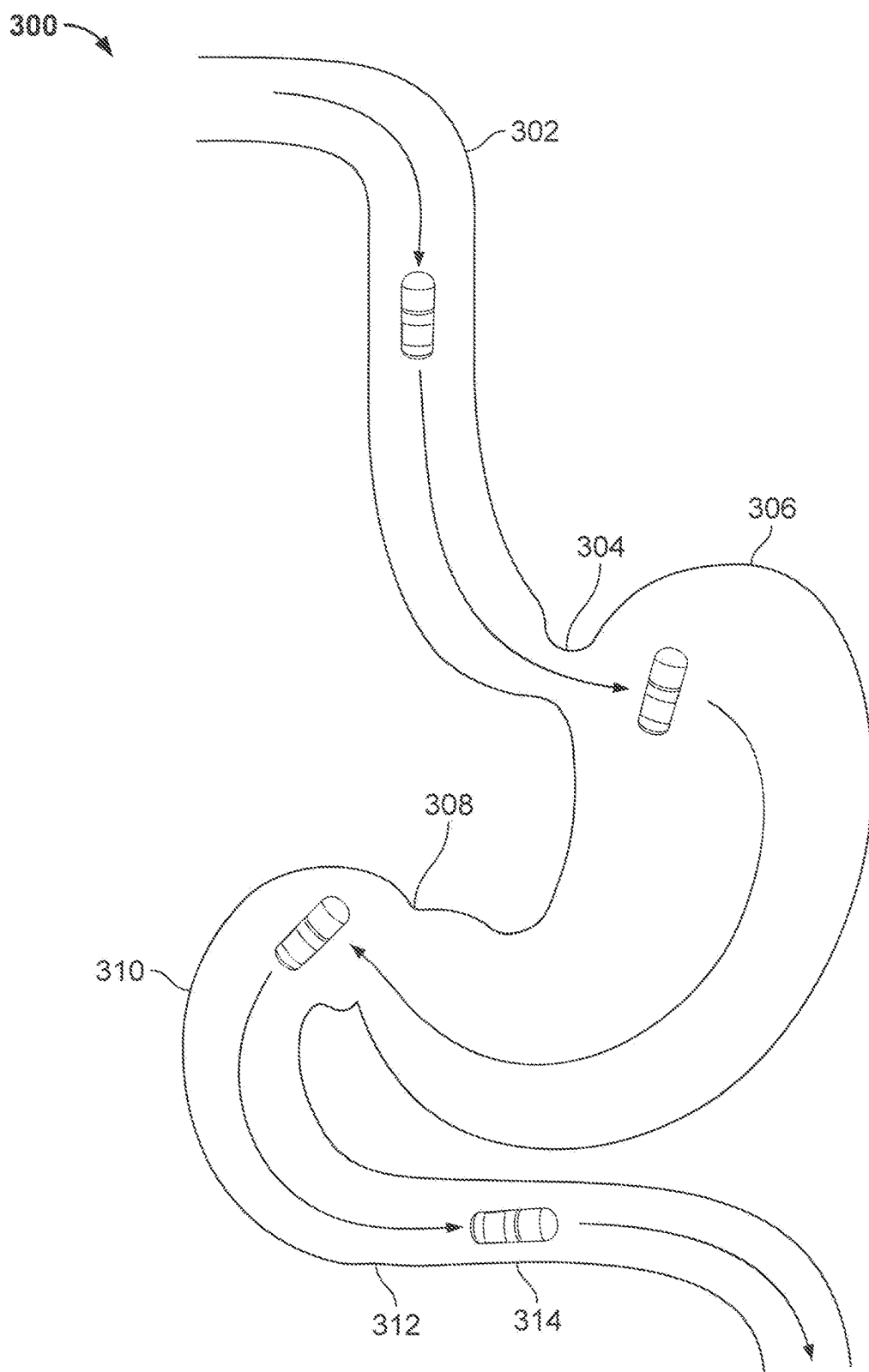


FIG. 3

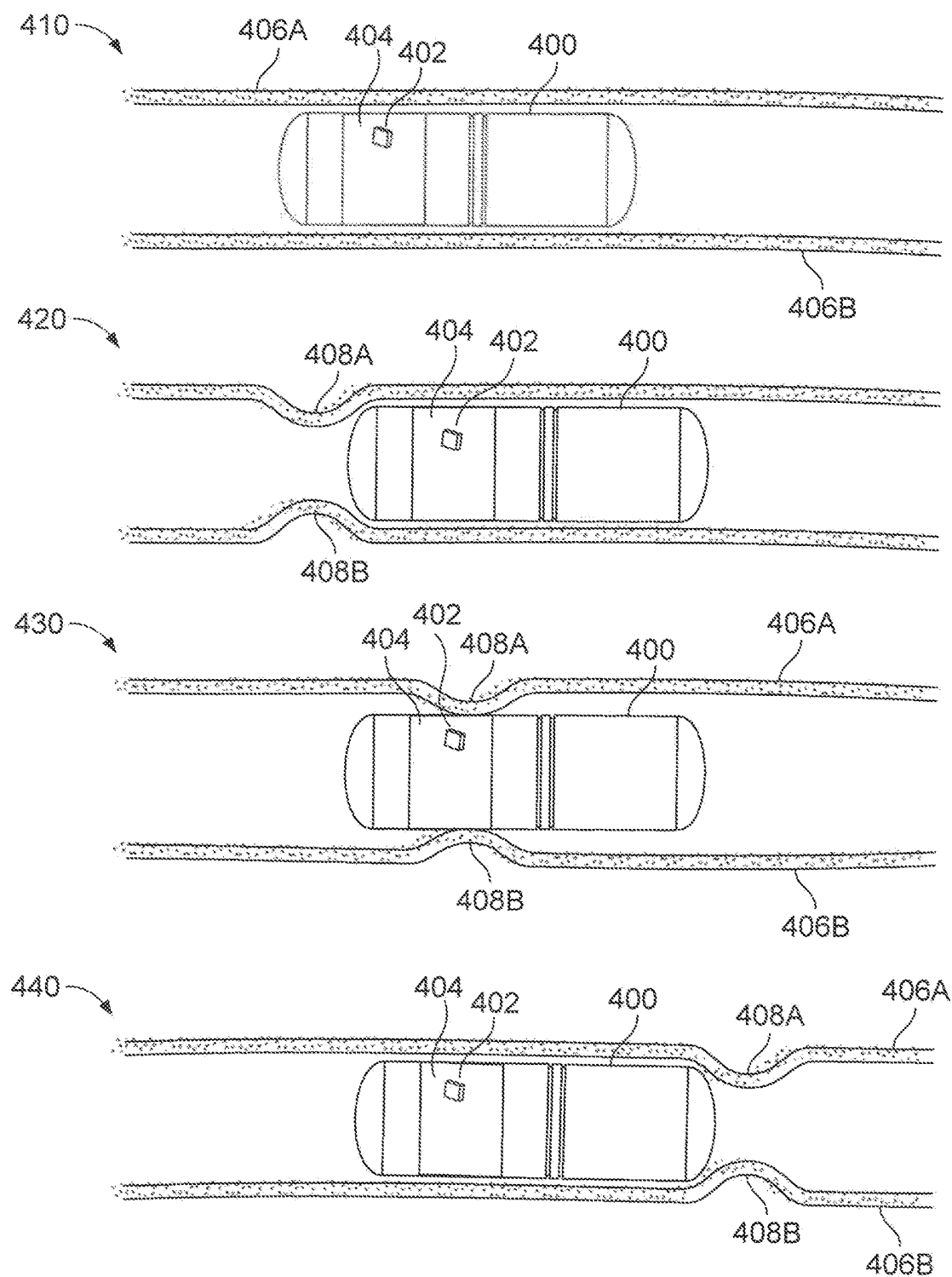


FIG. 4

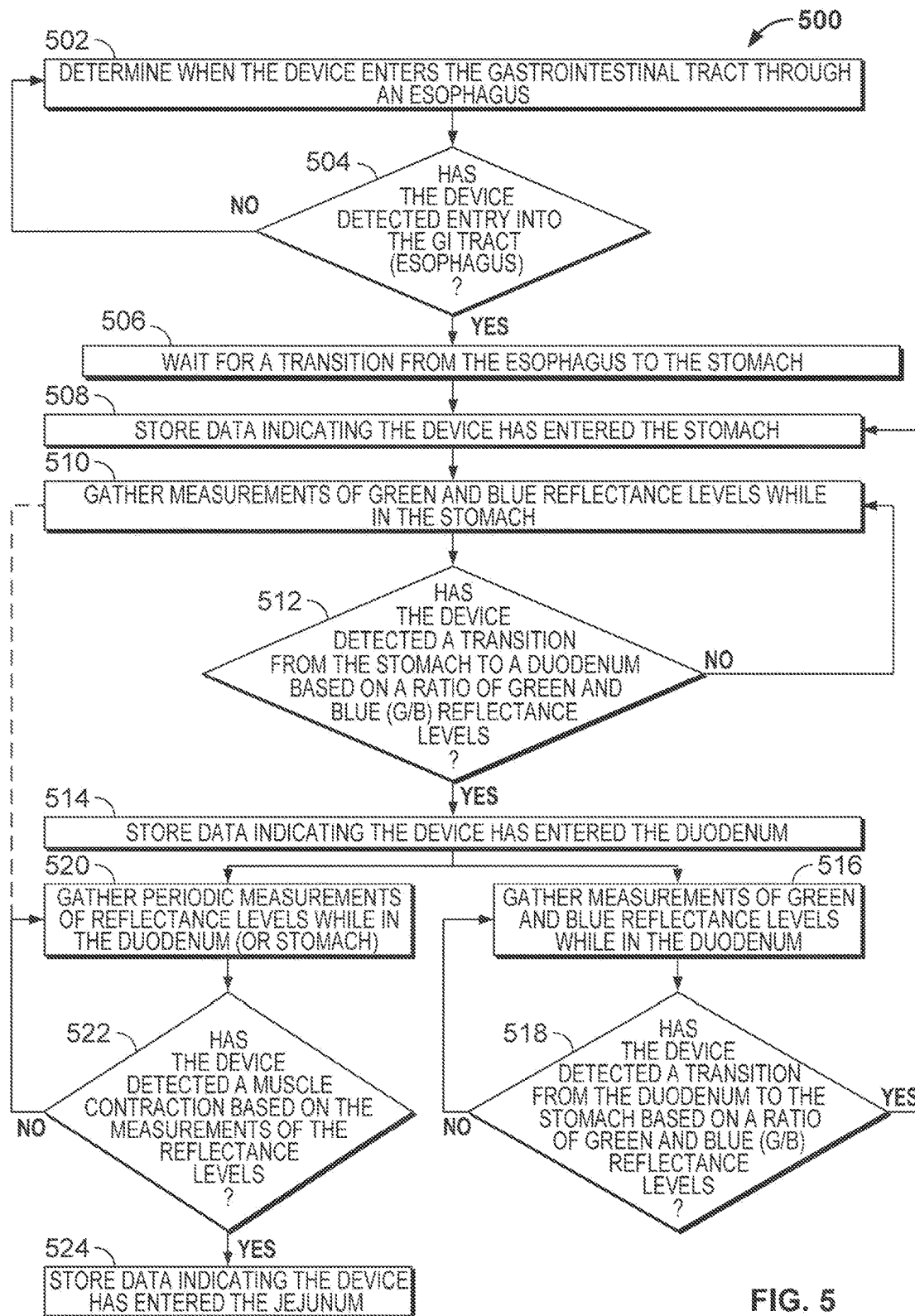


FIG. 5

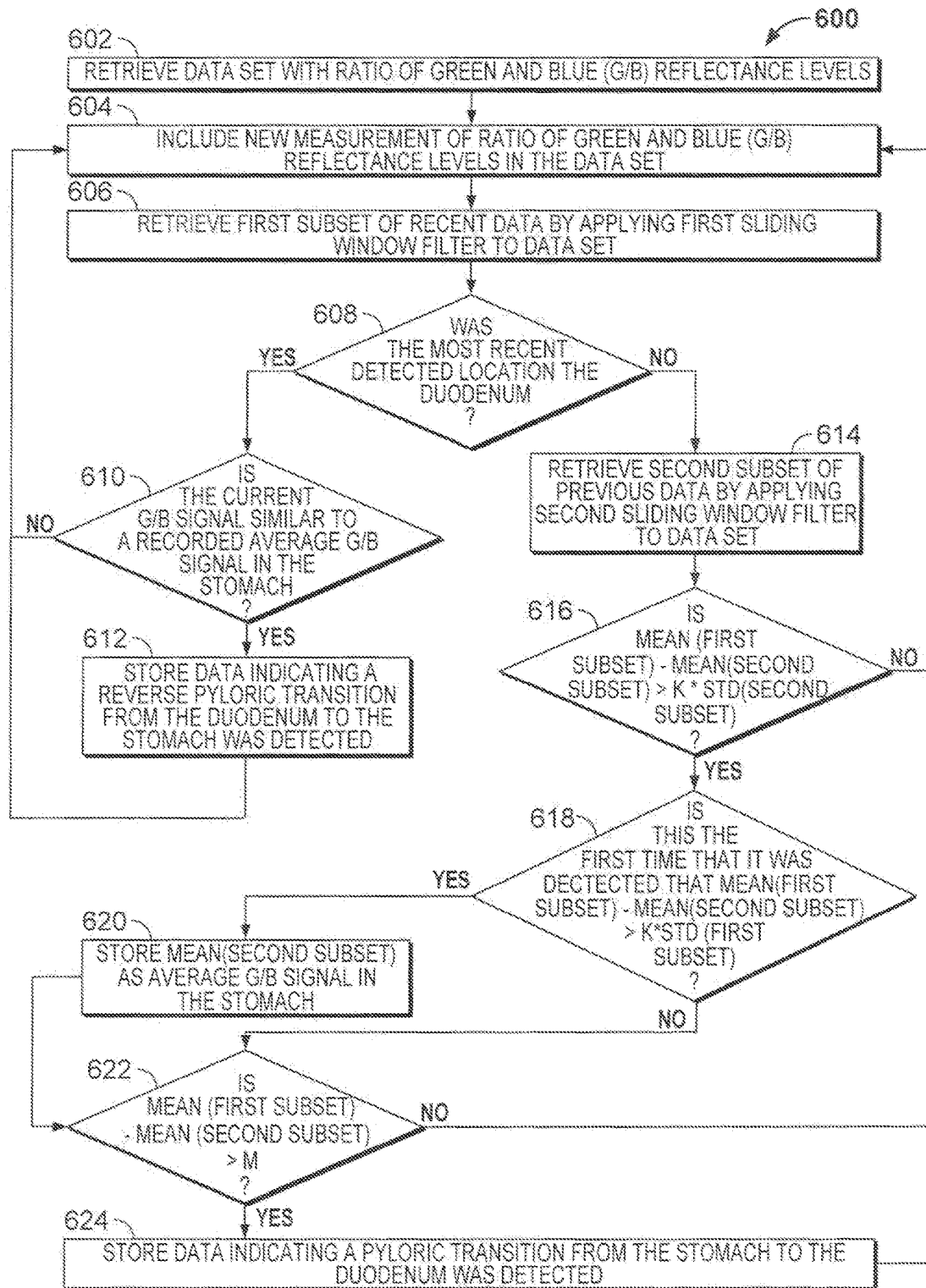


FIG. 6

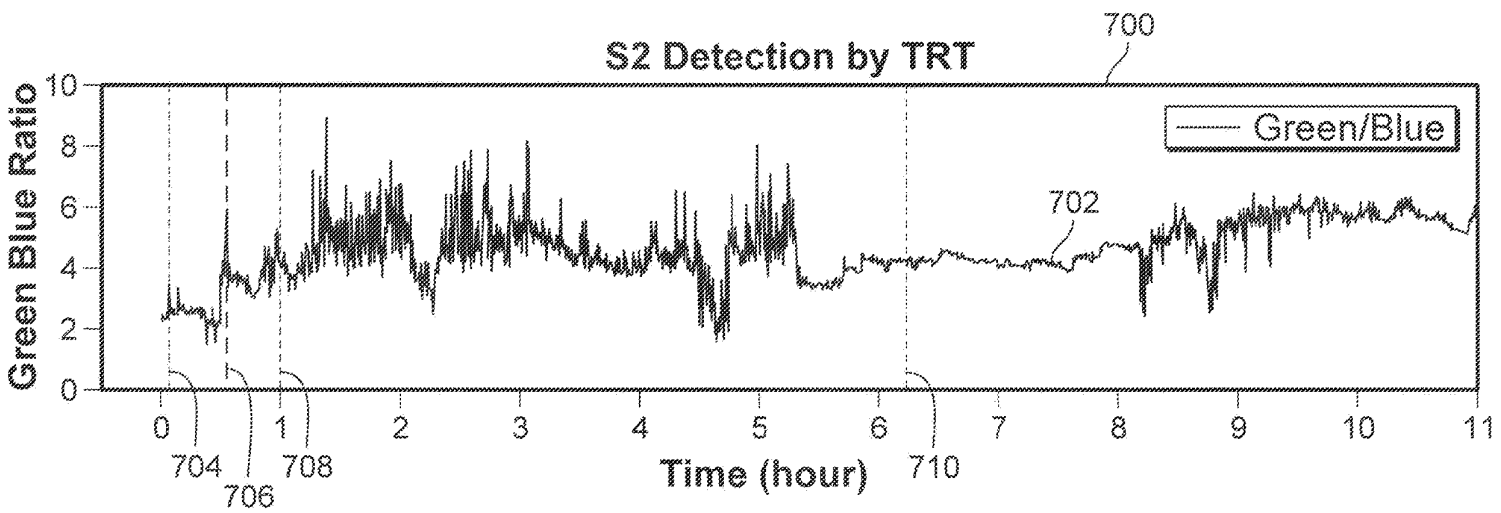


FIG. 7

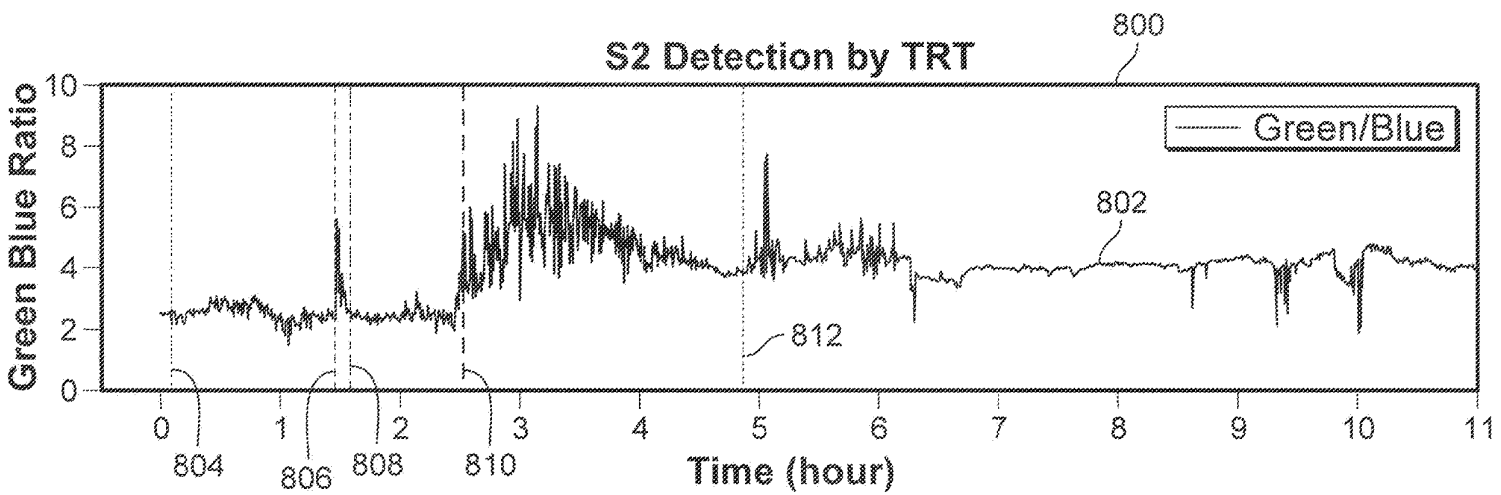


FIG. 8

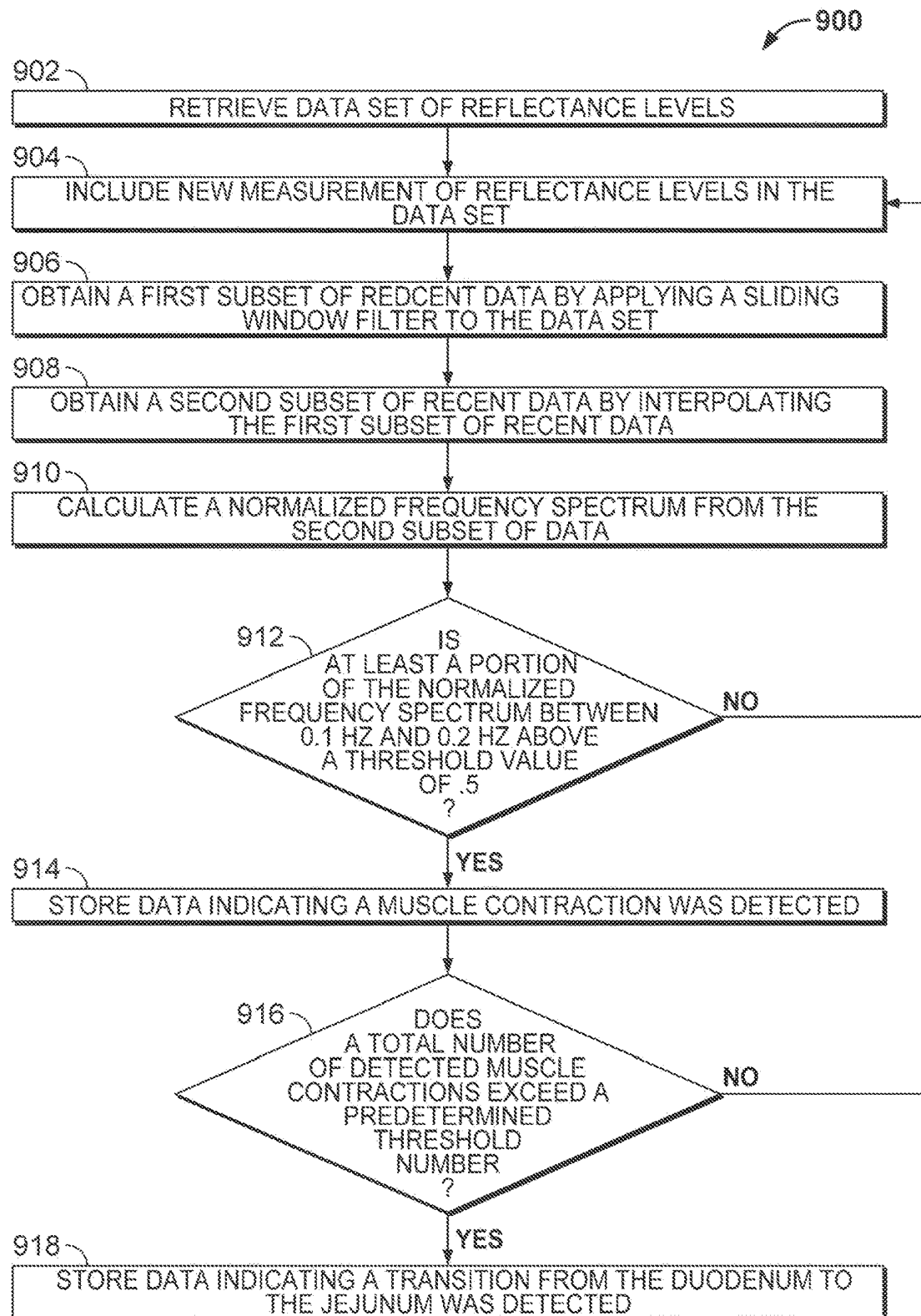
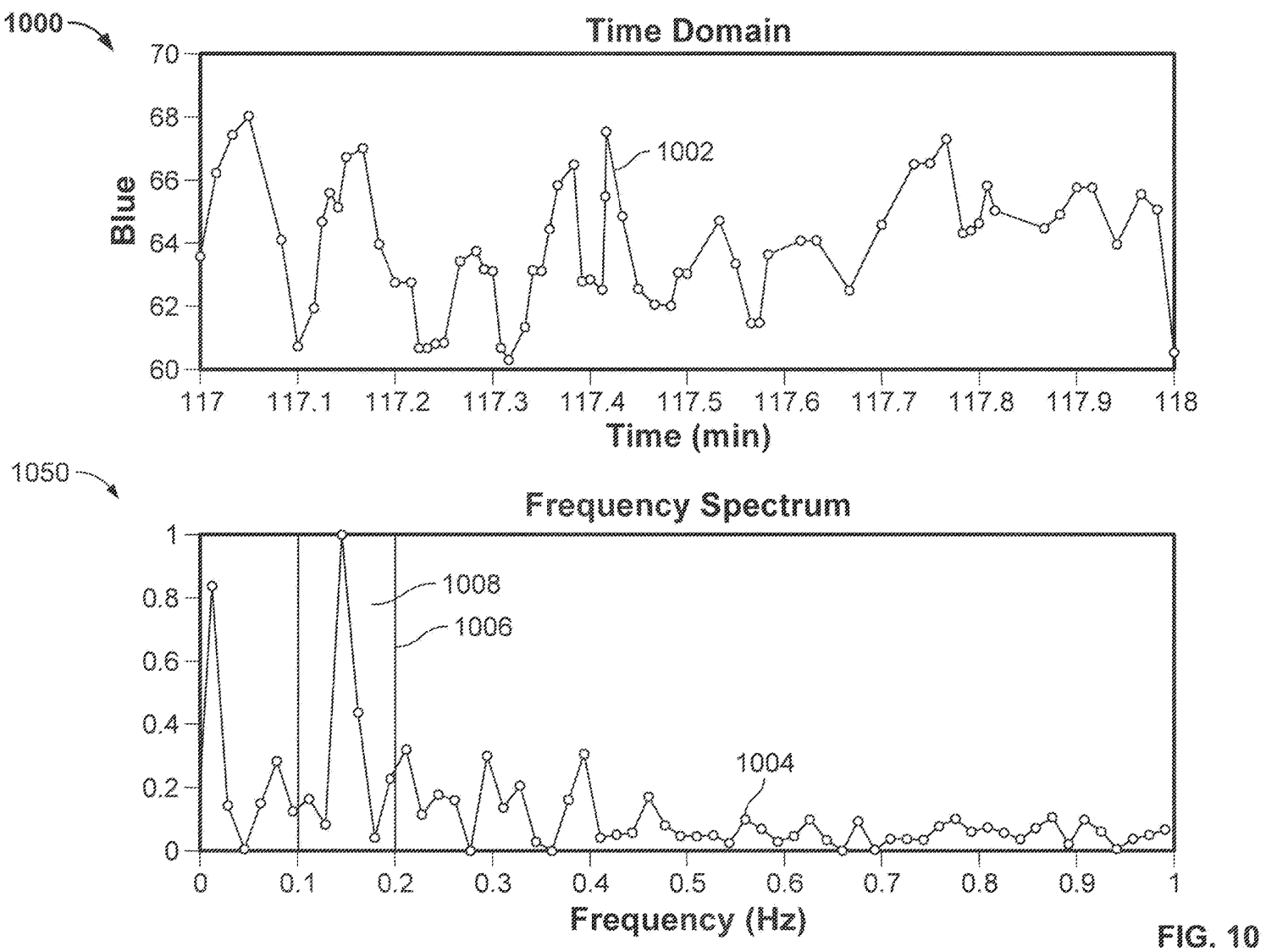
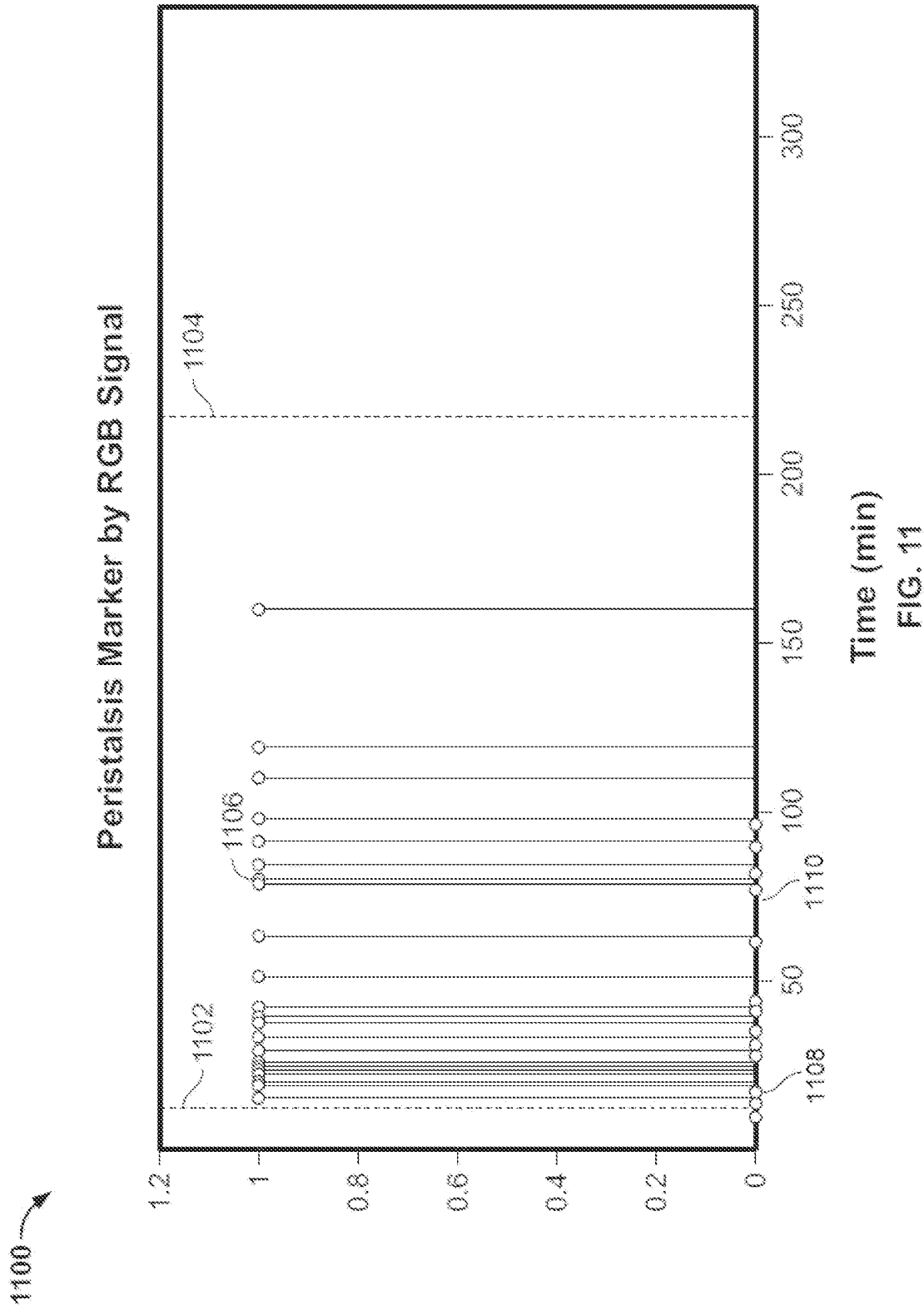


FIG. 9





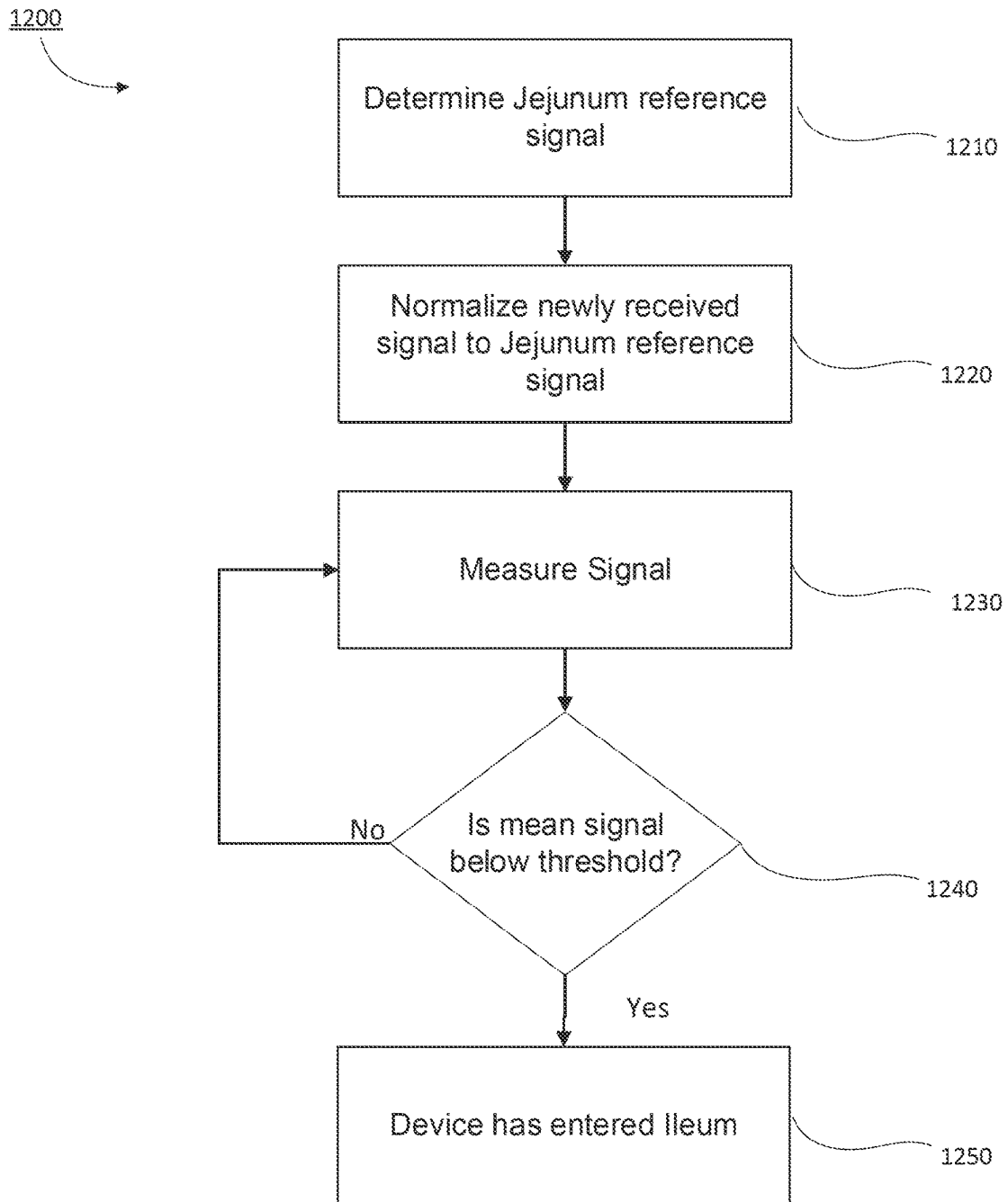


FIG. 12

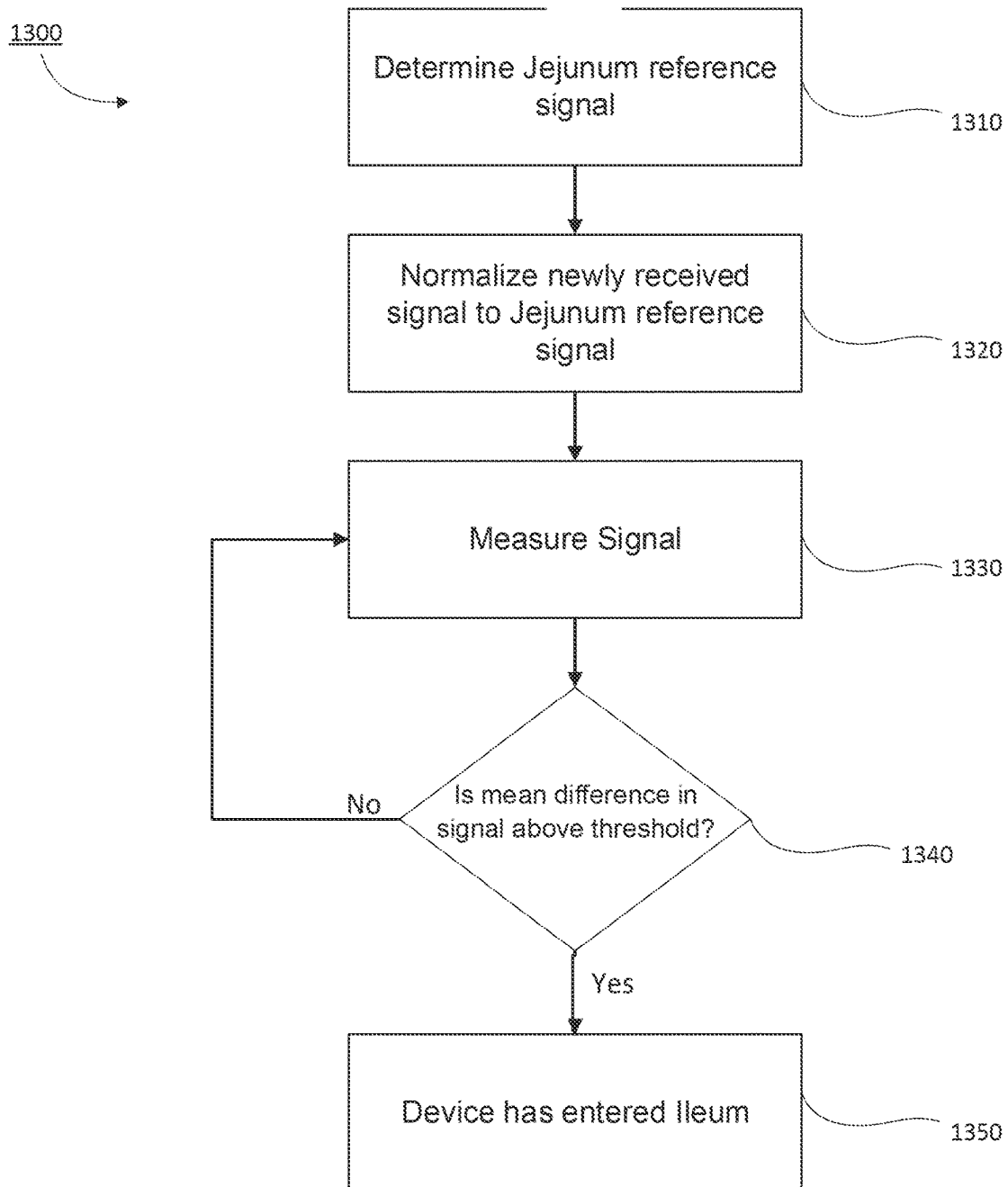


FIG. 13

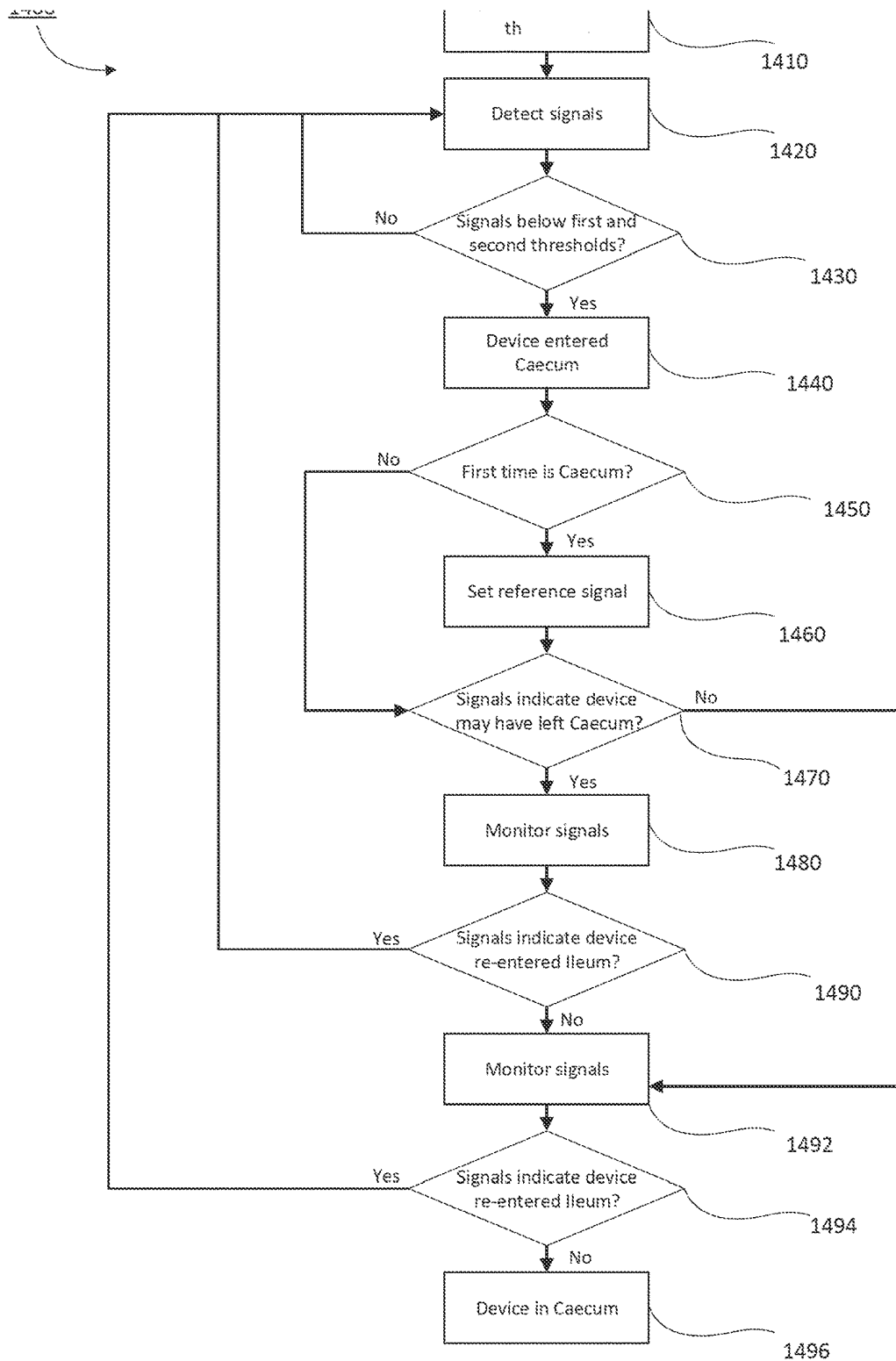


FIG. 14

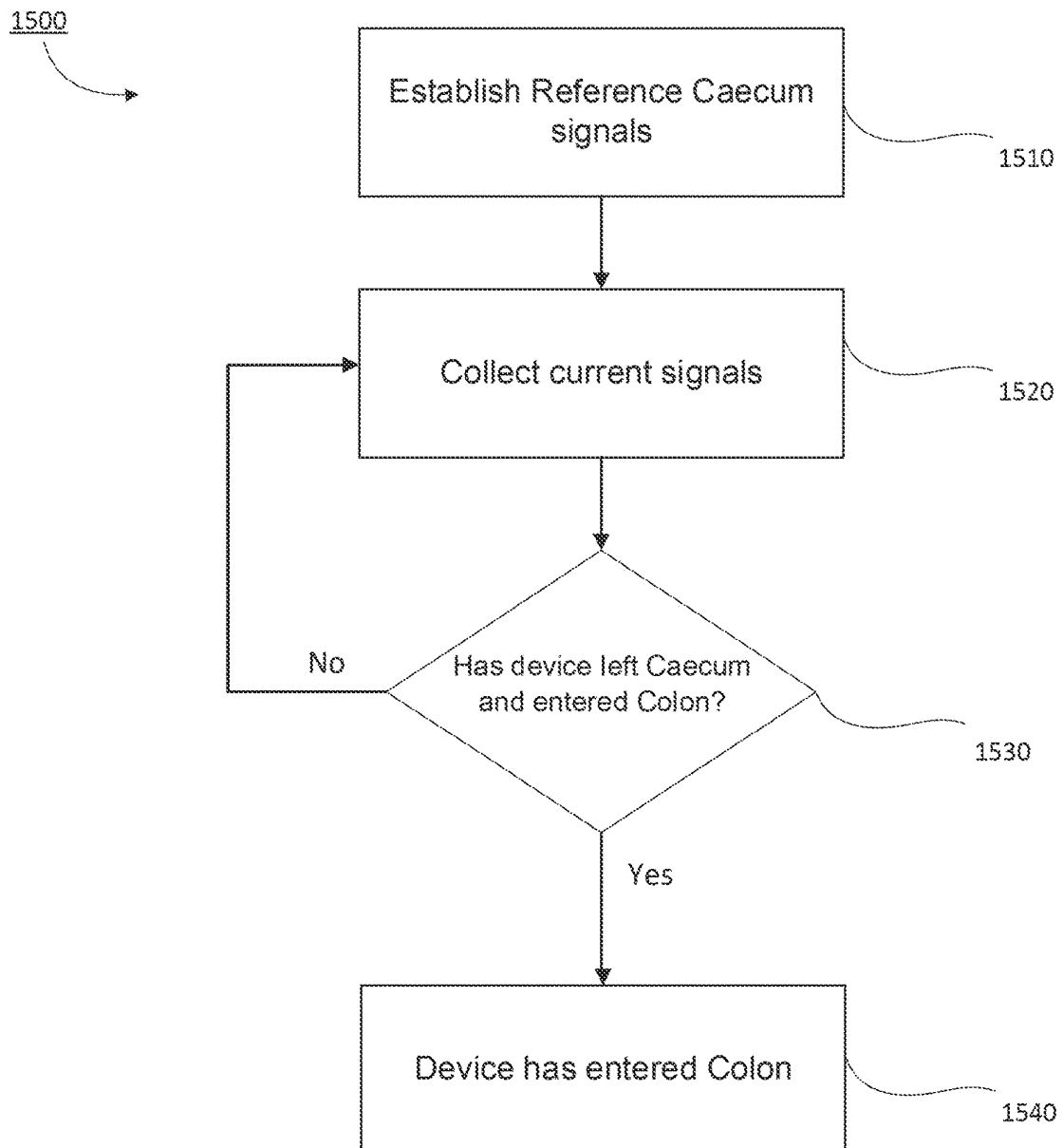


FIG. 15

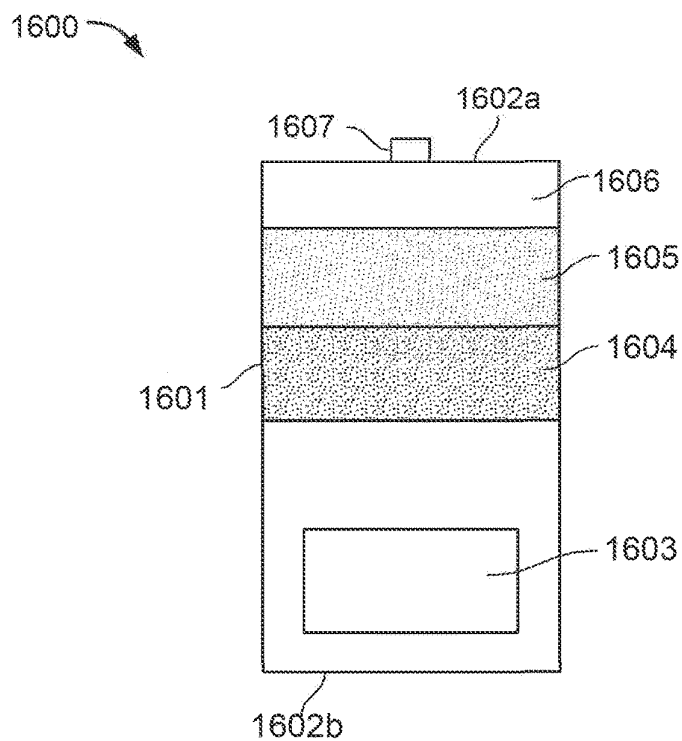


FIG. 16

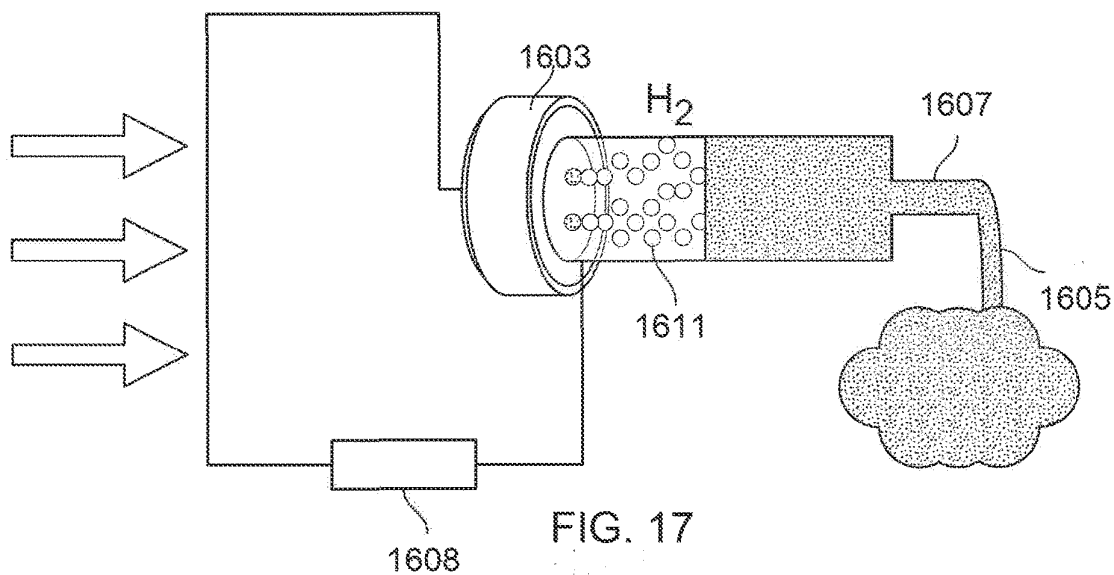


FIG. 17

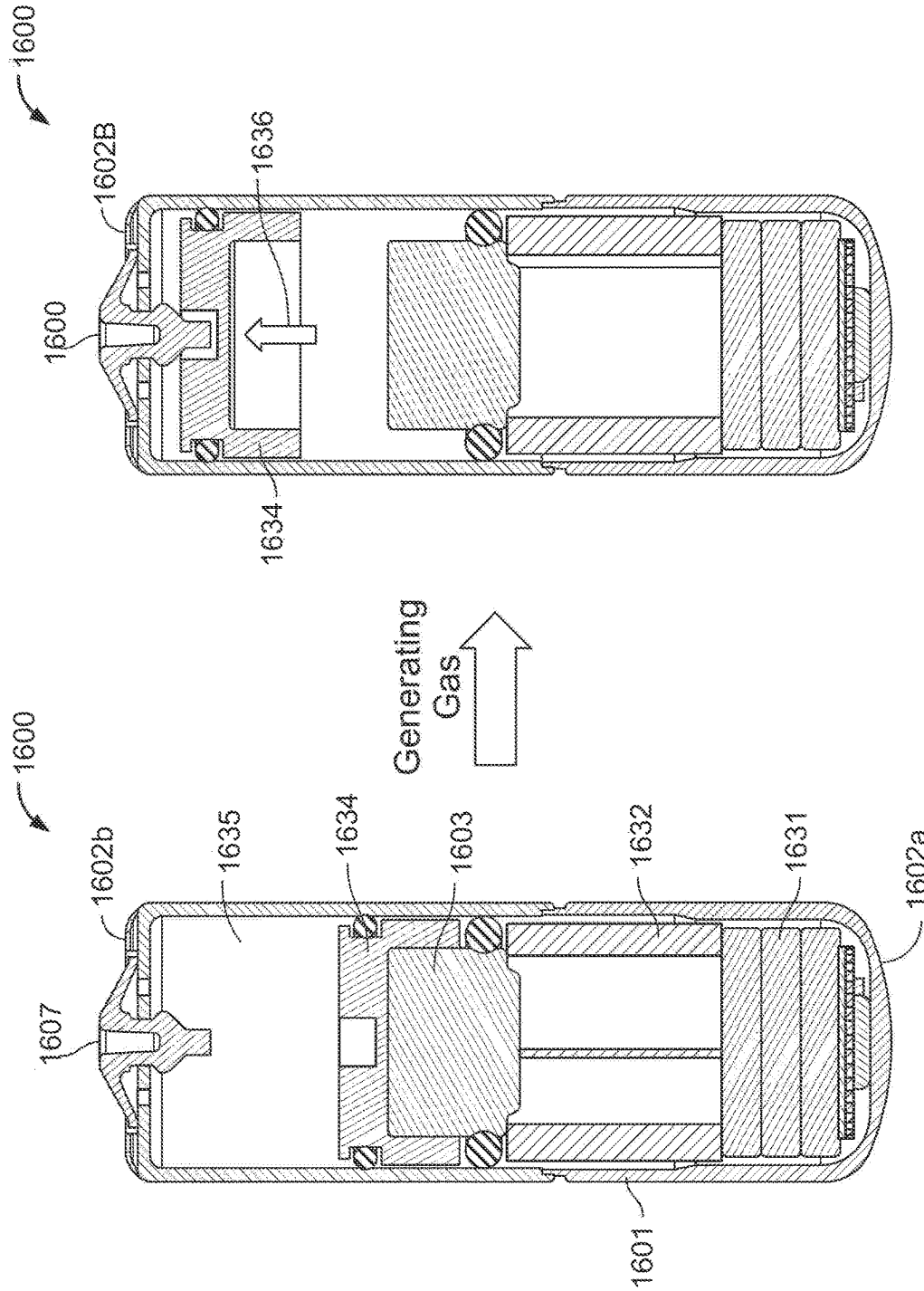


FIG. 18

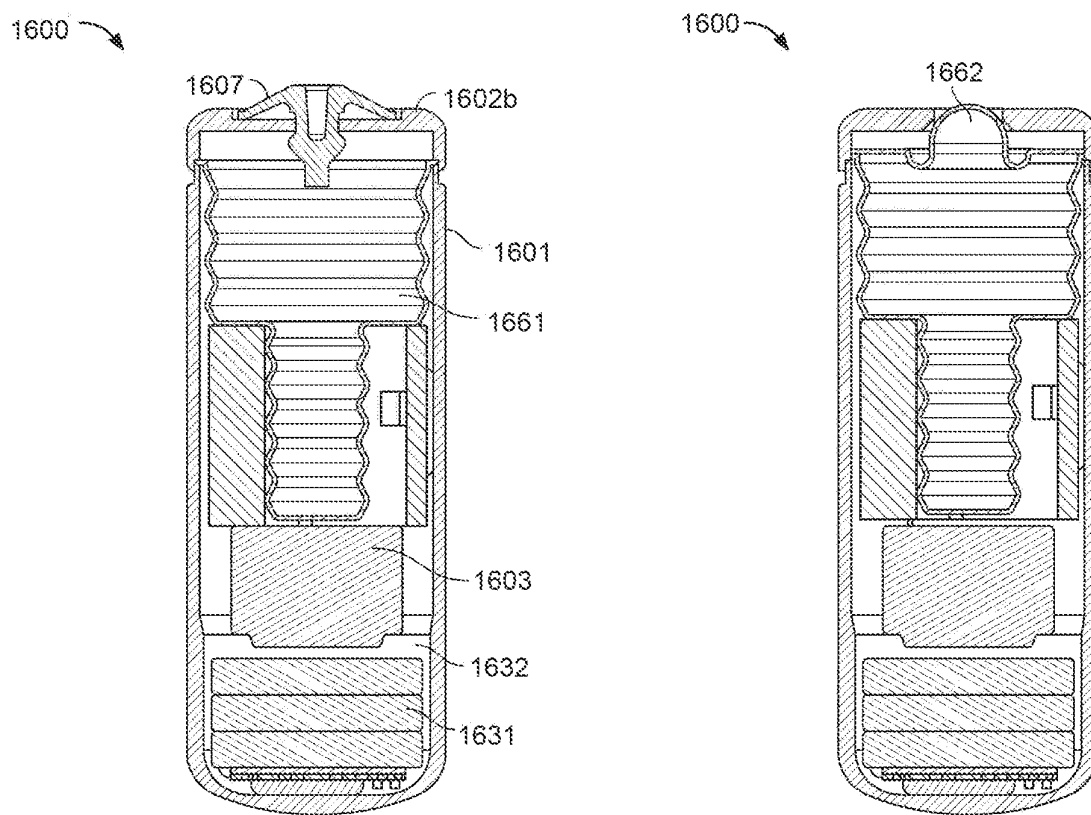


FIG. 19

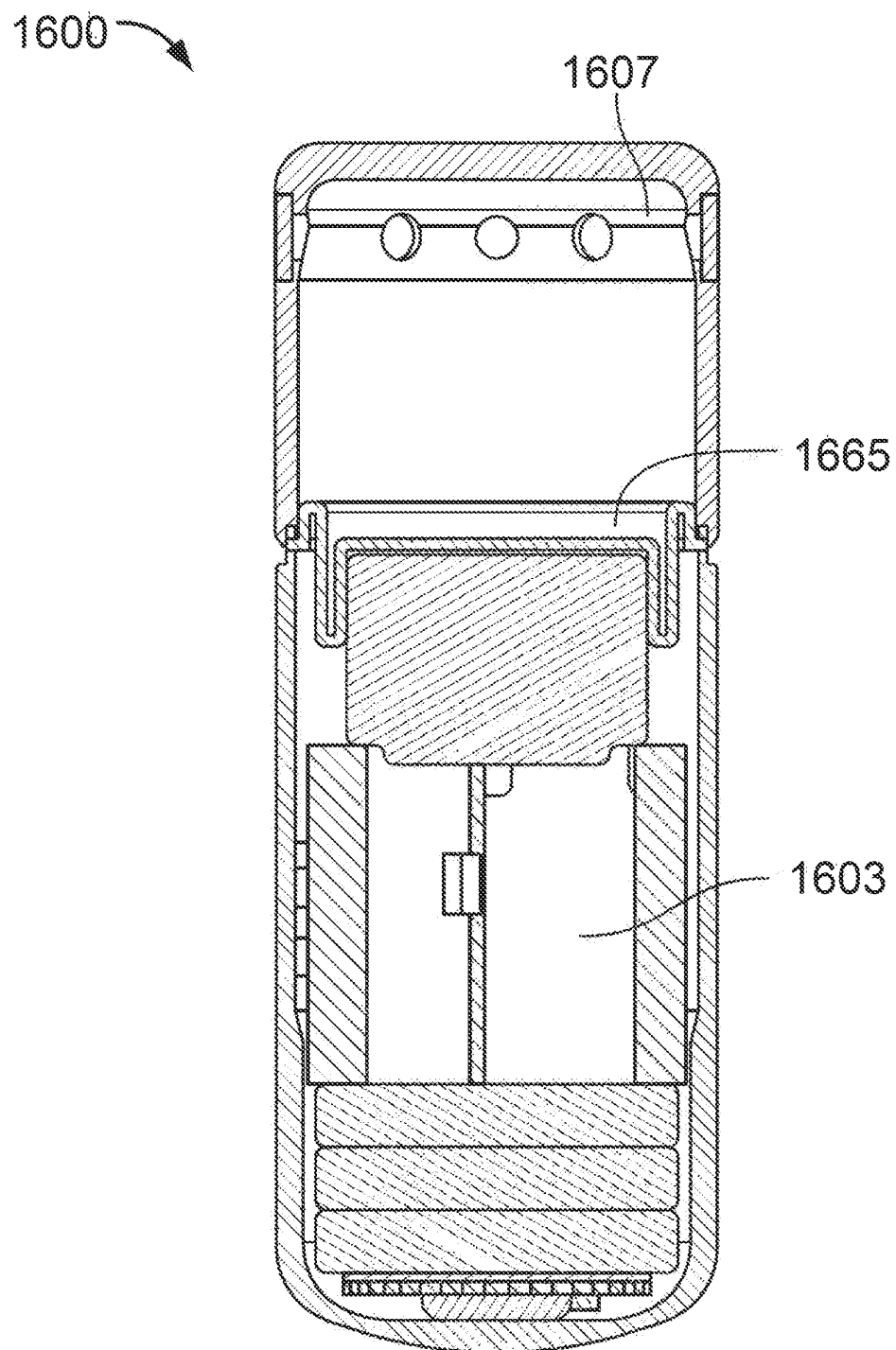


FIG. 20

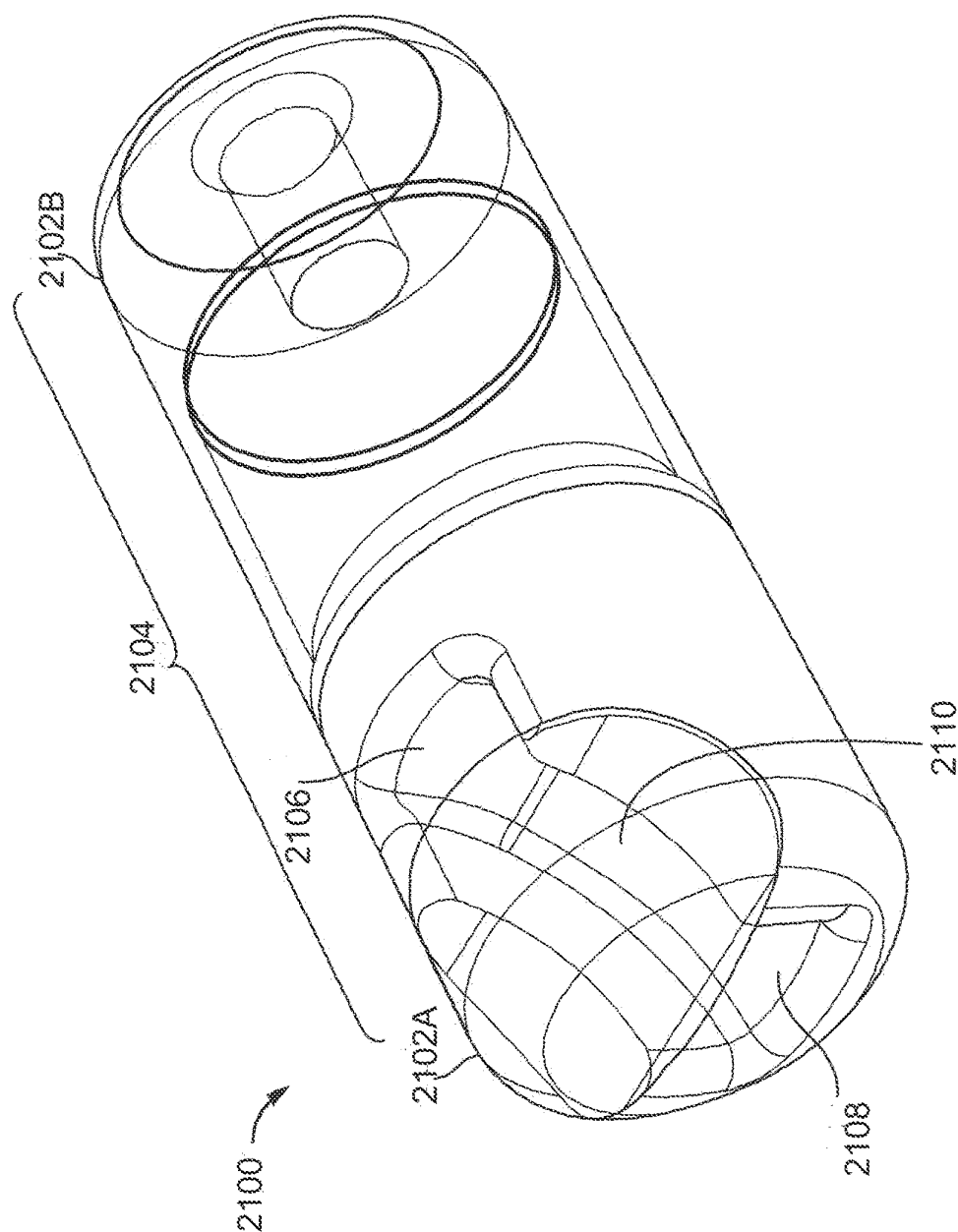


FIG. 21

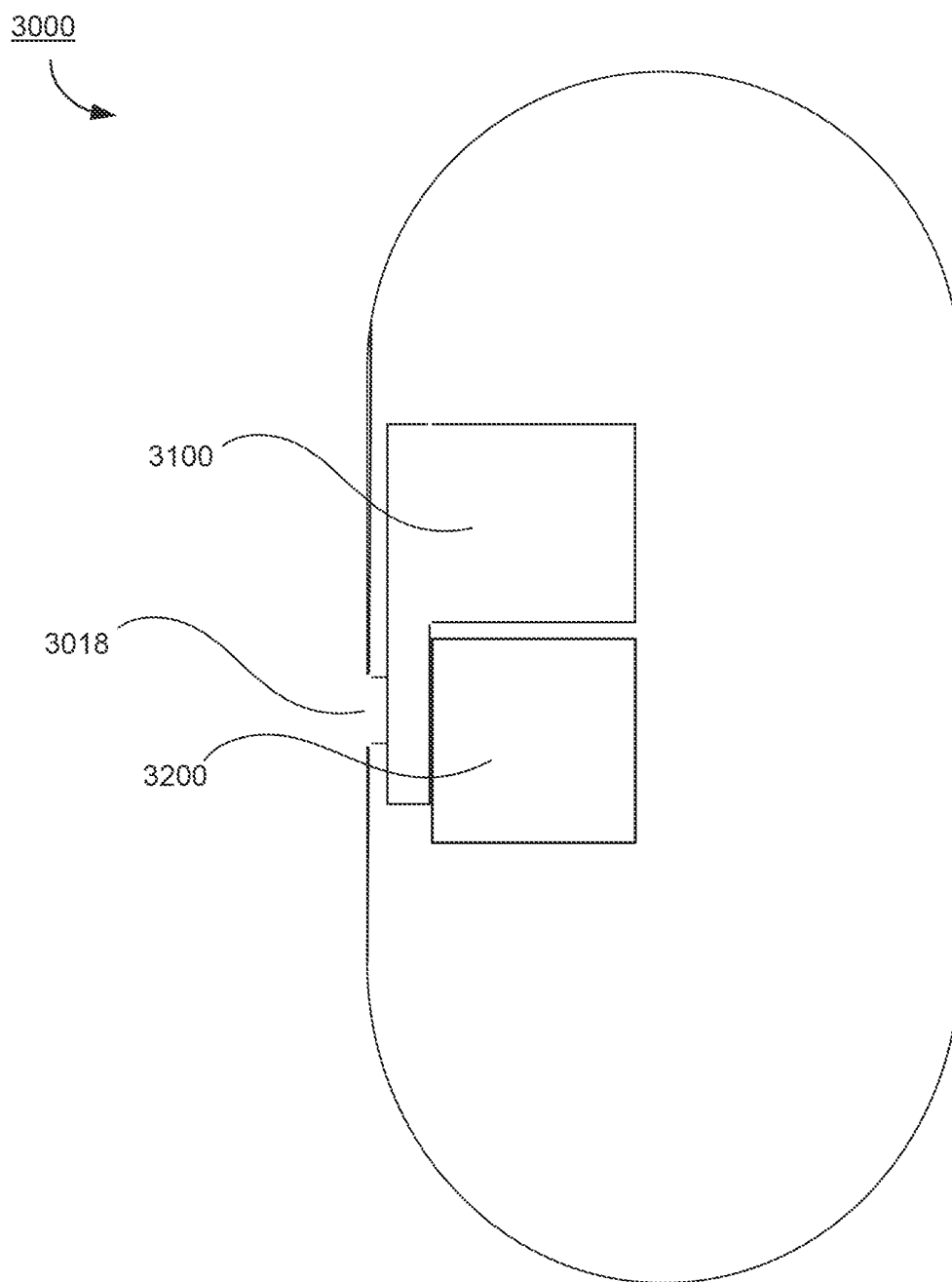


FIG. 22

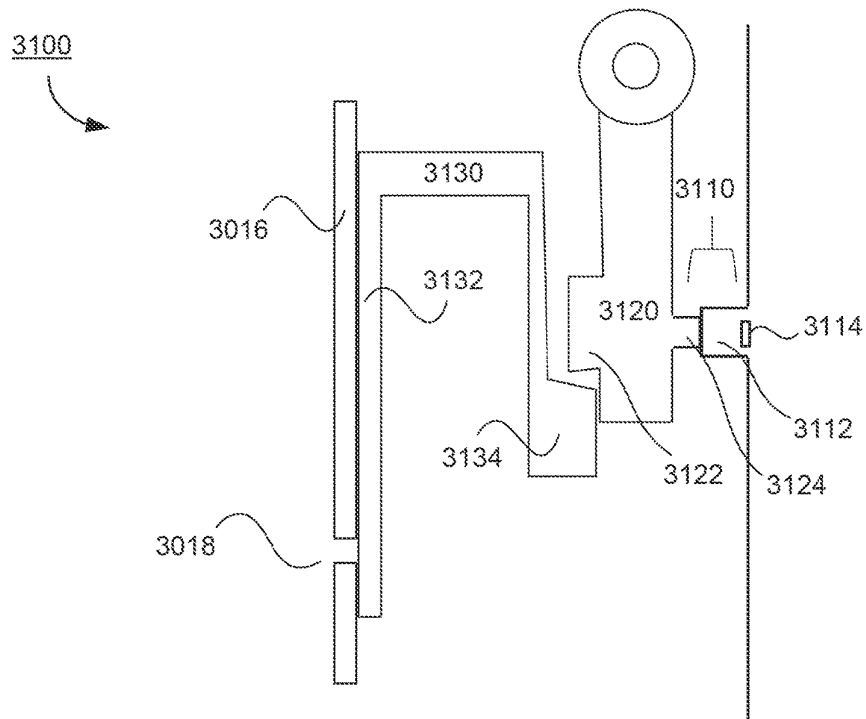


FIG. 23

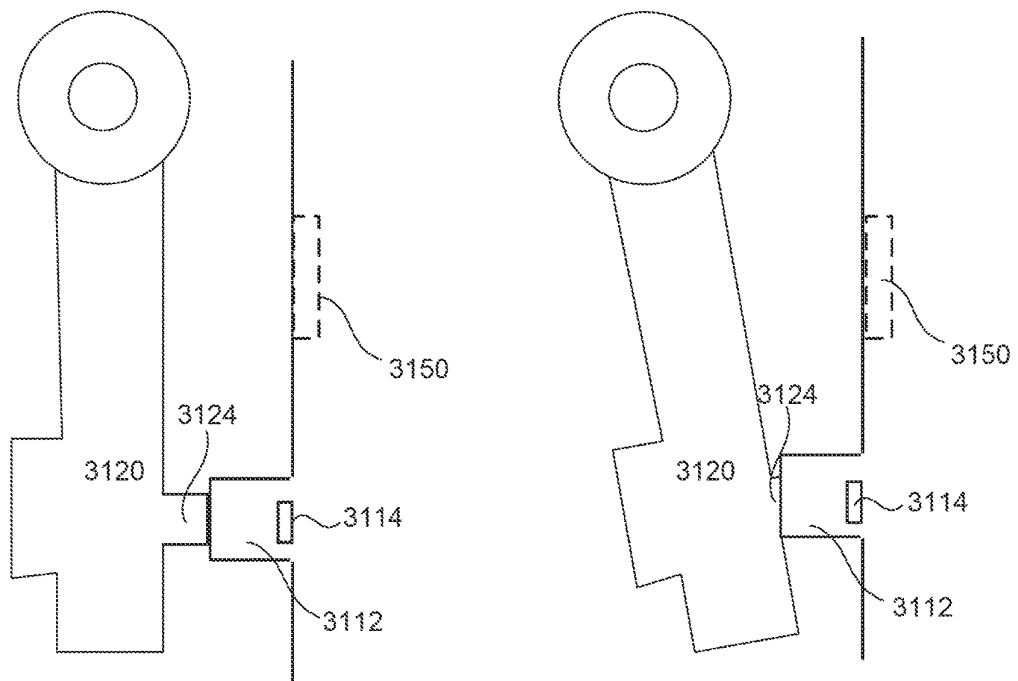


FIG. 24A

FIG. 24B

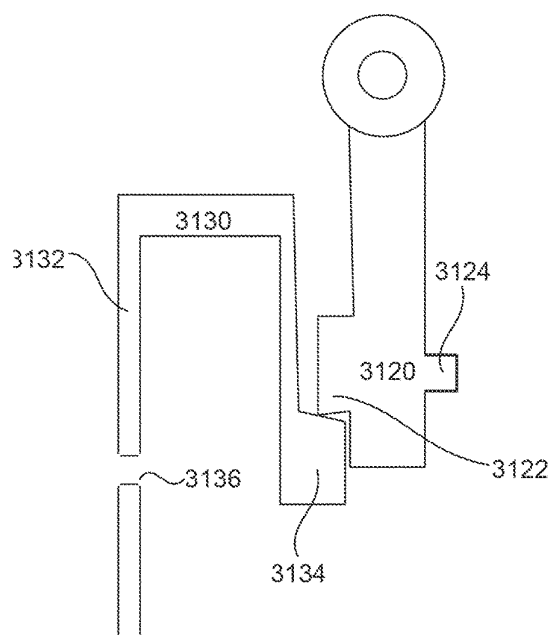


FIG. 25A

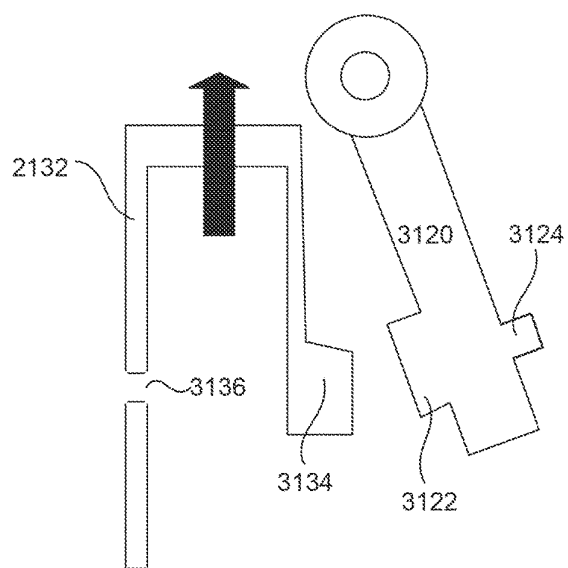


FIG. 25B

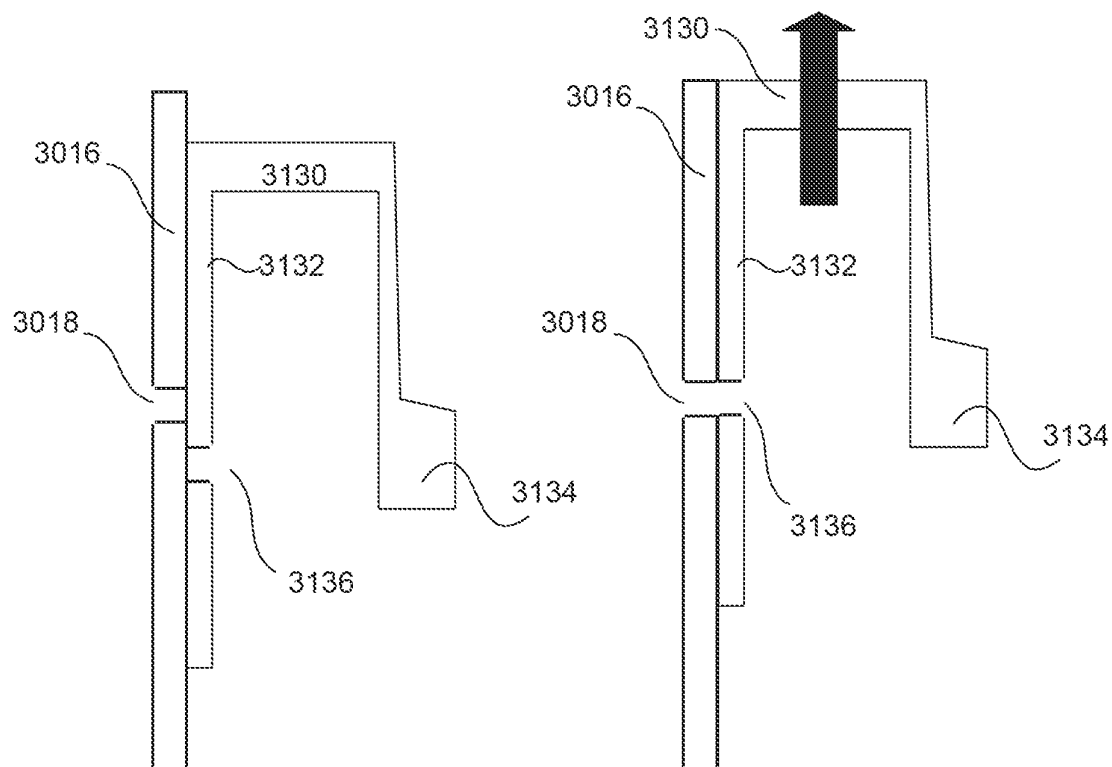


FIG. 26A

FIG. 26B

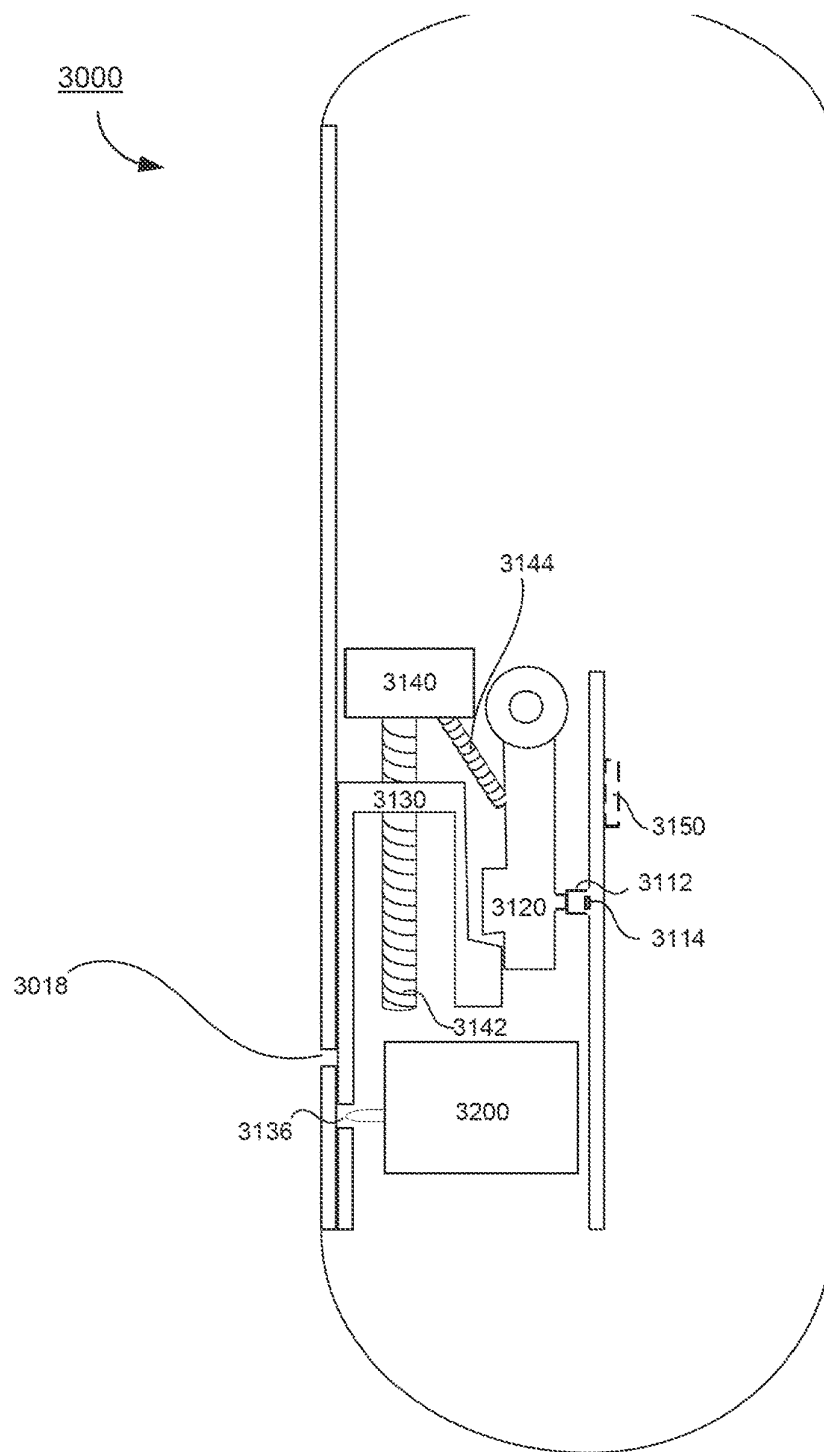


FIG. 27

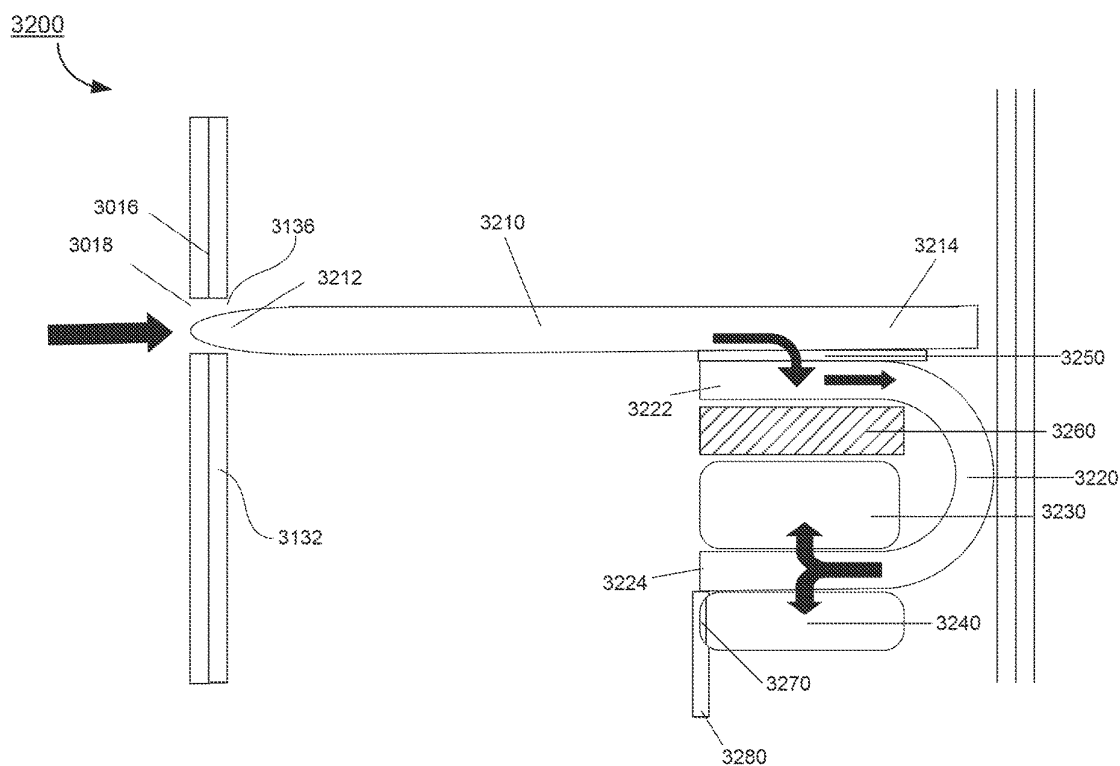


FIG. 28

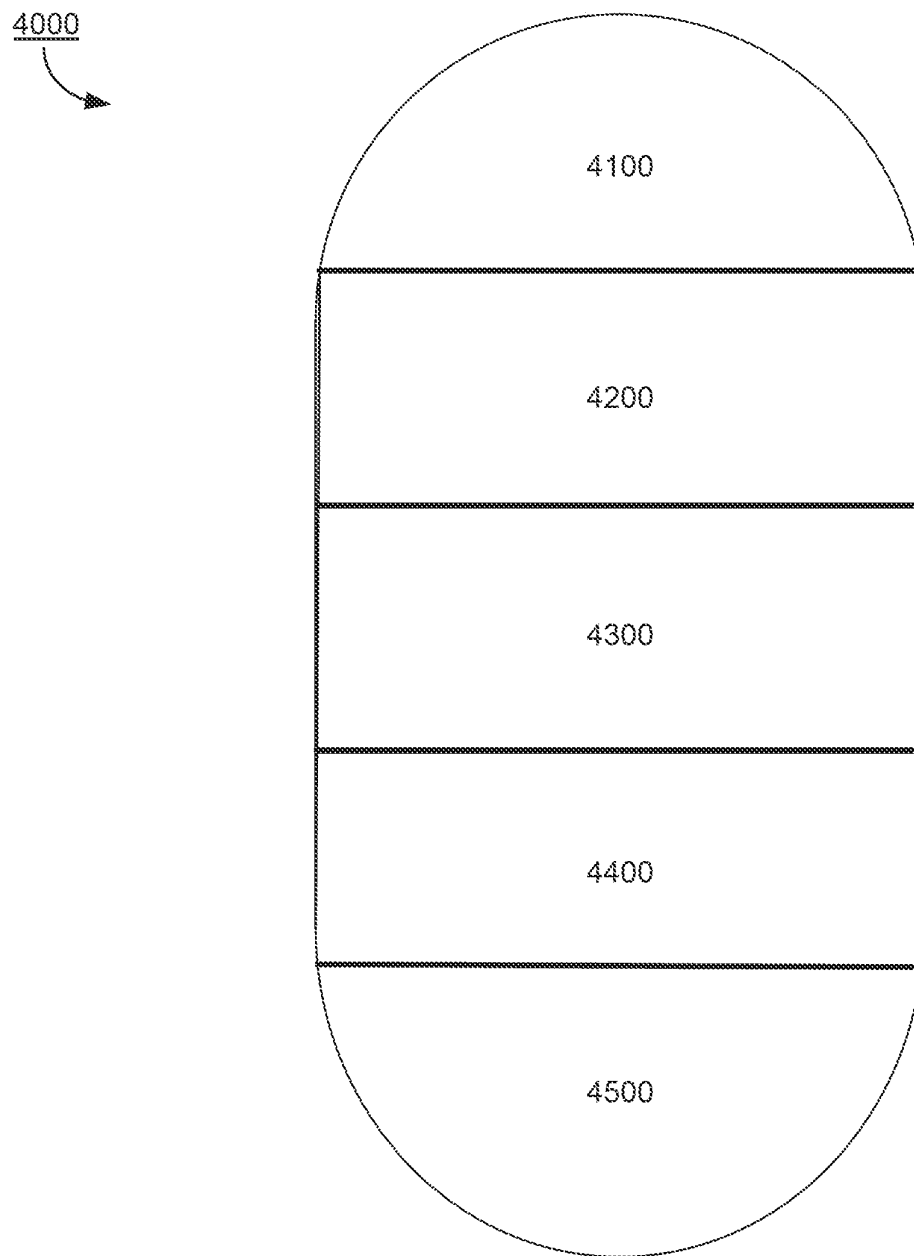


FIG. 29

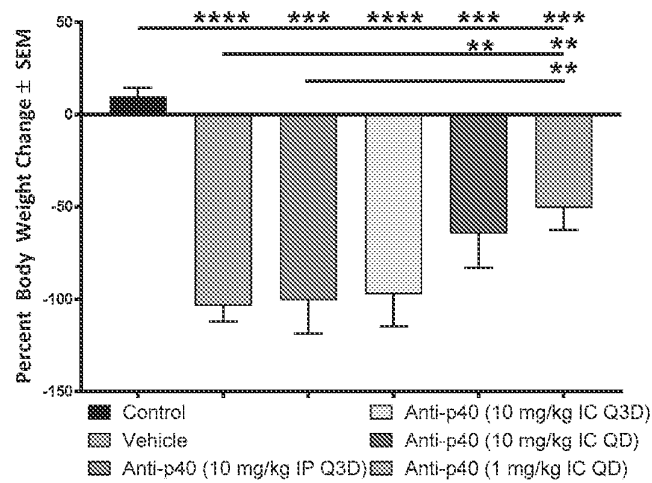


FIG. 30

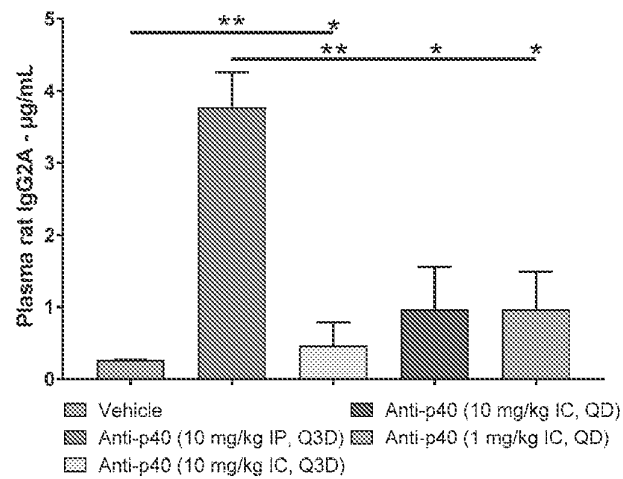


FIG. 31

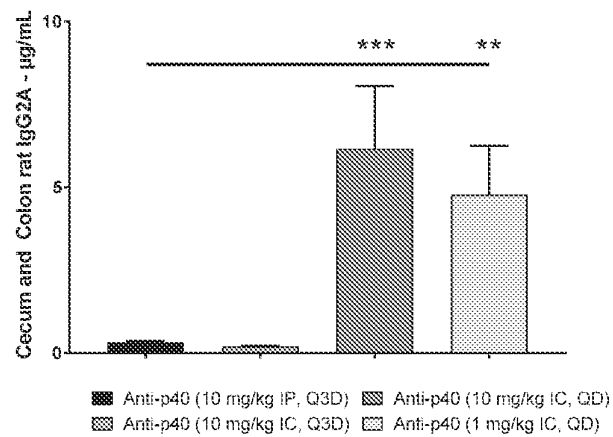


FIG. 32

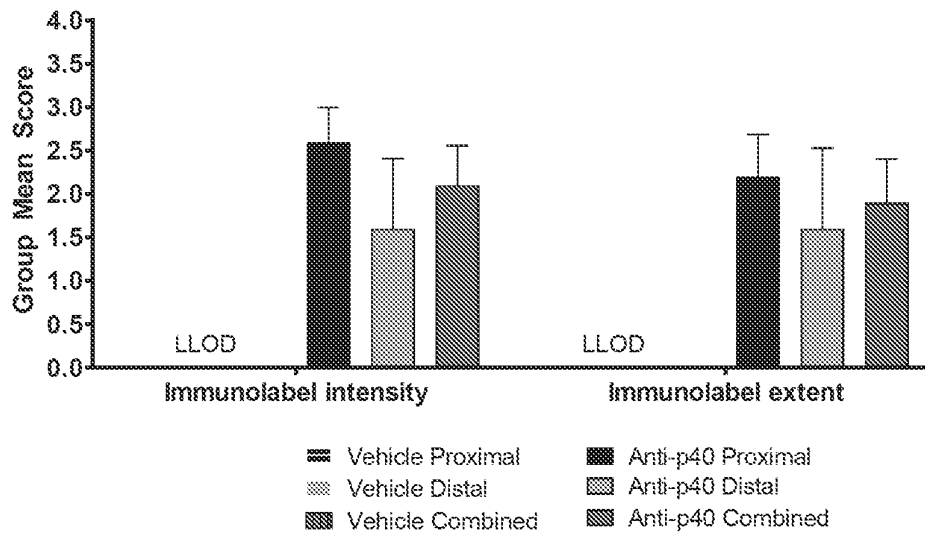


FIG. 33

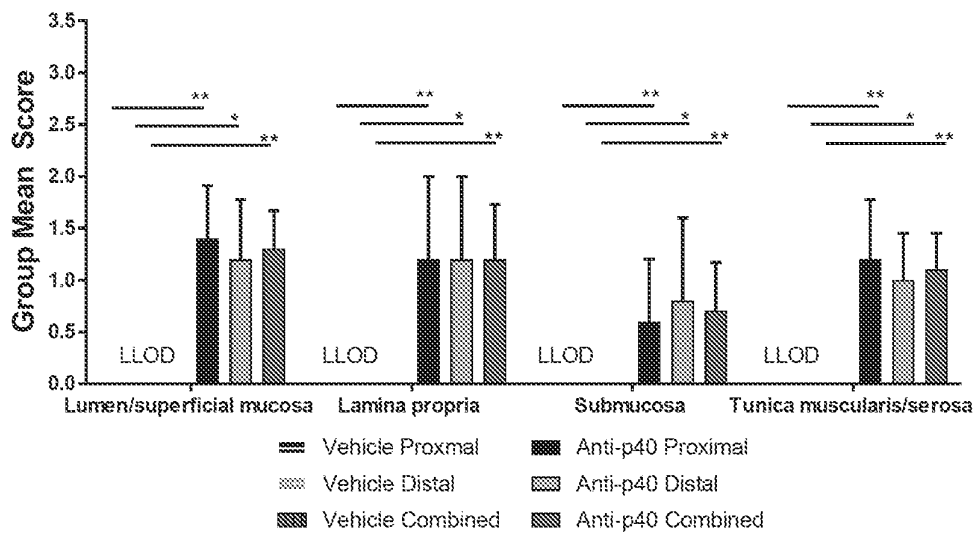
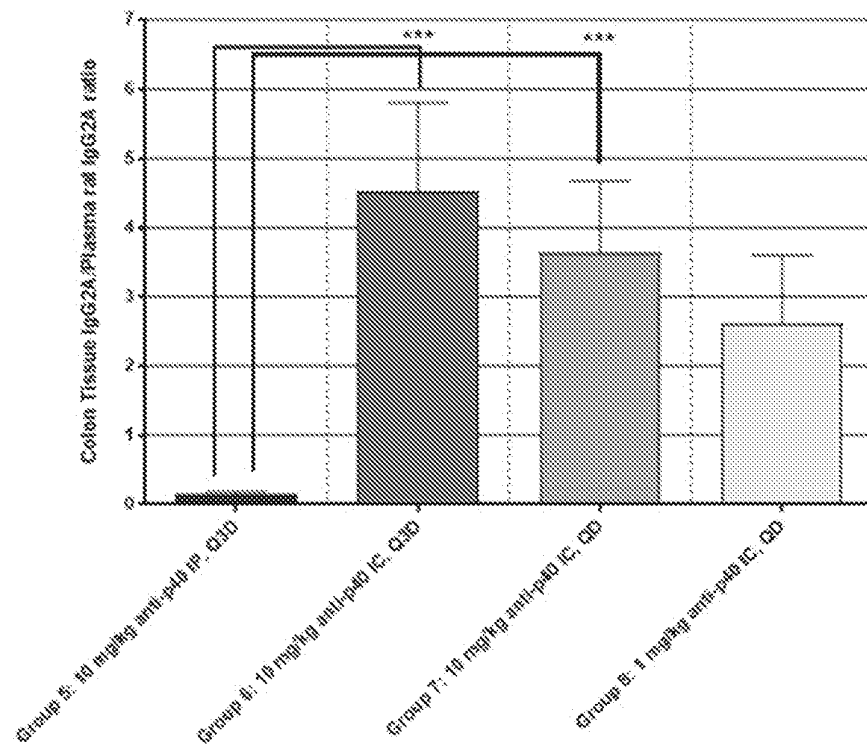


FIG. 34



^Outlier removed from Group 5

FIG. 35

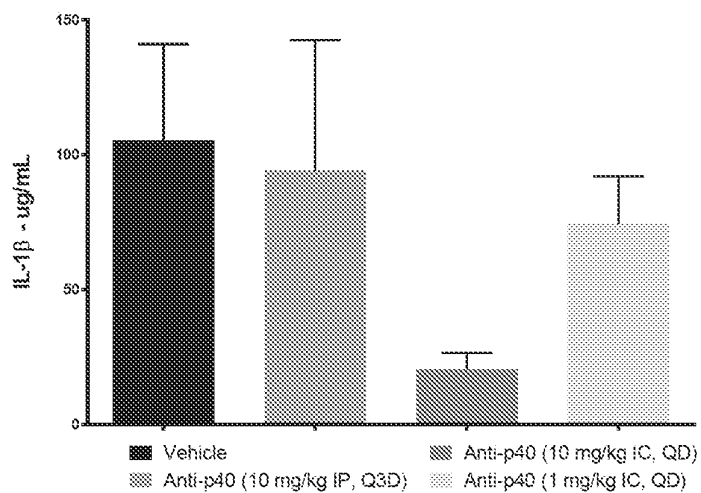


FIG. 36

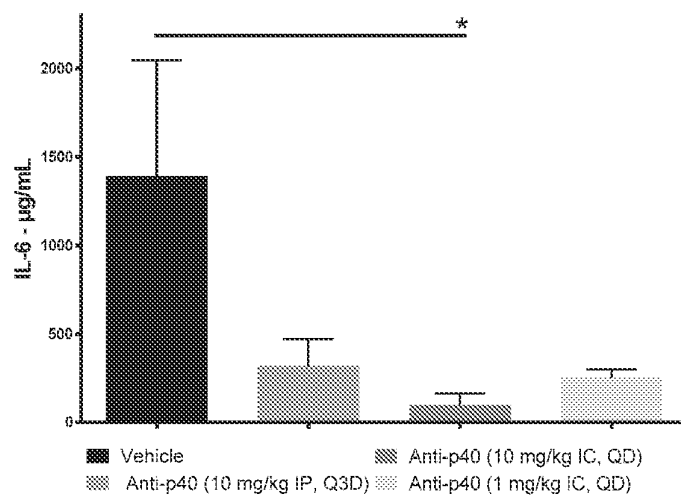


FIG. 37

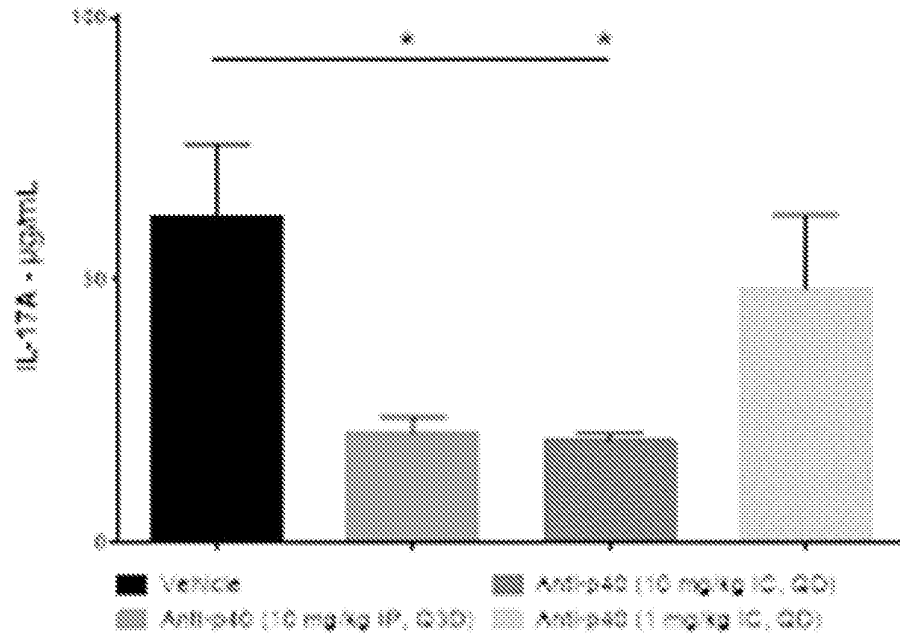


FIG. 38

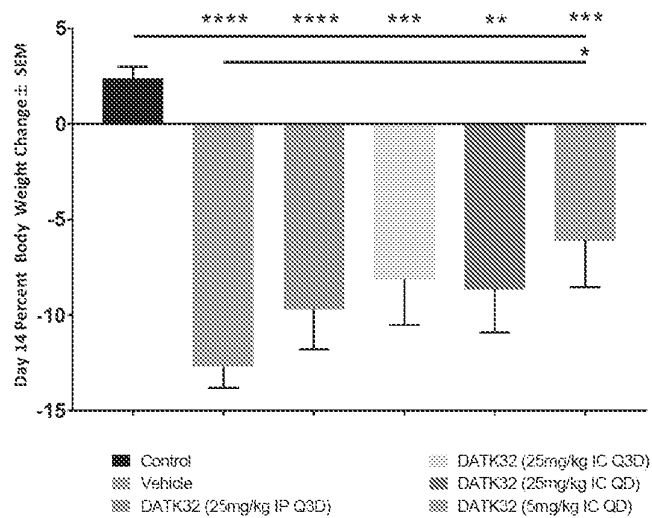


FIG. 39

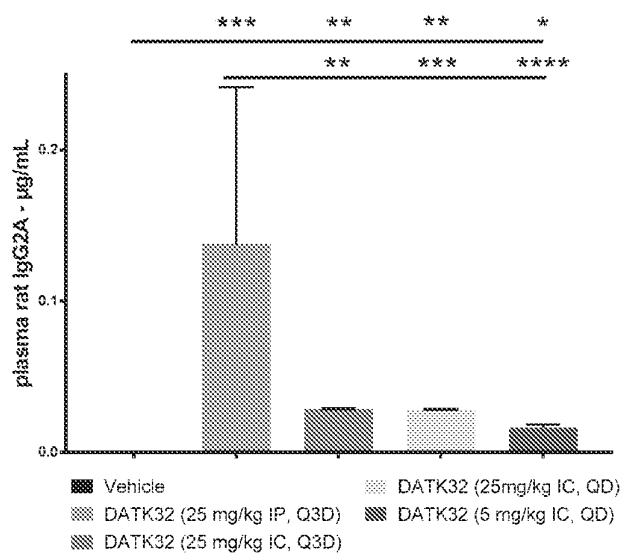


FIG. 40

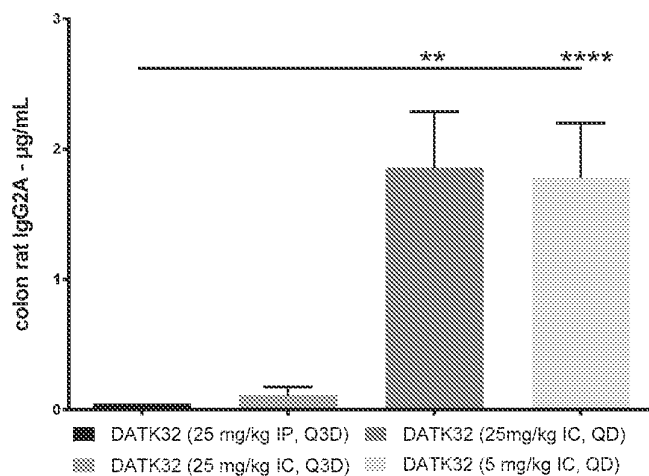


FIG. 41

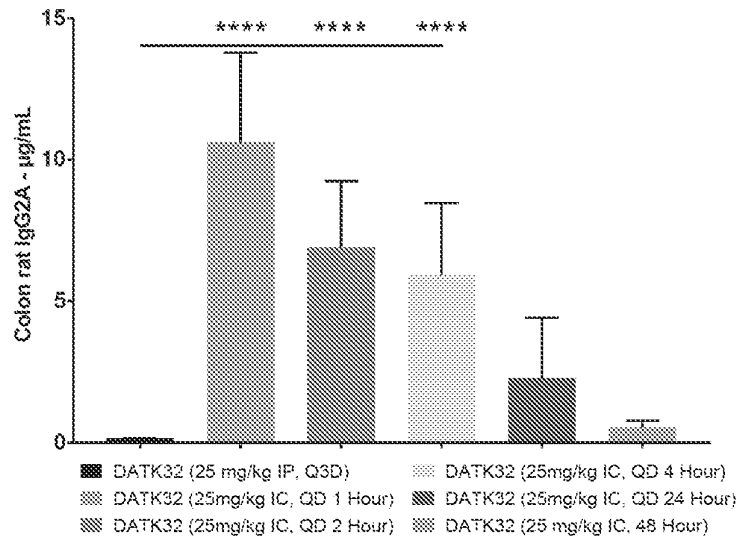


FIG. 42

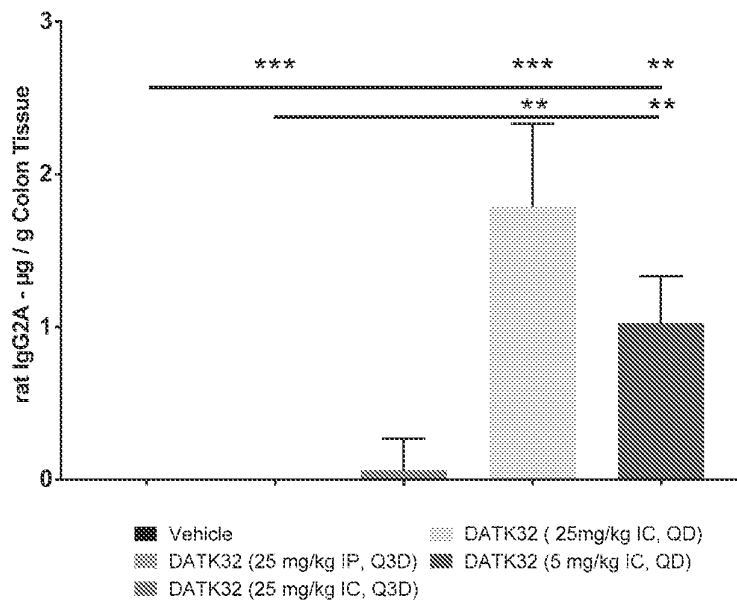


FIG. 43

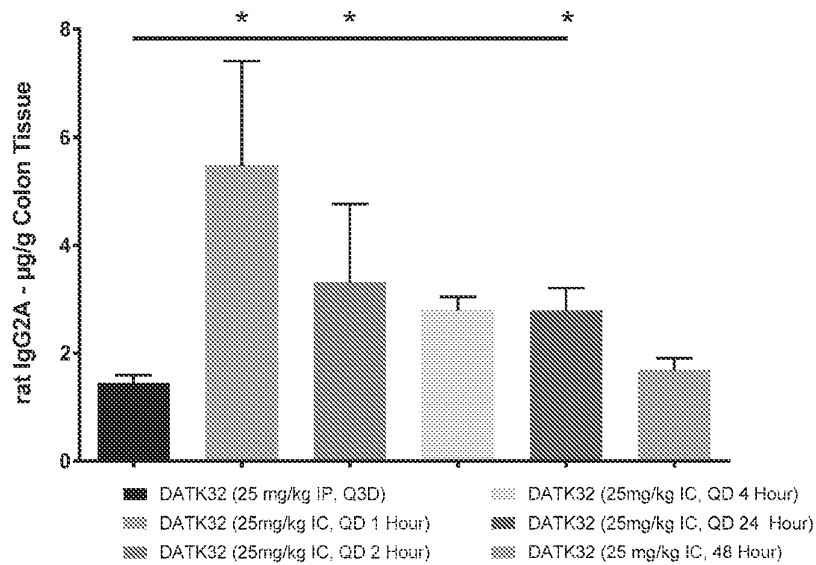


FIG. 44

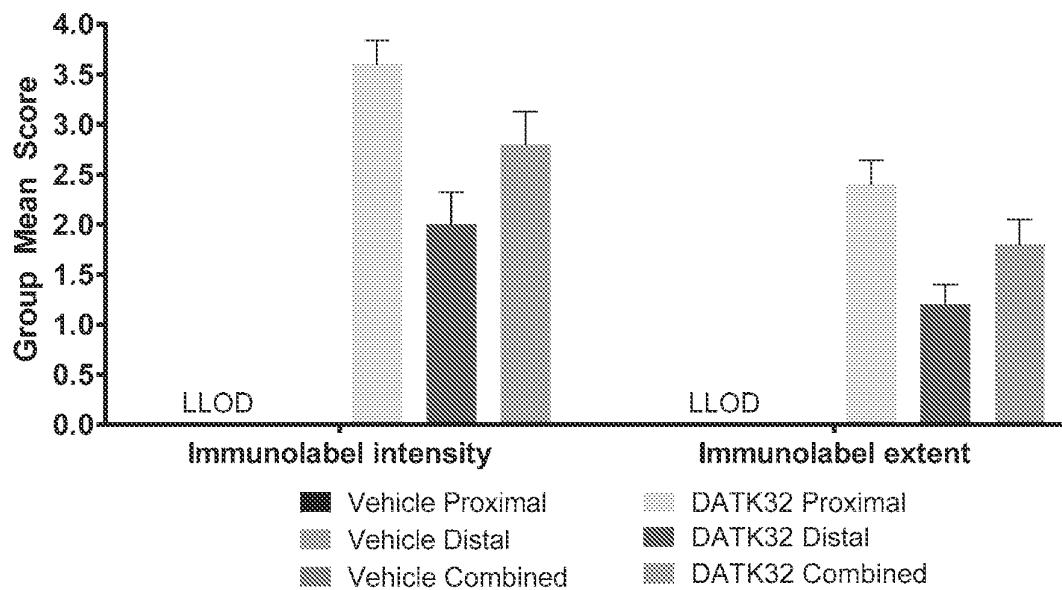


FIG. 45

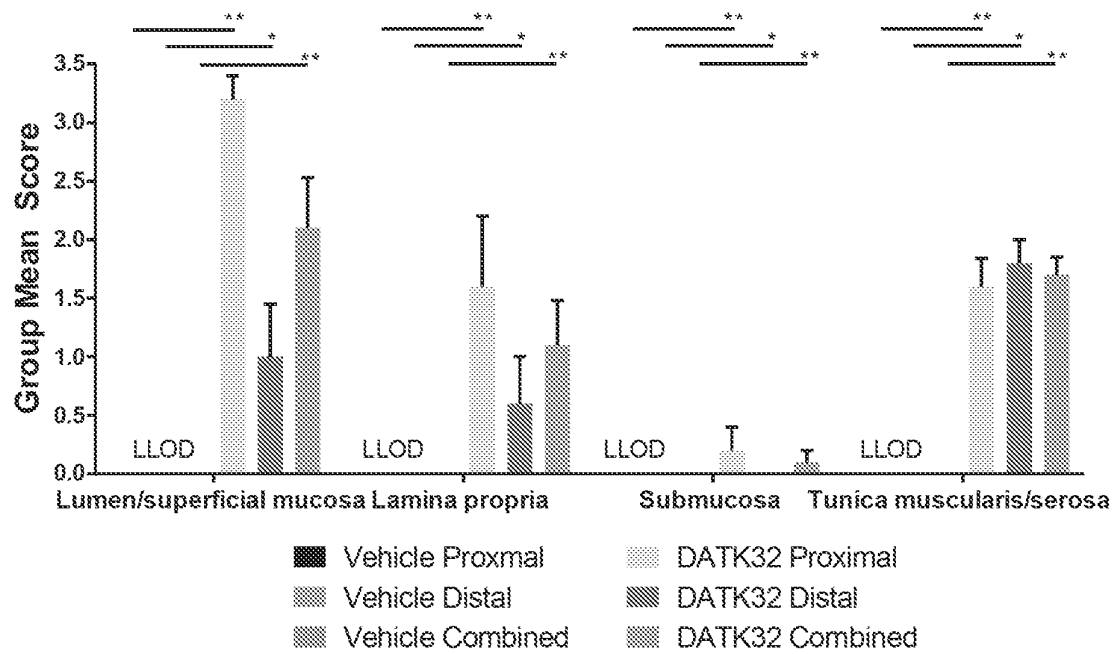


FIG. 46

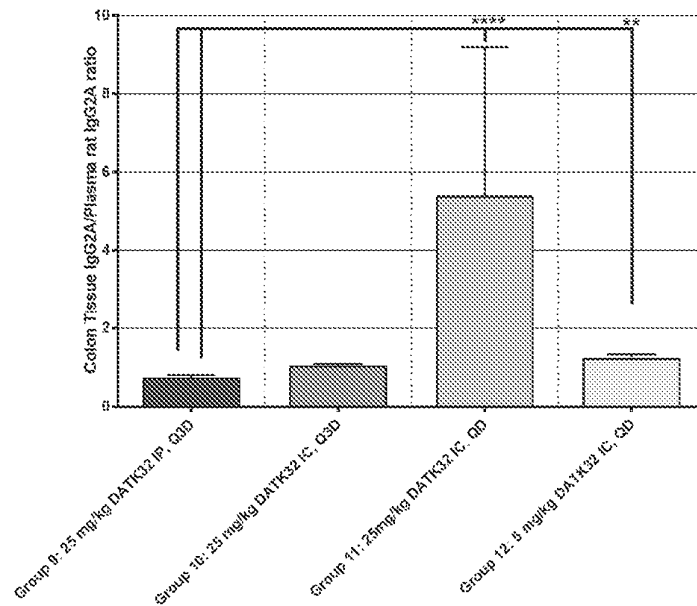


FIG. 47

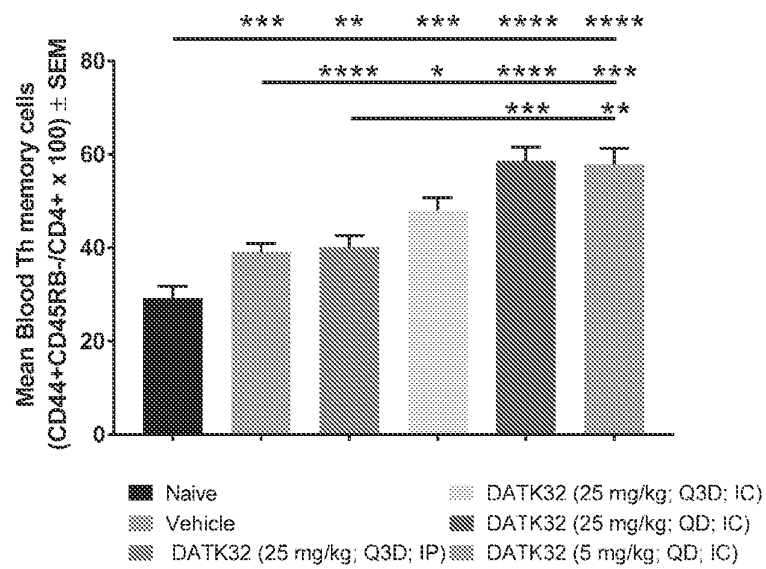


FIG. 48

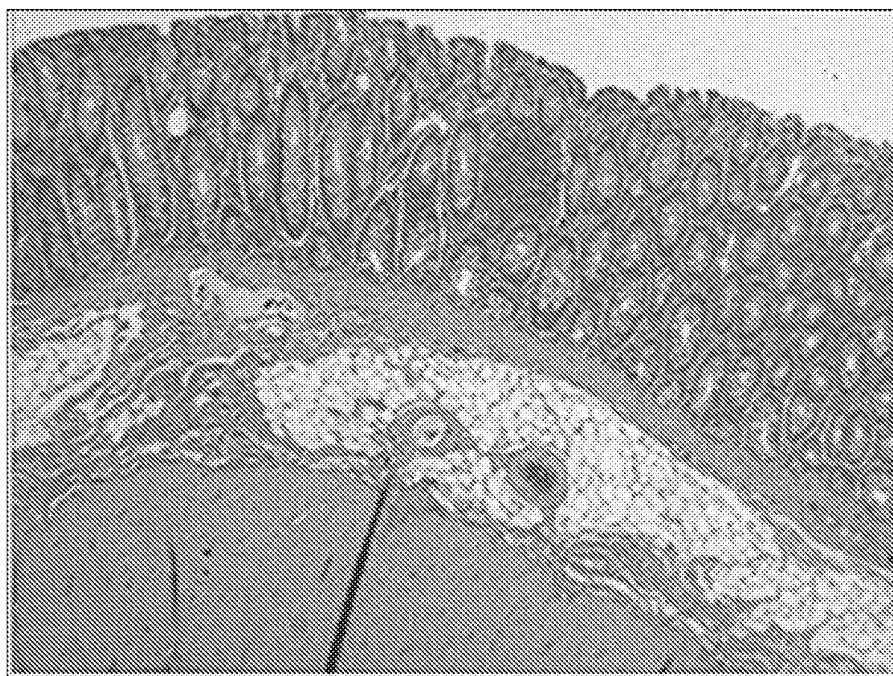


FIG. 49

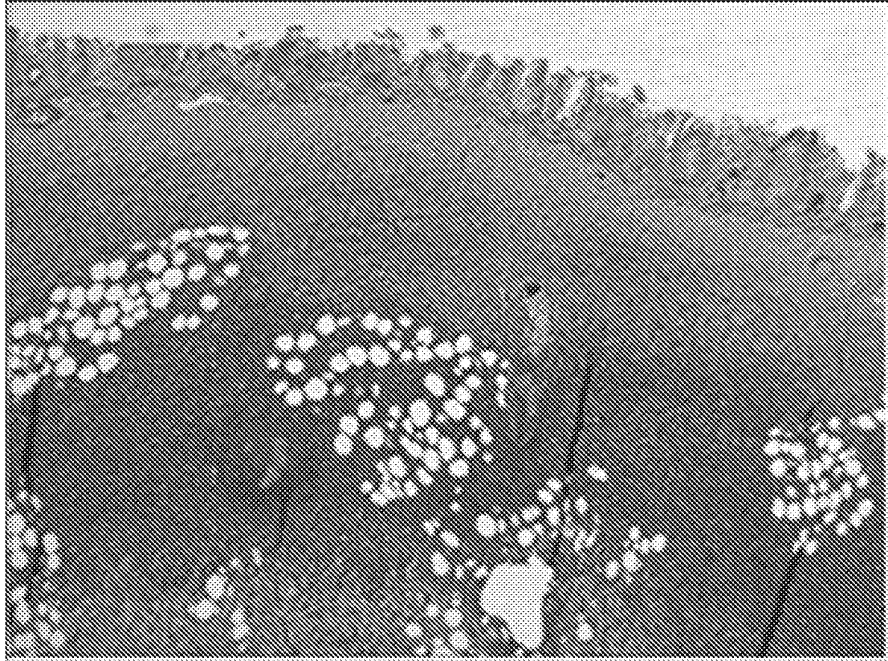


FIG. 50

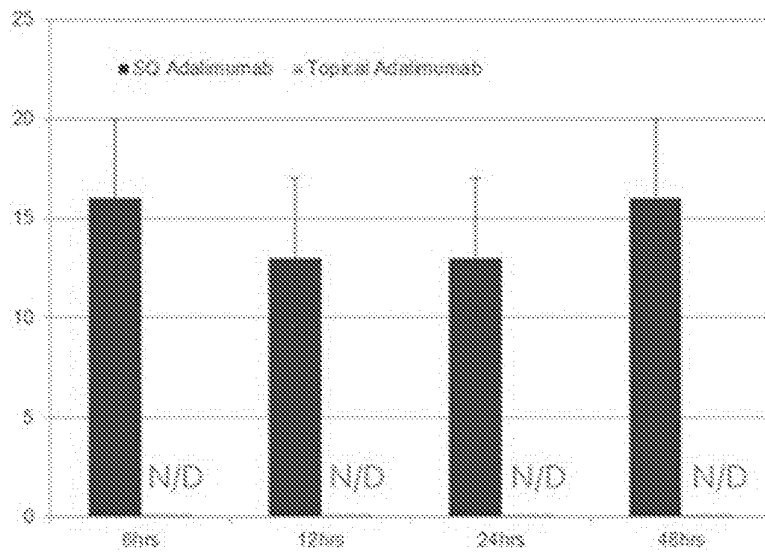


FIG. 51

Time	SQ Adalimumab Plasma concentration µgs/ml	Topical Adalimumab Plasma concentration µgs/ml
6hrs	16 +/-8	0.01
12hrs	13 +/-4	0.01
24hrs	13 +/-3	0.01
48hrs	16 +/-5	0.01

FIG. 52

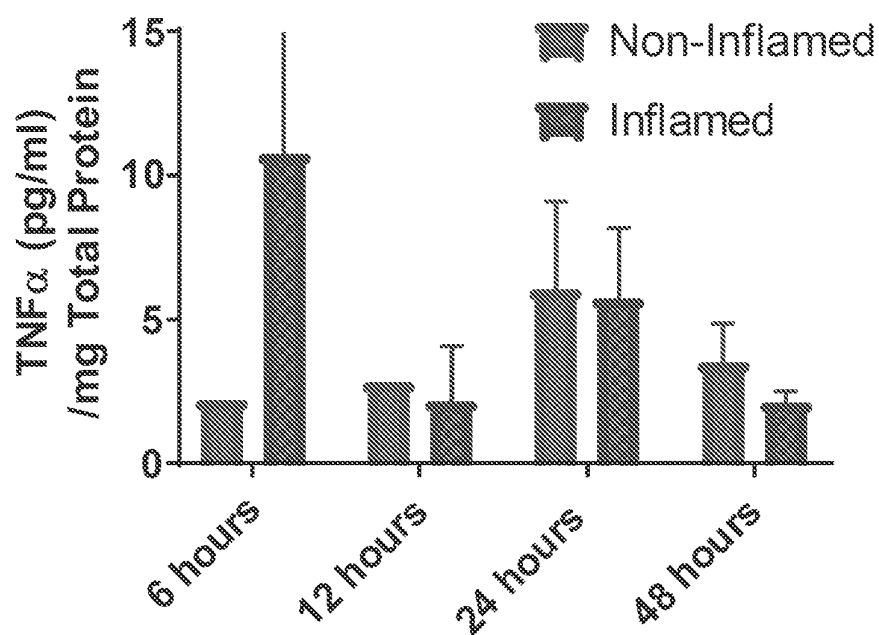


FIG. 53

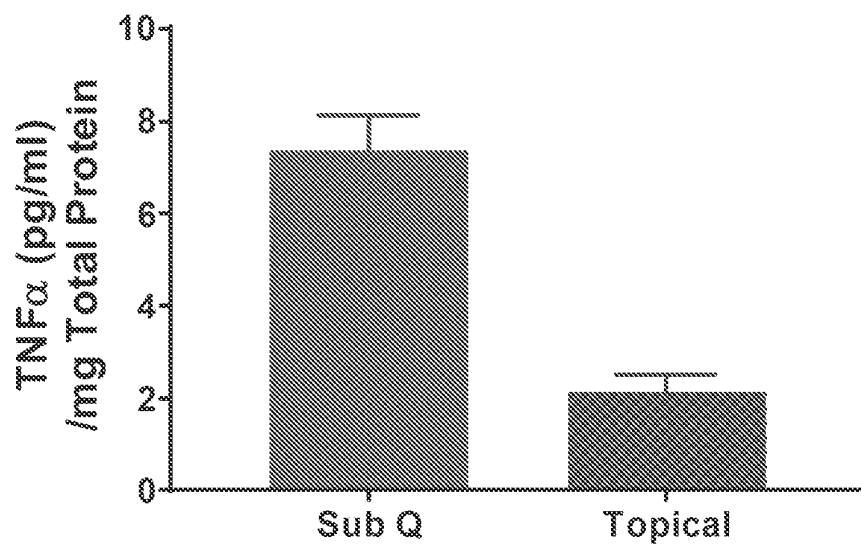


FIG. 54

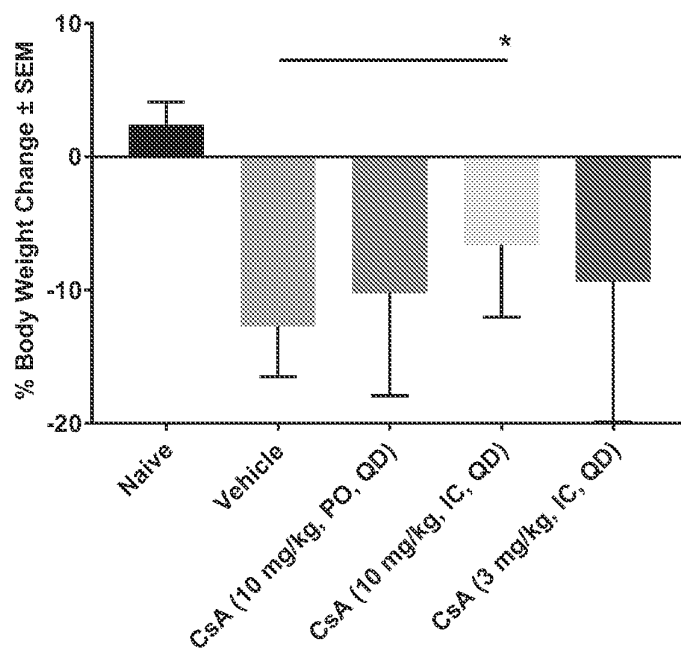


FIG. 55

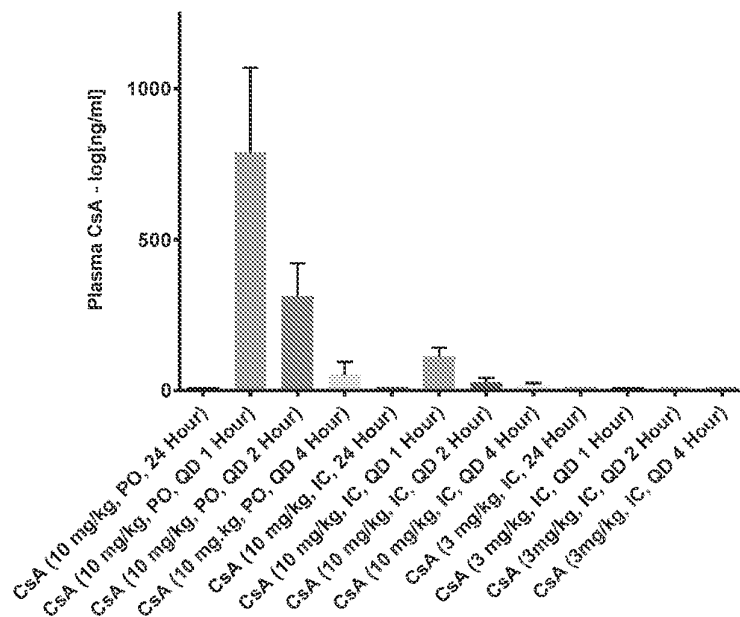


FIG. 56

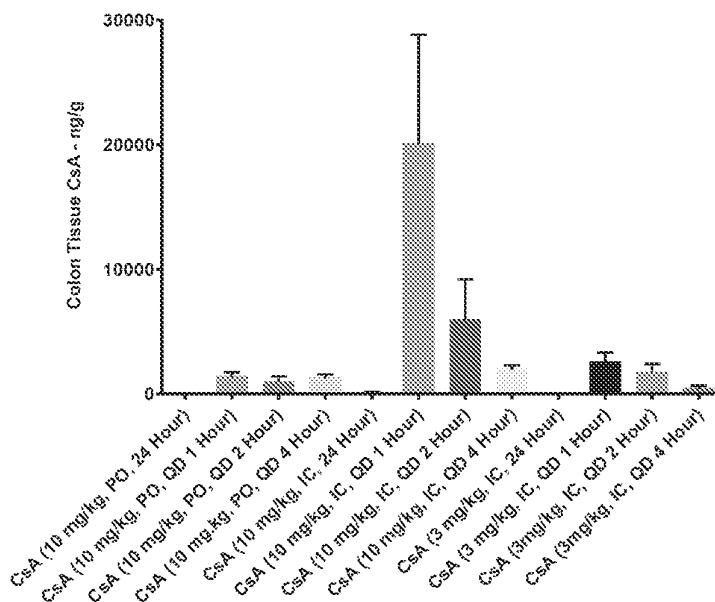


FIG. 57

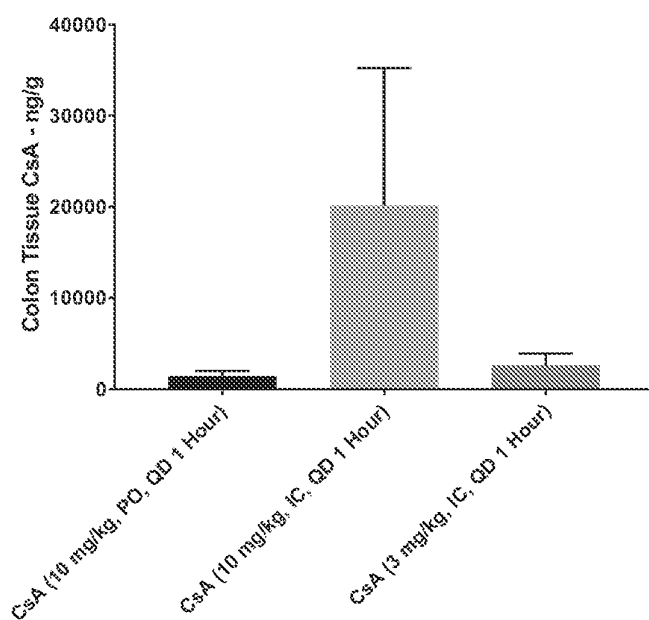


FIG. 58

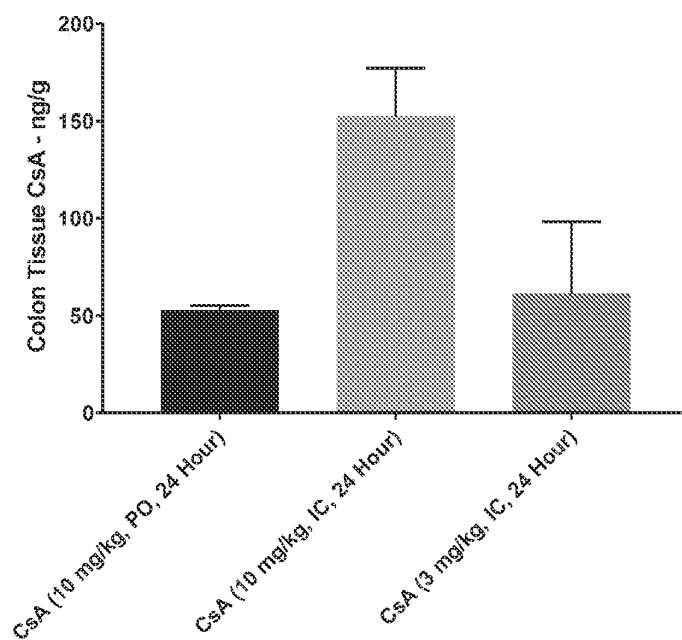


FIG. 59

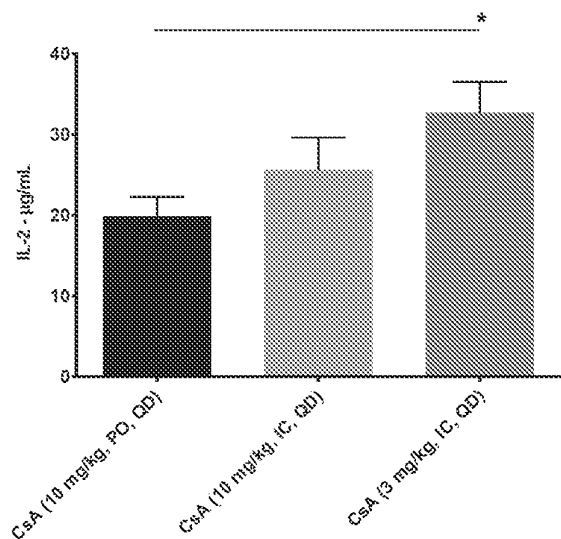


FIG. 60

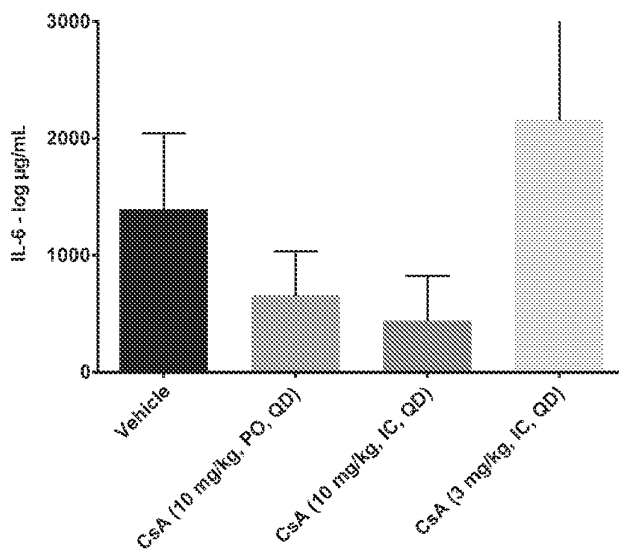


FIG. 61

Digital Health Monitoring to Drive Therapeutic Use

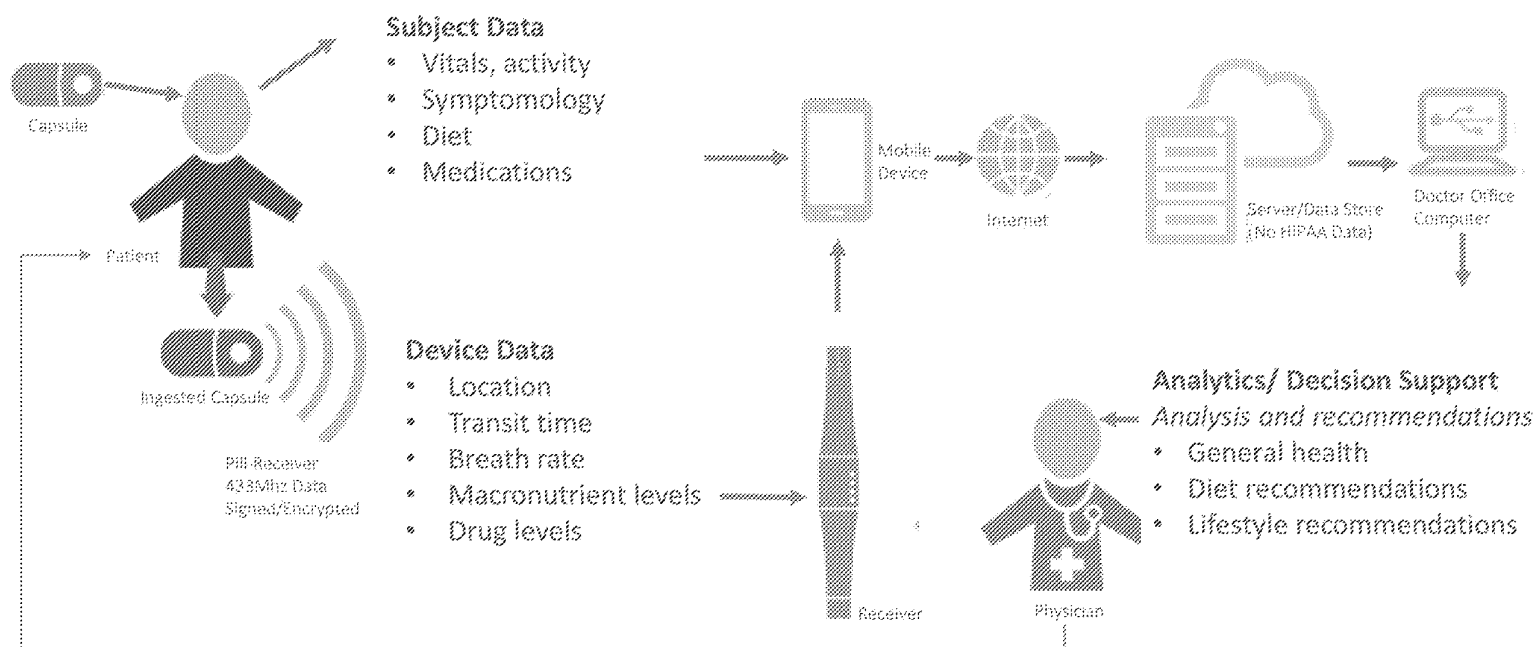


FIG. 62

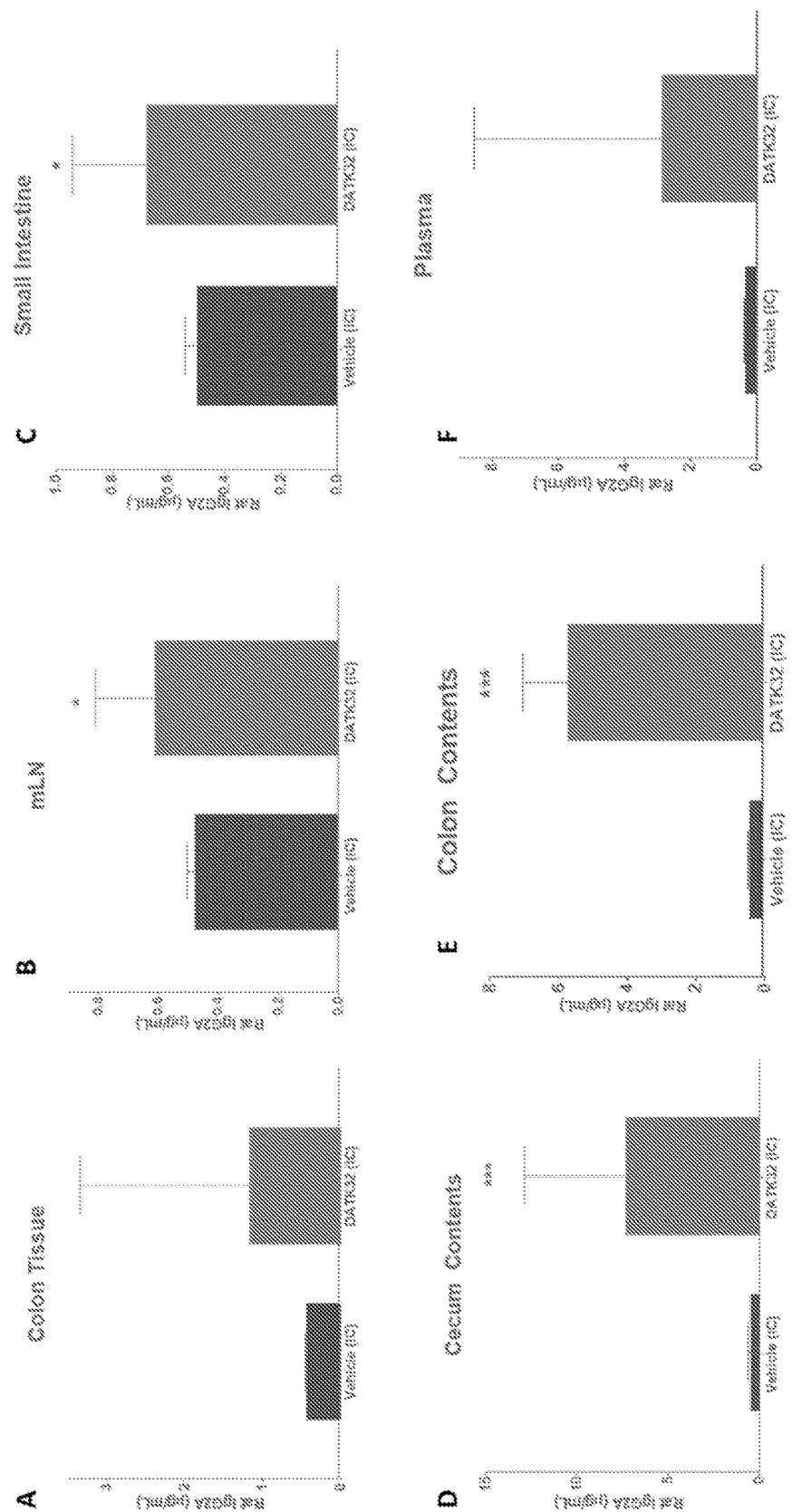


FIG. 63

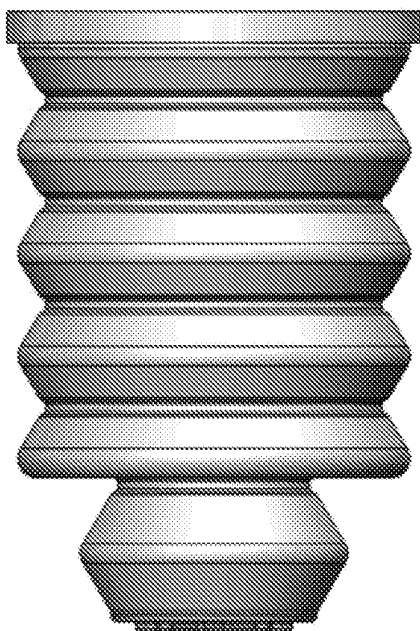


FIG. 64

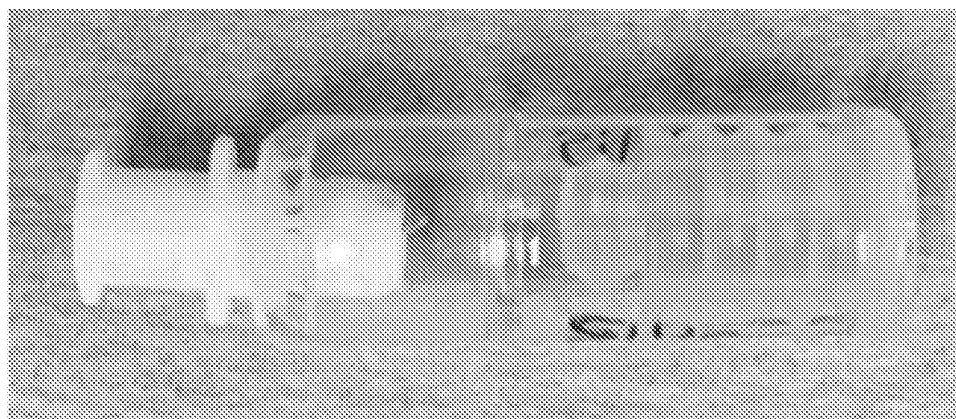


FIG. 65

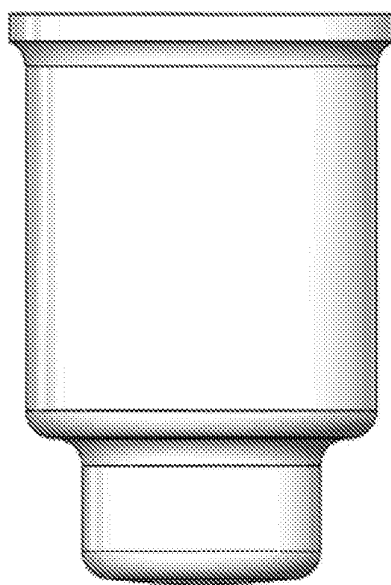


FIG. 66

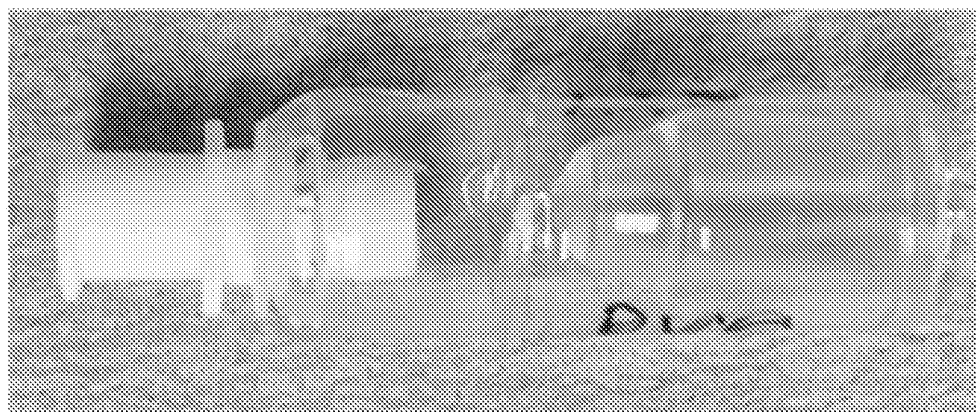


FIG. 67

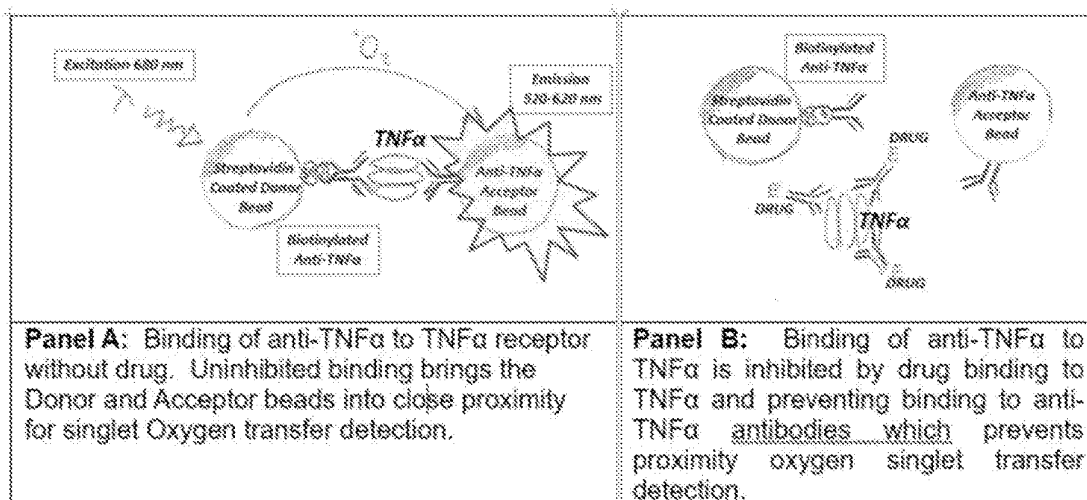


FIG. 68

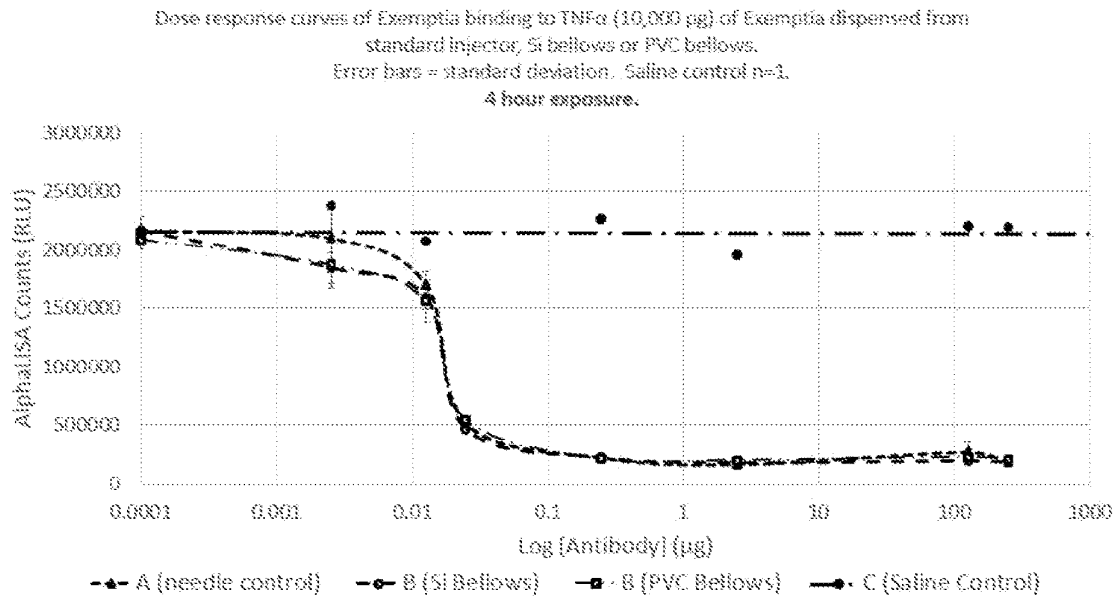


FIG. 69

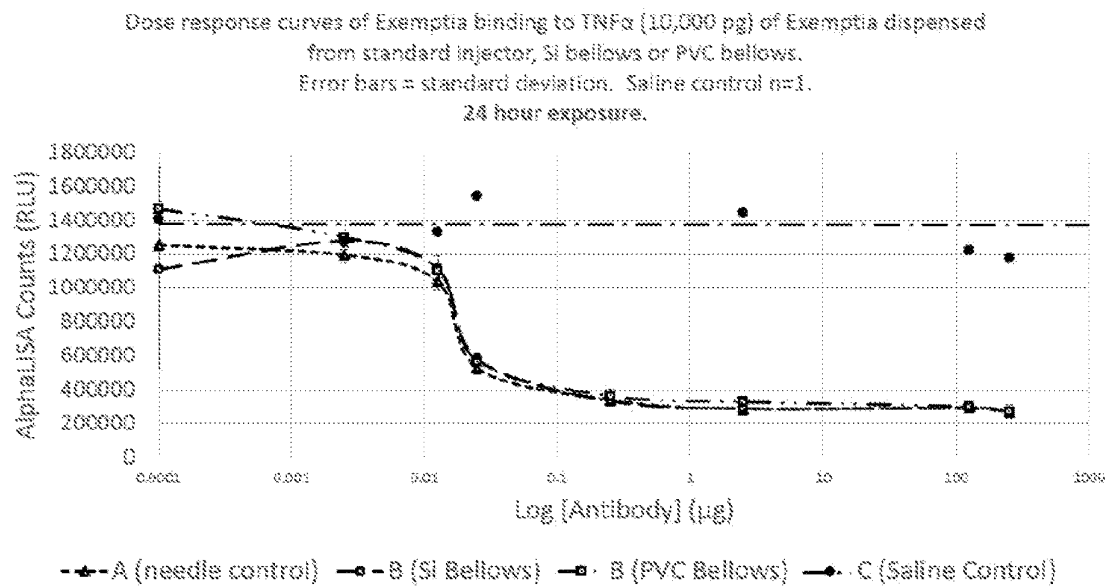


FIG. 70

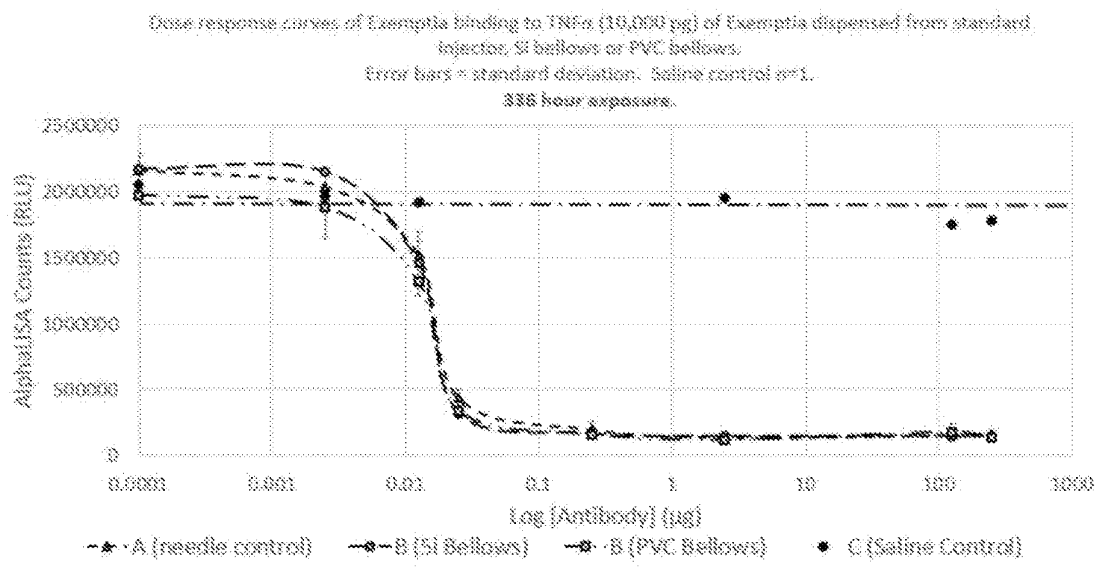
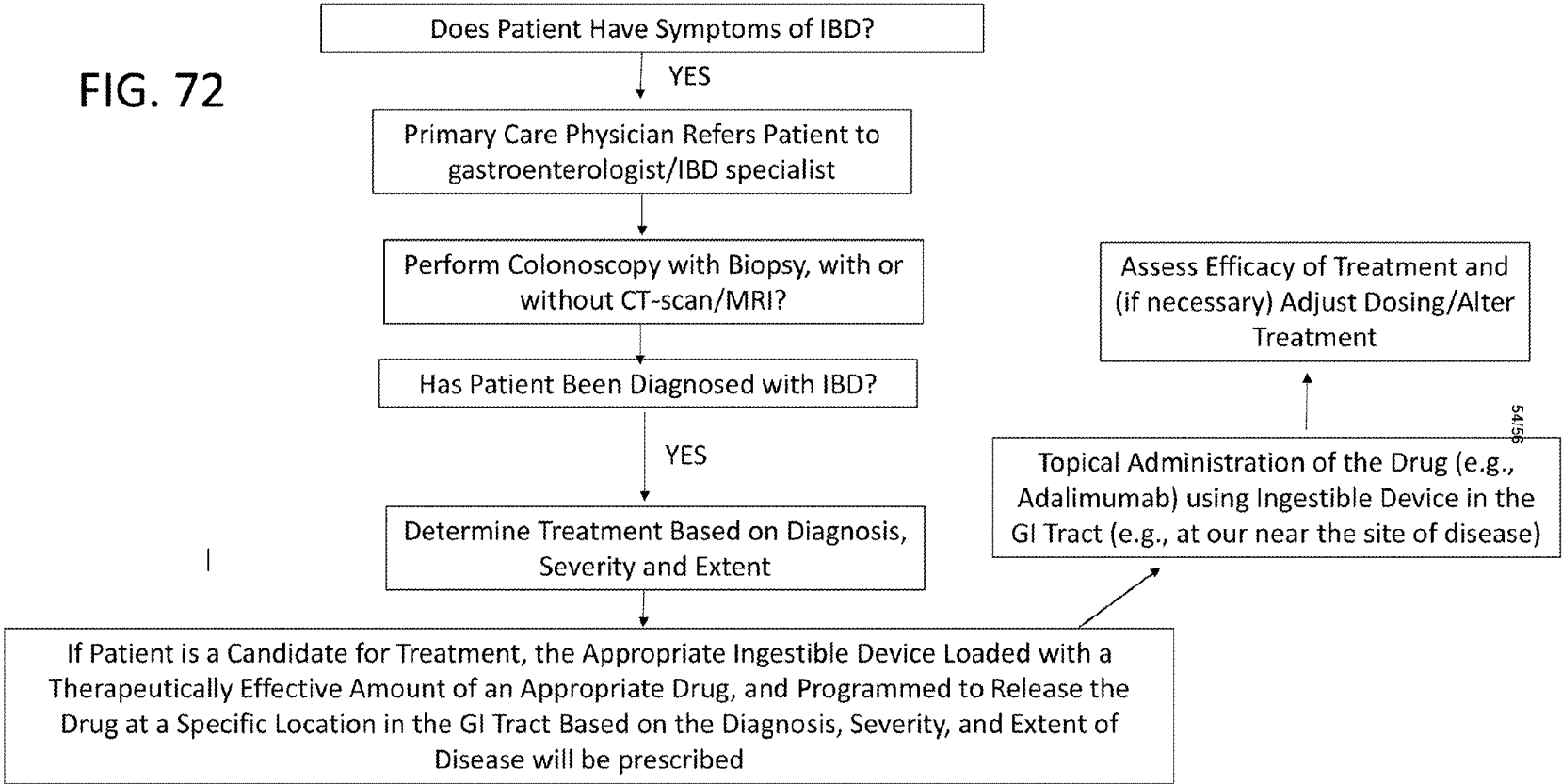


FIG. 71

FIG. 72



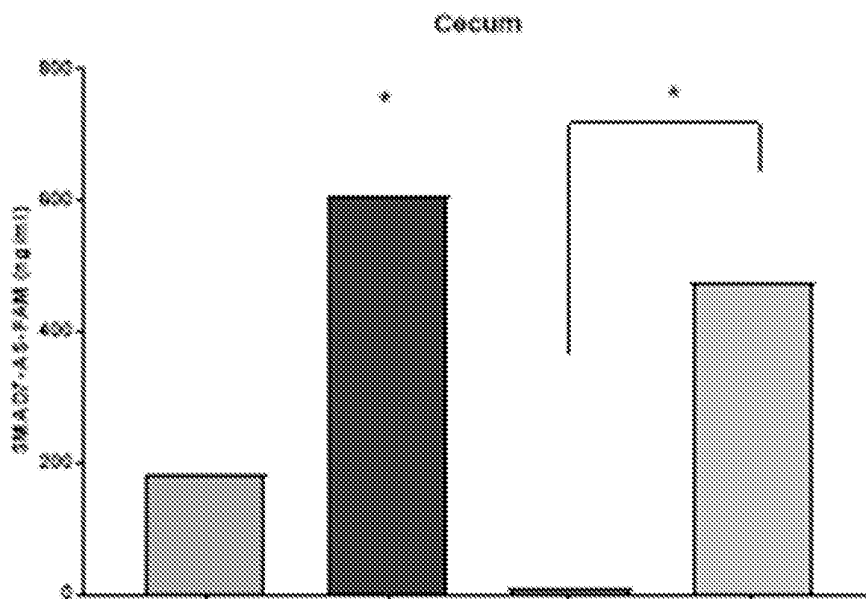


FIG. 73

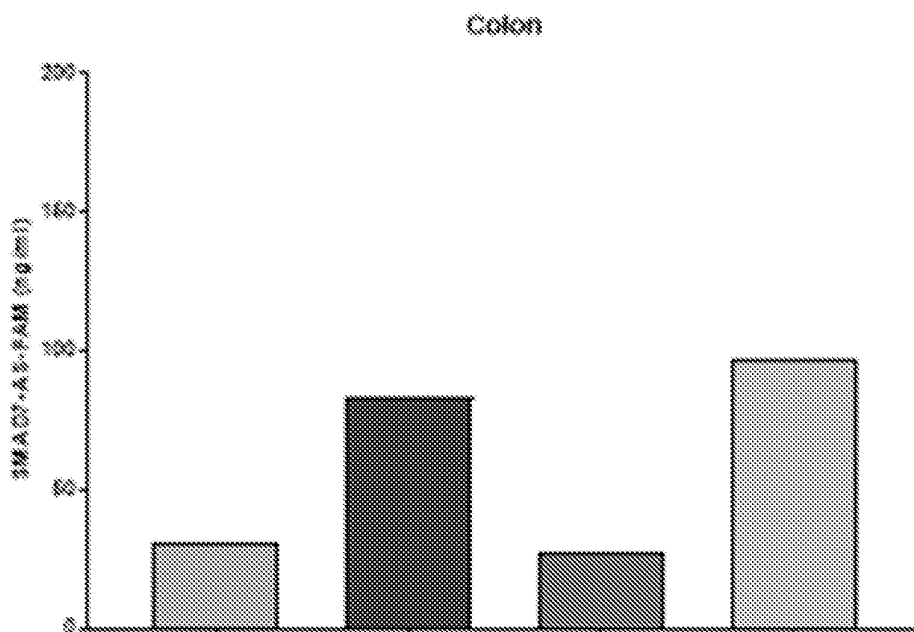


FIG. 74

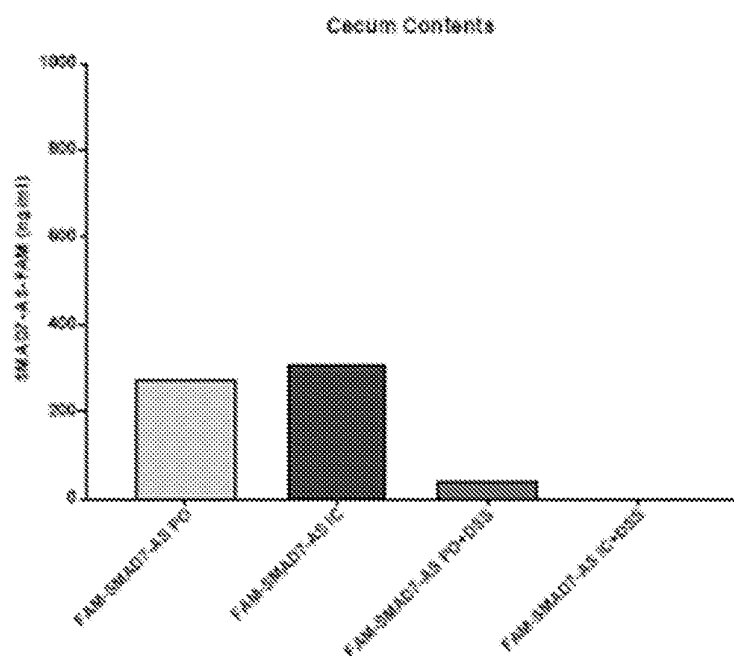


FIG. 75

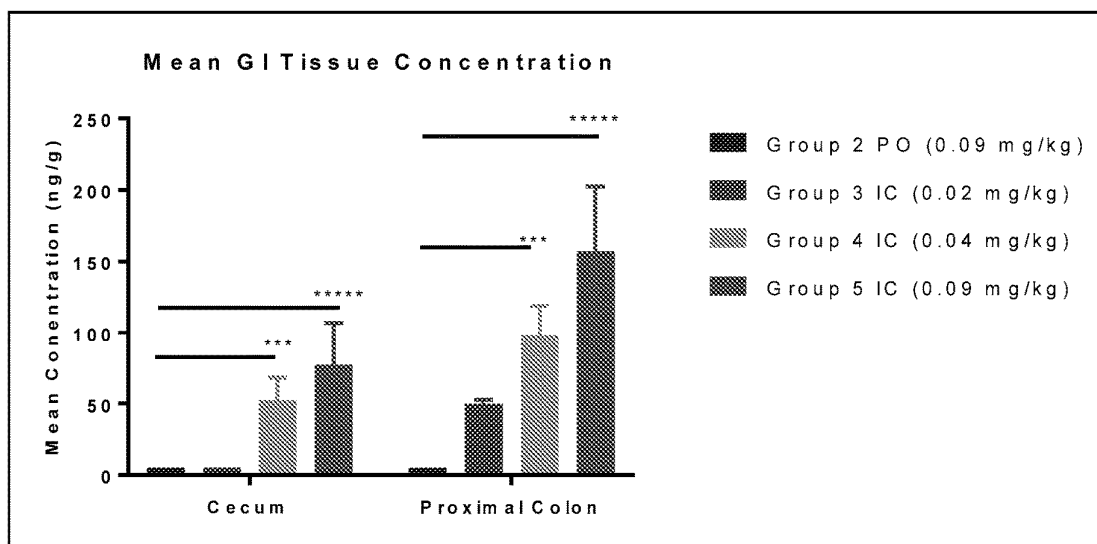


FIG. 76

TREATMENT OF A DISEASE OF THE GASTROINTESTINAL TRACT WITH AN IL-12/IL-23 INHIBITOR RELEASED USING AN INGESTIBLE DEVICE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of the following U.S. Provisional Applications 62/434,348 filed Dec. 14, 2016; 62/478,744 filed Mar. 30, 2017; 62/545,188 filed Aug. 14, 2017; and 62/583,797 filed Nov. 9, 2017. This disclosure of the prior applications is considered part of (and is incorporated by reference in its entirety) the disclosure of this application.

TECHNICAL FIELD

[0002] This disclosure features methods and compositions for treating diseases of the gastrointestinal tract with an IL-12/IL-23 inhibitor.

BACKGROUND

[0003] Interleukin-23 (IL-23) is a heterodimeric cytokine composed of an IL-12p40 subunit (that is shared with IL-12) and the IL-23p19 subunit. IL-23 is primarily produced by professional antigen-presenting cells (e.g. dendritic cells and macrophages) and monocytes in response to an infection with variety of bacterial and fungal pathogens. IL-23R is expressed on various adaptive and innate immune cells including Th17 cells, $\gamma\delta$ T cells, natural killer (NK) cells, dendritic cells, macrophages, and innate lymphoid cells, which are found abundantly in the intestine. IL-23R and downstream effector cytokines have a primary role in disease pathogenesis of inflammatory bowel disease (IBD) in acute and chronic mouse models. In patients with IBD, gene expression and protein levels of IL-23R are elevated at the intestine mucosal surface. Without wishing to be bound by theory, it is believed that IL-23 mediates its pathogenic effects by promoting the development of a pathogenic CD4⁺ T cell population that produces IL-6, IL-17, and tumor necrosis factor (e.g., TNF- α).

[0004] Interleukin 12 (IL-12) is an interleukin that is naturally produced by a variety of cell types including macrophages, neutrophils, dendritic cells, and human B-lymphoblastoid cells (NC-37). It is a heterodimeric cytokine comprising four alpha helices that are encoded by two separate genes: IL-12A (p35) and IL-12B (p40). IL-12 plays a role in balancing T cell-mediated pro- and anti-inflammatory immune responses, and are thought to have a role in the regulation of intestinal homeostasis, and ultimately, the pathogenesis of inflammatory bowel disorders.

[0005] The gastrointestinal (GI) tract generally provides a therapeutic medium for an individual's body. At times, therapeutic drugs may need to be dispensed to specified locations within the small intestine or large intestine, which is more effective than oral administration of the therapeutic drugs to cure or alleviate the symptoms of some medical conditions. For example, therapeutic drugs dispensed directly within the small intestine would not be contaminated, digested or otherwise compromised in the stomach, and thus allow a higher dose to be delivered at a specific location within the small intestine. However, dispensing therapeutic drugs directly within the small intestine inside a human body (e.g., the cecum, the ascending colon) can be

difficult, because a device or mechanism (e.g., special formulation) would be needed to transport a therapeutically effective dose of drug to a desired location within the small intestine and then automatically deliver the therapeutic drug at the desired location. Dispensing therapeutic drugs directly within other locations in the GI tract of the human body can be similarly difficult. Such a device or mechanism also would also need to be operated in a safe manner in that the device or mechanism needs to physically enter the human body.

[0006] In sum, there remains a significant unmet medical need for improved treatment regimens for gastrointestinal diseases, such as inflammatory bowel disease (IBD), including a need for regimens which can dispense therapeutics to specific locations within the GI tract, thereby reducing or avoiding the drawbacks of oral or other forms of systemic administration.

SUMMARY

[0007] The present disclosure provides novel treatment paradigms for inflammatory conditions of the gastrointestinal tract. The methods and compositions described herein allow for the regio-specific release of therapeutic drugs at or near the site of disease in the gastrointestinal tract. By releasing a therapeutic drug locally instead of systemically, the bioavailability of the drug can be increased at the site of injury and/or decreased in the systemic circulation, thereby resulting in improved overall safety and/or efficacy and fewer adverse side effects. Advantages may include one or more of increased drug engagement at the target, leading to new and more efficacious treatment regimens, and/or lower systemic drug levels, which can translate to reduced toxicity and reduced immunogenicity, e.g., in the case of biologics. In some instances, releasing a therapeutic drug locally also provides for new modes of action that may be unique to local delivery in the GI tract as opposed to systemic administration. For patients, clinicians and payors, this can mean an easier or simpler route of administration, fewer co-medications (e.g., immunomodulators), fewer side effects, and/or better outcomes.

[0008] Accordingly, described herein are methods for treating disorders of the gastrointestinal (GI) tract. The methods can include one or more of:

[0009] diagnosing a GI disease in a subject; and/or

[0010] mapping, sampling, and/or assessing the site, severity, pathology, and extent of a GI disease in the GI tract of a subject and/or mapping, sampling, and/or assessing a patient response to a therapeutic agent, e.g., in the patient's GI tract; and/or

[0011] identifying, quantifying, and/or monitoring one or more markers of a GI disease in the GI tract of the subject and/or one or more markers of patient response to a therapeutic agent, e.g., in the patient's GI tract; and/or

[0012] releasing a therapeutic agent, e.g., proximate to the site of a GI disease.

[0013] The present disclosure accordingly provides patients and physicians more personalized treatment options for GI disorders by facilitating regimens which can release a therapeutic agent according to desired (e.g., customized or optimized) dosage, timing, and/or location parameters. In some cases, the treatment methods can employ one or more ingestible devices to achieve the benefits disclosed herein.

[0014] In some embodiments, provided herein is a method of treating a disease of the gastrointestinal tract in a subject, comprising:

[0015] administering to the subject a pharmaceutical formulation that comprises an IL-12/IL-23 inhibitor,

[0016] wherein the pharmaceutical formulation is released at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease.

[0017] In some embodiments, provided herein the pharmaceutical formulation is administered in an ingestible device. In some embodiments, the pharmaceutical formulation is released from an ingestible device. In some embodiments, the ingestible device comprises a housing, a reservoir containing the pharmaceutical formulation, and a release mechanism for releasing the pharmaceutical formulation from the device,

[0018] wherein the reservoir is releasably or permanently attached to the exterior of the housing or internal to the housing.

[0019] In some embodiments, provided herein is a method of treating a disease of the gastrointestinal tract in a subject, comprising:

[0020] administering to the subject an ingestible device comprising a housing, a reservoir containing a pharmaceutical formulation, and a release mechanism for releasing the pharmaceutical formulation from the device,

[0021] wherein the reservoir is releasably or permanently attached to the exterior of the housing or internal to the housing;

[0022] wherein the pharmaceutical formulation comprises an IL-12/IL-23 inhibitor, and

[0023] the ingestible device releases the pharmaceutical formulation at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease.

[0024] In some embodiments, the housing is non-biodegradable in the GI tract. In some embodiments, the release of the formulation is triggered autonomously. In some embodiments, the device is programmed to release the formulation with one or more release profiles that may be the same or different at one or more locations. In some embodiments, the device is programmed to release the formulation at a location proximate to one or more sites of disease. In some embodiments, the location of one or more sites of disease is predetermined.

[0025] In some embodiments, the reservoir is made of a material that allows the formulation to leave the reservoir, such as a biodegradable material.

[0026] In some embodiments, the release of the formulation is triggered by a pre-programmed algorithm. In some embodiments, the release of the formulation is triggered by data from a sensor or detector to identify the location of the device. In some more particular embodiments, the data is not based solely on a physiological parameter (such as pH, temperature, and/or transit time).

[0027] In some embodiments, the device comprises a detector configured to detect light reflectance from an environment external to the housing. In some more particular embodiments, the release is triggered autonomously or based on the detected reflectance.

[0028] In some embodiments, the device releases the formulation at substantially the same time as one or more sites of disease are detected. In some embodiments, the one or more sites of disease are detected by the device (e.g., by imaging the GI tract).

[0029] In some embodiments, the release mechanism is an actuation system. In some embodiments, the release mechanism is a chemical actuation system. In some embodiments, the release mechanism is a mechanical actuation system. In some embodiments, the release mechanism is an electrical actuation system. In some embodiments, the actuation system comprises a pump and releasing the formulation comprises pumping the formulation out of the reservoir. In some embodiments, the actuation system comprises a gas generating cell. In some embodiments, the device further comprises an anchoring mechanism. In some embodiments, the formulation comprises a therapeutically effective amount of the IL-12/IL-23 inhibitor. In some embodiments, the formulation comprises a human equivalent dose (HED) of the IL-12/IL-23 inhibitor.

[0030] In some embodiments, the device is a device capable of releasing a solid IL-12/IL-23 inhibitor or a solid formulation comprising the IL-12/IL-23 inhibitor. In some embodiments, the device is a device capable of releasing a liquid IL-12/IL-23 inhibitor or a liquid formulation comprising the IL-12/IL-23 inhibitor. Accordingly, in some embodiments of the methods herein, the pharmaceutical formulation release from the device is a solid formulation. Accordingly, in some embodiments of the methods herein, the pharmaceutical formulation release from the device is a liquid formulation.

[0031] The devices disclosed herein are capable of releasing an IL-12/IL-23 inhibitor or a formulation comprising the IL-12/IL-23 inhibitor irrespective of the particular type of IL-12/IL-23 inhibitor. For example, the IL-12/IL-23 inhibitor may be a small molecule, a biological, a nucleic acid, an antibody, a fusion protein, and so on.

[0032] In some embodiments, provided herein is a method of releasing an IL-12/IL-23 inhibitor into the gastrointestinal tract of a subject for treating one or more sites of disease within the gastrointestinal tract, the method comprising:

[0033] administering to the subject a therapeutically effective amount of the IL-12/IL-23 inhibitor housed in an ingestible device, wherein the ingestible device comprises:

[0034] a detector configured to detect the presence of the one or more sites of disease, and

[0035] a controller or processor configured to trigger the release of the IL-12/IL-23 inhibitor proximate to the one or more sites of disease in response to the detector detecting the presence of the one or more sites of disease.

[0036] In some embodiments, provided herein is a method of releasing an IL-12/IL-23 inhibitor into the gastrointestinal tract of a subject for treating one or more pre-determined sites of disease within the gastrointestinal tract, the method comprising:

[0037] administering to the subject a therapeutically effective amount of the IL-12/IL-23 inhibitor contained in an ingestible device, wherein the ingestible device comprises:

[0038] a detector configured to detect the location of the device within the gastrointestinal tract, and

[0039] a controller or processor configured to trigger the release of the IL-12/IL-23 inhibitor proximate to the one or more predetermined sites of disease in response to the detector detecting a location of the device that corresponds to the location of the one or more pre-determined sites of disease.

[0040] In some embodiments, provided herein is a method of releasing an IL-12/IL-23 inhibitor into the gastrointestinal

tract of a subject for treating one or more sites of disease within the gastrointestinal tract, the method comprising:

[0041] administering to the subject a therapeutically effective amount of the IL-12/IL-23 inhibitor contained in an ingestible device;

[0042] receiving at an external receiver from the device a signal transmitting environmental data;

[0043] assessing the environmental data to confirm the presence of the one or more sites of disease; and

[0044] when the presence of the one or more sites of disease is confirmed, sending from an external transmitter to the device a signal triggering the release of the IL-12/IL-23 inhibitor proximate to the one or more sites of disease.

[0045] In some embodiments, provided herein is a method of releasing an IL-12/IL-23 inhibitor into the gastrointestinal tract of a subject for treating one or more sites of disease within the gastrointestinal tract, the method comprising:

[0046] administering to the subject a therapeutically effective amount of the IL-12/IL-23 inhibitor contained in an ingestible device;

[0047] receiving at an external receiver from the device a signal transmitting environmental or optical data;

[0048] assessing the environmental or optical data to confirm the location of the device within the gastrointestinal tract; and

[0049] when the location of the device is confirmed, sending from an external transmitter to the device a signal triggering the release of the IL-12/IL-23 inhibitor proximate to the one or more sites of disease.

[0050] Provided herein in one embodiment is a method of treating a disease of the gastrointestinal tract in a subject, comprising:

[0051] delivering a IL-12/IL-23 inhibitor at a location in the gastrointestinal tract of the subject,

[0052] wherein the method comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the IL-12/IL-23 inhibitor.

[0053] Provided herein in one embodiment is a method of treating a disease of the large intestine in a subject, comprising:

[0054] delivering a IL-12/IL-23 inhibitor at a location in the proximal portion of the large intestine of the subject,

[0055] wherein the method comprises administering endoscopically to the subject a therapeutically effective amount of the IL-12/IL-23 inhibitor.

[0056] Provided herein in one embodiment is a method of treating a disease of the gastrointestinal tract in a subject, comprising:

[0057] releasing a IL-12/IL-23 inhibitor at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease,

[0058] wherein the method comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the IL-12/IL-23 inhibitor.

[0059] Provided herein in one embodiment is a method of treating a disease of the gastrointestinal tract in a subject, comprising:

[0060] releasing a IL-12/IL-23 inhibitor at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease,

[0061] wherein the method comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the IL-12/IL-23 inhibitor, wherein the pharmaceutical composition is an ingestible

device, and the method comprises administering orally to the subject the pharmaceutical composition.

[0062] Provided herein in one embodiment is a method of treating a disease of the gastrointestinal tract in a subject, comprising:

[0063] releasing a IL-12/IL-23 inhibitor at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease, wherein the method comprises administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the IL-12/IL-23 inhibitor, wherein the method provides a concentration of the IL-12/IL-23 inhibitor in the plasma of the subject that is less than 3 µg/ml.

[0064] Provided herein in one embodiment is a method of treating a disease of the large intestine in a subject, comprising:

[0065] releasing a IL-12/IL-23 inhibitor at a location in the proximal portion of the large intestine of the subject that is proximate to one or more sites of disease,

[0066] wherein the method comprises administering endoscopically to the subject a therapeutically effective amount of the IL-12/IL-23 inhibitor.

[0067] In another aspect of the present invention, there is provided an IL-12/IL-23 inhibitor for use in a method of treating a disease of the gastrointestinal tract in a subject, wherein the method comprises orally administering to the subject an ingestible device loaded with the IL-12/IL-23 inhibitor, wherein the IL-12/IL-23 inhibitor is released by the device at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease.

[0068] In another aspect, the present invention provides a composition comprising or consisting of an ingestible device loaded with a therapeutically effective amount of an IL-12/IL-23 inhibitor, for use in a method of treatment, wherein the method comprises orally administering the composition to the subject, wherein the IL-12/IL-23 inhibitor is released by the device at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease.

[0069] In another aspect, the present invention provides an ingestible device loaded with a therapeutically effective amount of a IL-12/IL-23 inhibitor, wherein the device is controllable to release the IL-12/IL-23 inhibitor at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease. The device may be for use in a method of treatment of the human or animal body, for example, any method as described herein.

[0070] In still another aspect, the present invention provides an ingestible device for use in a method of treating a disease of the gastrointestinal tract in a subject, wherein the method comprises orally administering to the subject the ingestible device loaded with a therapeutically effective amount of a IL-12/IL-23 inhibitor, wherein the IL-12/IL-23 inhibitor is released by the device at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease.

[0071] An ingestible device as used in the present invention may comprise one or more mechanical and/or electrical mechanisms which actively control release of the IL-12/IL-23 inhibitor. For example, in any of the above aspects and embodiments, the ingestible device as used in the present invention may comprise a release mechanism for release of the IL-12/IL-23 inhibitor (e.g., from a reservoir comprising the IL-12/IL-23 inhibitor) and an actuator controlling the release mechanism.

[0072] In one embodiment, the ingestible device comprises:

[0073] an ingestible housing comprising a reservoir having a therapeutically effective amount of the IL-12/IL-23 inhibitor stored therein;

[0074] a release mechanism having a closed state which retains the IL-12/IL-23 inhibitor in the reservoir and an open state which releases the IL-12/IL-23 inhibitor from the reservoir to the exterior of the device; and

[0075] an actuator which changes the state of the release mechanism from the closed to the open state.

[0076] In one embodiment, the ingestible device comprises

[0077] a housing defined by a first end, a second end substantially opposite from the first end;

[0078] a reservoir located within the housing and containing the IL-12/IL-23 inhibitor wherein a first end of the reservoir is attached to the first end of the housing;

[0079] a mechanism for releasing the IL-12/IL-23 inhibitor from the reservoir;

[0080] and

[0081] an exit valve configured to allow the IL-12/IL-23 inhibitor to be released out of the housing from the reservoir.

[0082] Here, the exit valve can be considered as the release mechanism having a closed state which retains the IL-12/IL-23 inhibitor in the reservoir and an open state which releases the IL-12/IL-23 inhibitor from the reservoir to the exterior of the device, and the mechanism for releasing the IL-12/IL-23 inhibitor from the reservoir can be considered as the actuator.

[0083] In some embodiments of methods of treatment as described herein, the one or more disease sites may have been pre-determined (e.g., determined in a step preceding the administration of the composition of the present invention). The disease site(s) may have been determined by imaging the gastrointestinal tract. For example, the disease site(s) may have been pre-determined by endoscopy (e.g., a step of colonoscopy, enteroscopy, or using a capsule endoscope). Determination that the device is proximate to the disease site may therefore comprise a determining that the device is in a location corresponding to this previously-determined disease site.

[0084] In some embodiments, the location of the device in the gut may be detected by tracking the device. For example, the device may comprise a localization mechanism which may be a communication system for transmitting localization data, e.g., by radiofrequency transmission. The device may additionally or alternatively comprise a communication system for receiving a signal remotely triggering the actuator and thus causing release of the IL-12/IL-23 inhibitor. The signal may be sent when it is determined that the device is in the correct location in the gut.

[0085] Thus, the ingestible device may comprise:

[0086] an ingestible housing comprising a reservoir having a therapeutically effective amount of the IL-12/IL-23 inhibitor stored therein;

[0087] a release mechanism having a closed state which retains the IL-12/IL-23 inhibitor in the reservoir and an open state which releases the IL-12/IL-23 inhibitor from the reservoir to the exterior of the device;

[0088] a communication system for transmitting localization data to an external receiver and for receiving a signal from an external transmitter; and

[0089] an actuator which changes the state of the release mechanism from the closed to the open state and which can be triggered by the signal.

[0090] In other embodiments, the ingestible device as used in the present invention may comprise an environmental sensor for detecting the location of the device in the gut and/or for detecting the presence of disease in the GI tract. For example, the environment sensor may be an image sensor for obtaining images in vivo.

[0091] Detecting the presence of disease may comprise, for example, detecting the presence of inflamed tissue, and/or lesions such as ulceration e.g., aphthoid ulcerations, "punched-out ulcers" and/or superficial ulcers of the mucosa, cobblestoning, stenosis, granulomas, crypt abscesses, fissures, e.g., extensive linear fissures, villous atrophy, fibrosis, and/or bleeding.

[0092] Detecting the presence of disease may also comprise molecular sensing, such as detecting the amount of an inflammatory cytokine or other marker of inflammation. Such a marker can be measured locally from a biopsy or systemically in the serum.

[0093] Where the ingestible device comprises an environmental sensor, actuation of the release mechanism may be triggered by a processor or controller communicably coupled to the environmental sensor. Thus, in some embodiments, the device may not require any external signal or control in order to release the drug.

[0094] In one embodiment, the ingestible device may comprise:

[0095] an ingestible housing comprising a reservoir having a therapeutically effective amount of the IL-12/IL-23 inhibitor stored therein;

[0096] a release mechanism having a closed state which retains the IL-12/IL-23 inhibitor in the reservoir and an open state which releases the IL-12/IL-23 inhibitor from the reservoir to the exterior of the device;

[0097] an actuator which controls the transition of the release mechanism from the closed to the open state;

[0098] a detector for detecting the location of the device in the gut and/or the presence of diseased tissue; and

[0099] a processor or controller which is coupled to the detector and to the actuator and which triggers the actuator to cause the release mechanism to transition from its closed state to its open state when it is determined that the device is in the presence of diseased tissue and/or in a location in the gut that has been predetermined to be proximal to diseased tissue.

[0100] In another embodiment, there is provided:

[0101] an ingestible housing comprising a reservoir having a therapeutically effective amount of the IL-12/IL-23 inhibitor stored therein;

[0102] a detector coupled to the ingestible housing, the detector configured to detect when the ingestible housing is proximate to a respective disease site of the one of the one or more sites of disease;

[0103] a valve system in fluid communication with the reservoir system; and

[0104] a controller communicably coupled to the valve system and the detector, the controller configured to cause the valve system to open in response to the detector detecting that the ingestible housing is proximate to the respective disease site so as to release the therapeutically effective amount of the IL-12/IL-23 inhibitor at the respective disease site.

[0105] As above, detection that the ingestible housing is proximate to the respective disease site may be based on environmental data indicating the location of the device in the GI tract (and reference to a pre-determined disease site) or on environmental data directly indicating the presence of diseased tissue.

[0106] Additionally, or alternatively, the device may further comprise a communication system adapted to transmit the environment data to an external receiver (e.g., outside of the body). This data may be used, for example, for diagnostic purposes. The external receiver may comprise means for displaying the data.

[0107] In some embodiments, this data may be analyzed externally to the device and used to determine when the drug should be released: an external signal may then be sent to the device to trigger release of the drug. Thus, the communication system may further be adapted to receive a signal remotely triggering the actuator and thus causing release of the IL-12/IL-23 inhibitor. The signal may be sent from an external transmitter in response to receipt/analysis and/or assessment of the environmental data, e.g., data indicating that the device has reached the desired location of the gut (where the location of the diseased tissue has been pre-determined) and/or data indicating the presence of diseased tissue. "External" may be "outside of the body".

[0108] Thus, in another embodiment, the ingestible device may comprise:

[0109] an ingestible housing comprising a reservoir having a therapeutically effective amount of the IL-12/IL-23 inhibitor stored therein;

[0110] a release mechanism having a closed state which retains the IL-12/IL-23 inhibitor in the reservoir and an open state which releases the IL-12/IL-23 inhibitor from the reservoir to the exterior of the device;

[0111] an environmental detector for detecting environmental data indicating the location of the device in the gut and/or the presence of diseased tissue;

[0112] a communication system for transmitting the environmental data to an external receiver and for receiving a signal from an external transmitter; and

[0113] an actuator which controls the transition of the release mechanism from the closed to the open state in response to the signal.

[0114] It will be understood from the above that when the device comprises one or more environmental detectors, e.g., comprises an image detector, the compositions may be used both for disease detection and for disease treatment.

[0115] Accordingly, in a further embodiment, there is provided an IL-12/IL-23 inhibitor for use in a method of detecting and treating a disease of the gastrointestinal tract in a subject, wherein the method comprises orally administering to the subject an ingestible device loaded with the IL-12/IL-23 inhibitor, wherein the ingestible device comprises an environmental sensor for determining the presence of diseased tissue in the GI tract, and wherein the IL-12/IL-23 inhibitor is released by the device at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease, as detected by the environmental sensor. The device may be according to any of the embodiments described herein.

[0116] In another embodiment, there is provided a composition for use in a method of detecting and treating a disease of the gastrointestinal tract in a subject, wherein the composition comprises or consists of an ingestible device

loaded with a therapeutically effective amount of an IL-12/IL-23 inhibitor, wherein the ingestible device comprises an environmental sensor for determining the presence of diseased tissue in the GI tract, and wherein the IL-12/IL-23 inhibitor is released by the device at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease, as detected by the environmental sensor. Again, the device may be according to any of the embodiments described herein.

[0117] In some embodiments, where the ingestible device as used in the present invention comprises an environmental sensor for detecting the presence of disease in the GI tract and a communication system as described above, the method of treatment may comprise:

[0118] i) receiving at an external receiver from the ingestible device a signal transmitting the environmental data;

[0119] ii) assessing the environmental data to confirm the presence of the disease; and

[0120] iii) when the presence of the disease is confirmed, sending from an external transmitter to the ingestible device a signal triggering release of the IL-12/IL-23 inhibitor.

[0121] For example, the presence of disease may be confirmed based on the presence of inflamed tissue and/or lesions associated with any of the disease states referred to herein. For example, the presence of disease may be confirmed based on the presence of inflammation, ulceration e.g., aphthoid ulcerations, "punched-out ulcers" and/or superficial ulcers of the mucosa, cobblestoning, stenosis, granulomas, crypt abscesses, fissures, e.g., extensive linear fissures, villous atrophy, fibrosis, and/or bleeding.

[0122] In some embodiments, the present invention may relate to a system comprising:

[0123] an ingestible device loaded with a therapeutically effective amount of an IL-12/IL-23 inhibitor, a release mechanism for release of the IL-12/IL-23 inhibitor (e.g., from a reservoir comprising the IL-12/IL-23 inhibitor), an actuator controlling the release mechanism, an environmental sensor for determining the location of the device in the gut and/or for detecting the presence of diseased tissue and a communication system adapted to transmit the environment data and receive a signal triggering the actuator;

[0124] a receiver and display module for receiving and displaying outside of the body the environment data from the ingestible device;

[0125] a transmitter for sending to the ingestible device a signal triggering the actuator.

[0126] In any of the above embodiments, the ingestible device may further comprise an anchoring system for anchoring the device or a portion thereof in a location and an actuator for the anchoring system. This may be triggered in response to a determination that the device is at a location in the gastrointestinal tract of the subject proximate to one or more sites of disease. For instance, this may be detected by the environmental sensor. The triggering may be controlled by a processor in the device, that is, autonomously. A device where the triggering is controlled by a processor in the device is said to be an autonomous device. Alternatively, it may be controlled by a signal sent from outside of the body, as described above.

[0127] In any of the above aspects and embodiments, disease of the GI tract may be an inflammatory bowel disease.

[0128] In some embodiments, the disease of the GI tract is ulcerative colitis.

[0129] In some embodiments, the disease of the GI tract is Crohn's disease.

[0130] In general, apparatuses, compositions, and methods disclosed herein are useful in the treatment of diseases of the gastrointestinal tract. Exemplary gastrointestinal tract diseases that can be treated include, without limitation, inflammatory bowel disease (IBD), Crohn's disease (e.g., active Crohn's disease, refractory Crohn's disease, or fistulizing Crohn's disease), ulcerative colitis, indeterminate colitis, microscopic colitis, infectious colitis, drug or chemical-induced colitis, diverticulitis, and ischemic colitis, gastritis, peptic ulcers, stress ulcers, bleeding ulcers, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, short-bowel (anastomosis) syndrome, a hypersecretory state associated with systemic mastocytosis or basophilic leukemia or hyperhistaminemia, Celiac disease (e.g., nontropical Sprue), enteropathy associated with seronegative arthropathies, microscopic colitis, collagenous colitis, eosinophilic gastroenteritis, colitis associated with radiotherapy or chemotherapy, colitis associated with disorders of innate immunity as in leukocyte adhesion deficiency-1, chronic granulomatous disease, food allergies, gastritis, infectious gastritis or enterocolitis (e.g., *Helicobacter pylori*-infected chronic active gastritis), other forms of gastrointestinal inflammation caused by an infectious agent, pseudomembranous colitis, hemorrhagic colitis, hemolytic-uremic syndrome colitis, diversion colitis, irritable bowel syndrome, irritable colon syndrome, and pouchitis.

[0131] In some embodiments, apparatuses, compositions, and methods disclosed herein are used to treat one gastrointestinal disease. In some embodiments, apparatuses, compositions, and methods disclosed herein are used to treat more than one gastrointestinal disease. In some embodiments, apparatuses, compositions, and methods disclosed herein are used to treat multiple gastrointestinal diseases that occur in the same area of the gastrointestinal tract (e.g., each disease can occur in the small intestine, large intestine, colon, or any sub-region thereof). In some embodiments, apparatuses, compositions, and methods disclosed herein are used to treat multiple gastrointestinal diseases that occur in different areas of the gastrointestinal tract. In some embodiments, administration (e.g., local administration to the gastrointestinal tract) of IL-12/IL-23 inhibitor is useful in the treatment of gastrointestinal diseases including, but not limited to, inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, or any of the other gastrointestinal diseases described herein.

[0132] In some embodiments, administration (e.g., local administration to the gastrointestinal tract) of IL-12/IL-23 inhibitor is useful in the treatment of gastrointestinal diseases including, but not limited to, inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, or any of the other gastrointestinal diseases described herein.

[0133] Aspects and embodiments as described herein are intended to be freely combinable. For example, any details or embodiments described herein for methods of treatment apply equally to an IL-12/IL-23 inhibitor, composition or ingestible device for use in said treatment. Any details or embodiments described for a device apply equally to methods of treatment using the device, or to an IL-12/IL-23 inhibitor or composition for use in a method of treatment involving the device.

BRIEF DESCRIPTION OF THE DRAWINGS

[0134] FIG. 1 is a view of an example embodiment of an ingestible device, in accordance with some embodiments of the disclosure;

[0135] FIG. 2 is an exploded view of the ingestible device of FIG. 1, in accordance with some embodiments of the disclosure;

[0136] FIG. 3 is a diagram of an ingestible device during an example transit through a GI tract, in accordance with some embodiments of the disclosure;

[0137] FIG. 4 is a diagram of an ingestible device during an example transit through a jejunum, in accordance with some embodiments of the disclosure;

[0138] FIG. 5 is a flowchart of illustrative steps for determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0139] FIG. 6 is a flowchart of illustrative steps for detecting transitions from a stomach to a duodenum and from a duodenum back to a stomach, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0140] FIG. 7 is a plot illustrating data collected during an example operation of an ingestible device, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0141] FIG. 8 is another plot illustrating data collected during an example operation of an ingestible device, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0142] FIG. 9 is a flowchart of illustrative steps for detecting a transition from a duodenum to a jejunum, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0143] FIG. 10 is a plot illustrating data collected during an example operation of an ingestible device, which may be used when detecting a transition from a duodenum to a jejunum, in accordance with some embodiments of the disclosure;

[0144] FIG. 11 is a plot illustrating muscle contractions detected by an ingestible device over time, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0145] FIG. 12 is a flowchart of illustrative steps for detecting a transition from a jejunum to an ileum, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0146] FIG. 13 is a flowchart of illustrative steps for detecting a transition from a jejunum to an ileum, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0147] FIG. 14 is a flowchart of illustrative steps for detecting a transition from an ileum to a cecum, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0148] FIG. 15 is a flowchart of illustrative steps for detecting a transition from a cecum to a colon, which may be used when determining a location of an ingestible device as it transits through a GI tract, in accordance with some embodiments of the disclosure;

[0149] FIG. 16 illustrates an ingestible device for delivering a substance in the GI tract;

[0150] FIG. 17 illustrates aspects of a mechanism for an ingestible device with a gas generating cell configured to generate a gas to dispense a substance;

[0151] FIG. 18 illustrates an ingestible device having a piston to push for drug delivery;

[0152] FIG. 19 illustrates an ingestible device having a bellow structure for a storage reservoir of dispensable substances;

[0153] FIG. 20 illustrates an ingestible device having a flexible diaphragm to deform for drug delivery;

[0154] FIG. 21 shows an illustrative embodiment of an ingestible device with multiple openings in the housing;

[0155] FIG. 22 shows a highly cross-section of an ingestible device including a valve system and a sampling system;

[0156] FIG. 23 illustrates a valve system;

[0157] FIGS. 24A and 24B illustrate a portion of a two-stage valve system in its first and second stages, respectively;

[0158] FIGS. 25A and 25B illustrate a portion of a two-stage valve system in its first and second stages, respectively;

[0159] FIGS. 26A and 26B illustrate a portion of a two-stage valve system in its first and second stages, respectively;

[0160] FIG. 27 illustrates a more detailed view of an ingestible device including a valve system and a sampling system;

[0161] FIG. 28 illustrates a portion of an ingestible device including a sampling system and a two-stage valve system in its second stage; and

[0162] FIG. 29 is a highly schematic illustrate of an ingestible device.

[0163] FIG. 30 is a graph showing the percentage (%) change in body weight at day 14 ($\pm$ SEM) for DSS mice treated with anti-IL-12 p40 antibody intraperitoneally (10 mg/kg) every third day (Q3D) or intracecally (10 mg/kg or 1 mg/kg) daily (QD), when compared to mice treated with anti-IL-12 p40 antibody intraperitoneally (10 mg/kg) every third day (Q3D) and vehicle control (Vehicle). Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0164] FIG. 31 is a graph showing the concentration of anti-IL-12 p40 rat IgG2A (μ g/mL) in plasma of anti-IL-12 p40 intraperitoneally (10 mg/kg) and intracecally (10 mg/kg and 1 mg/kg) administered treatment groups given daily (QD) or every third day (Q3D) when compared to vehicle control (Vehicle) and when IP is compared to IC. ELISA analysis was used to determine the concentration of anti-IL-12 p40 (IgG2A). Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0165] FIG. 32 is a graph showing the concentration of anti-IL-12 p40 antibody (IgG2A) (μ g/mL) in the cecum and

colon content of anti-IL-12 p40 antibody intraperitoneally (10 mg/kg) and intracecally (10 mg/kg and 1 mg/kg) administered treatment groups given daily (QD) or every third day (Q3D), when compared to vehicle control (Vehicle) and when IP is compared to IC. ELISA analysis was used to determine the concentration of rat IgG2A. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0166] FIG. 33 is a graph showing the mean overall tissue immunolabel scores (intensity and extent) in acute DSS colitis mouse colon of anti-IL-12 p40 antibody intracecally-treated versus vehicle control-treated DSS mice. Data presented as mean $\pm$ SEM.

[0167] FIG. 34 is a graph showing the mean location-specific immunolabel scores in acute DSS colitis mouse colon of anti-IL-12 p40 intracecally-treated versus vehicle control-treated DSS mice. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0168] FIG. 35 is a graph showing the ratio of anti-IL-12 p40 antibody in the colon tissue to the plasma concentration of the anti-IL-12 p40 antibody in mice treated with the anti-IL-12 p40 antibody on day 0 (Q0) or day 3 (Q3D) of the study, when measured at the same time point after the initial dosing. An outlier animal was removed from Group 5.

[0169] FIG. 36 is a graph showing the concentration of IL-1 β (μ g/mL) in colon tissue lysate of acute DSS colitis mice treated with anti-IL-12 p40 intraperitoneally (10 mg/kg) every third day (Q3D) or intracecally (10 mg/kg or 1 mg/kg) administered daily (QD), when compared to vehicle control (Vehicle). Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0170] FIG. 37 is a graph showing the concentration of IL-6 (μ g/mL) in colon tissue lysate of acute DSS colitis mice treated with anti-IL-12 p40 intraperitoneally (10 mg/kg) every third day (Q3D) or intracecally (10 mg/kg or 1 mg/kg) administered daily (QD), when compared to vehicle control (Vehicle). Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0171] FIG. 38 is a graph showing the concentration of IL-17A (μ g/mL) in colon tissue lysate of acute DSS colitis mice treated with anti-IL-12 p40 intraperitoneally (10 mg/kg) every third day (Q3D) or intracecally (10 mg/kg and 1 mg/kg) administered daily (QD), when compared to vehicle control (Vehicle). Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0172] FIG. 39 is a graph showing the percentage (%) change in body weight at day 14 ($\pm$ SEM) for DSS mice treated with DATK32 (anti- α 4 β 7 antibody intraperitoneally (25 mg/kg) every third day (Q3D) or intracecally (25 mg/kg or 5 mg/kg) administered daily (QD), when compared to vehicle control (Vehicle) and when IC is compared to IP.

Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0173] FIG. 40 is a graph showing the plasma concentration of DATK32 rat IgG2A (g/mL) of intraperitoneally (25 mg/kg) and intracecally (25 mg/kg and 5 mg/kg) administered treatment groups given daily (QD) or every third day (Q3D), where IP is compared to IC. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0174] FIG. 41 is a graph showing the concentration of DATK32 rat IgG2A antibody (g/mL) in cecum and colon content of intraperitoneally (25 mg/kg) or intracecally (25 mg/kg and 5 mg/kg) administered treatment groups given daily (QD) or every third day (Q3D), where IP is compared to IC. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0175] FIG. 42 is a graph showing the concentration of DATK32 rat IgG2A (g/mL) in the colon content of intraperitoneally (25 mg/kg) or intracecally (25 mg/kg and 5 mg/kg) administered treatment groups given daily (QD), and concentration over time (1, 2, 4, 24, and 48 hours), where IP is compared to IC. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0176] FIG. 43 is a graph showing the concentration of DATK32 rat IgG2A (g/g) in colon tissue of intraperitoneally (25 mg/kg) or intracecally (25 mg/kg and 5 mg/kg) administered treatment groups given daily (QD) or every third day (Q3D), where IP is compared to IC. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0177] FIG. 44 is a graph showing the concentration of DATK32 rat IgG2A (g/g) in the colon tissue of intraperitoneally (25 mg/kg) or intracecally (25 mg/kg and 5 mg/kg) administered treatment groups given daily (QD), and the concentration over time (1, 2, 4, 24, and 48 hours) was determined, where IP is compared to IC. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0178] FIG. 45 is a graph showing the mean overall tissue immunolabel scores (intensity and extent) in acute DSS colitis mouse colon of DATK32 (anti- $\alpha 4\beta 7$ antibody treated versus vehicle control (Vehicle) treated DSS mice. The data are presented as mean $\pm$ SEM.

[0179] FIG. 46 is a graph showing the mean location-specific immunolabel scores in acute DSS colitis mouse colon of DATK32 (anti- $\alpha 4\beta 7$ antibody-treated versus vehicle control (Vehicle)-treated DSS mice. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and

Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0180] FIG. 47 is a graph showing the ratio of the DATK-32 antibody in the colon tissue to the plasma concentration of the DATK-32 antibody in mice treated with the DATK-32 antibody on day 0 (Q0) or day 3 (Q3D) of the study (Groups 9-12), when measured after initial dosing.

[0181] FIG. 48 is a graph showing the mean percentage of Th memory cells (mean $\pm$ SEM) in blood for DATK32 (anti- $\alpha 4\beta 7$ antibody intraperitoneally (25 mg/kg) or intracecally (25 mg/kg or 5 mg/kg) administered treatment groups given daily (QD) or every third day (Q3D), when compared to vehicle control (Vehicle) and when IP is compared to IC. Mean percentage Th memory cells were measured using FACS analysis. Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0182] FIG. 49 is an exemplary image of a histological section of a distal transverse colon of Animal 1501 showing no significant lesions (i.e., normal colon).

[0183] FIG. 50 is an exemplary image of a histological section of a distal transverse colon of Animal 2501 (treated with TNBS) showing areas of necrosis and inflammation.

[0184] FIG. 51 is a representative graph of plasma adalimumab concentrations over time following a single subcutaneous (SQ) or topical administration of adalimumab. The plasma concentrations of adalimumab were determined 6, 12, 24, and 48 hours after administration of adalimumab. N/D=not detectable.

[0185] FIG. 52 is a representative table of the plasma adalimumab concentrations (μ g/mL) as shown in FIG. 51.

[0186] FIG. 53 is a graph showing the concentration of TNF α (pg/mL per mg of total protein) in non-inflamed and inflamed colon tissue after intracecal administration of adalimumab, as measured 6, 12, 24, and 24 hours after the initial dosing.

[0187] FIG. 54 is a graph showing the concentration of TNF α (pg/mL per mg of total protein) in colon tissue after subcutaneous or intracecal (topical) administration of adalimumab, as measured 48 hours after the initial dosing.

[0188] FIG. 55 is a graph showing the percentage (%) change in body weight at day 14 ($\pm$ SEM) in acute DSS colitis mice treated with cyclosporine A orally (10 mg/kg) every third day (Q3D) or intracecally (10 mg/kg or 3 mg/kg) daily (QD), when compared to vehicle control (Vehicle). Data presented as mean $\pm$ SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0189] FIG. 56 is a graph showing the plasma cyclosporine A (CsA) (ng/mL) concentration over time (1 h, 2 h, 4 h, and 24 h) in acute DSS colitis mice treated daily (QD) with orally (PO) (10 mg/kg) or intracecally (IC) (10 mg/kg or 3 mg/kg) administered CsA. Data presented as mean $\pm$ SEM.

[0190] FIG. 57 is a graph showing the colon tissue cyclosporine A (CsA) (ng/g) concentration over time (1 h, 2 h, 4 h and 24 h) in acute DSS colitis mice treated daily (QD) with orally (PO) (10 mg/kg) or intracecally (IC) (10 mg/kg or 3 mg/kg) administered CsA. Data presented as mean $\pm$ SEM.

[0191] FIG. 58 is a graph showing the peak colon tissue cyclosporine A (CsA) (ng/g) concentration in acute DSS colitis mice treated daily (QD) with orally (PO) (10 mg/kg) or intracecally (IC) (10 mg/kg or 3 mg/kg) administered CsA. Data presented as mean±SEM.

[0192] FIG. 59 is a graph showing the trough tissue concentration of cyclosporine (CsA) (ng/g) in colon of acute DSS colitis mice treated daily (QD) with orally (PO) (10 mg/kg) or intracecally (IC) (10 mg/kg or 3 mg/kg) administered CsA. Data presented as mean±SEM.

[0193] FIG. 60 is a graph showing the interleukin-2 (IL-2) concentration (μg/mL) in colon tissue of acute DSS colitis mice treated daily (QD) with orally (PO) (10 mg/kg) or intracecally (IC) (10 mg/kg or 3 mg/kg) administered CsA, where PO is compared to IC. Data presented as mean±SEM. Mann-Whitney's U-test and Student's t-test were used for statistical analysis on non-Gaussian and Gaussian data respectively. A value of $p < 0.05$ was considered significant (Graph Pad Software, Inc.).

[0194] FIG. 61 is a graph showing the interleukin-6 (IL-6) concentration (μg/mL) in colon tissue of acute DSS colitis mice treated daily (QD) with orally (PO) (10 mg/kg) or intracecally (IC) (10 mg/kg or 3 mg/kg) administered CsA. Data presented as mean±SEM.

[0195] FIG. 62 illustrates a nonlimiting example of a system for collecting, communicating and/or analyzing data about a subject, using an ingestible device.

[0196] FIGS. 63A-F are graphs showing rat IgG2A concentration as measured in (A) colon homogenate, (B) mLN homogenate, (C) small intestine homogenate, (D) cecum contents, (E) colon contents, and (F) plasma by ELISA. Standards were prepared with plasma matrix. Samples were diluted 1:50 before analysis. Sample 20 was removed from cecum contents analysis graph (outlier). * $p < 0.05$; ** $p < 0.01$; **** $p < 0.001$ were determined using the unpaired t test.

[0197] FIG. 64 illustrates a tapered silicon bellows.

[0198] FIG. 65 illustrates a tapered silicone bellows in the simulated device jig.

[0199] FIG. 66 illustrates a smooth PVC bellows.

[0200] FIG. 67 illustrates a smooth PVC bellows in the simulated device jig.

[0201] FIG. 68 demonstrates a principle of a competition assay performed in an experiment.

[0202] FIG. 69 shows AlphaLISA data.

[0203] FIG. 70 shows AlphaLISA data.

[0204] FIG. 71 shows AlphaLISA data.

[0205] FIG. 72 is a flowchart of illustrative steps of a clinical protocol, in accordance with some embodiments of the disclosure.

[0206] FIG. 73 is a graph showing the level of FAM-SMAD7-AS oligonucleotide in the cecum tissue of DSS-induced colitis mice at 12-hours. The bars represent from left to right, Groups 2 through 5 in the experiment described in Example 9.

[0207] FIG. 74 is a graph showing the level of FAM-SMAD7-AS oligonucleotide in the colon tissue of DSS-induced colitis mice at 12-hours. The bars represent from left to right, Groups 2 through 5 in the experiment described in Example 9.

[0208] FIG. 75 is a graph showing the level of FAM-SMAD7-AS oligonucleotide in the cecum contents of DSS-induced colitis mice at 12-hours. The bars represent from left to right, Groups 2 through 5 in the experiment described in Example 9.

[0209] FIG. 76 is a graph showing the mean concentration of tacrolimus in the cecum tissue and the proximal colon tissue 12 hours after intra-cecal or oral administration of tacrolimus to swine as described in Example 10.

DETAILED DESCRIPTION

[0210] The present disclosure is directed to various methods and formulations for treating diseases of the gastrointestinal tract with an IL-12/IL-23 inhibitor. For example, in an embodiment, a method of treating a disease of the gastrointestinal tract in a subject comprises administering to the subject a pharmaceutical formulation comprising an IL-12/IL-23 inhibitor wherein the pharmaceutical formulation is released in the subject's gastrointestinal tract proximate to one or more sites of disease. For example, in an embodiment, the pharmaceutical formulation comprises a therapeutically effective amount of an IL-12/IL-23 inhibitor.

[0211] In some embodiments, the formulation is contained in an ingestible device, and the device releases the formulation at a location proximate to the site of disease. The location of the site of disease may be predetermined. For example, an ingestible device, the location of which within the GI tract can be accurately determined as disclosed herein, may be used to sample one or more locations in the GI tract and to detect one or more analytes, including markers of the disease, in the GI tract of the subject. A pharmaceutical formulation may be then administered via an ingestible device and released at a location proximate to the predetermined site of disease. The release of the formulation may be triggered autonomously, as further described herein.

[0212] The following disclosure illustrates aspects of the formulations and methods embodied in the claims.

[0213] Formulations, Including Pharmaceutical Formulations

[0214] As used herein, a "formulation" of an IL-12/IL-23 inhibitor may refer to either the IL-12/IL-23 inhibitor in pure form, such as, for example, a lyophilized IL-12/IL-23 inhibitor, or a mixture of the IL-12/IL-23 inhibitor with one or more physiologically acceptable carriers, excipients or stabilizers. Thus, therapeutic formulations or medicaments can be prepared by mixing the IL-12/IL-23 inhibitor having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) antibodies; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as

TWEEN™, PLURONICS™ or polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®), Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases. Exemplary lyophilized formulations are described in U.S. Pat. No. 6,267,958. Aqueous formulations include those described in U.S. Pat. No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[0215] A formulation of an IL-12/IL-23 inhibitor as disclosed herein, e.g., sustained-release formulations, can further include a mucoadhesive agent, e.g., one or more of polyvinyl pyrrolidone, methyl cellulose, sodium carboxyl methyl cellulose, hydroxyl propyl cellulose, carbopol, a polyacrylate, chitosan, a eudragit analogue, a polymer, and a thiomers. Additional examples of mucoadhesive agents that can be included in a formulation with an IL-12/IL-23 inhibitor are described in, e.g., Peppas et al., *Biomaterials* 17(16):1553-1561, 1996; Kharenko et al., *Pharmaceutical Chemistry J.* 43(4):200-208, 2009; Salamat-Miller et al., *Adv. Drug Deliv. Reviews* 57(11):1666-1691, 2005; Bernkop-Schnurch, *Adv. Drug Deliv. Rev.* 57(11):1569-1582, 2005; and Harding et al., *Biotechnol. Genet. Eng. News* 16(1):41-86, 1999.

[0216] In some embodiments, components of a formulation may include any one of the following components, or any combination thereof:

Acacia, Alginate, Alginic Acid, Aluminum Acetate, an antiseptic, Benzyl Alcohol, Butyl Paraben, Butylated Hydroxy Toluene, an antioxidant, Citric acid, Calcium carbonate, Candelilla wax, a binder, Croscarmellose sodium, Confectioner sugar, Colloidal silicone dioxide, Cellulose, Carnuba wax, Corn starch, Carboxymethylcellulose calcium, Calcium stearate, Calcium disodium EDTA, Chelation agents, Copolyvidone, Castor oil hydrogenated, Calcium hydrogen phosphate dehydrate, Cetylpyridine chloride, Cysteine HCl, Crosspovidone, Dibasic Calcium Phosphate, Disodium hydrogen phosphate, Dimethicone, Erythrosine Sodium, Ethyl Cellulose, Gelatin, Glyceryl monooleate, Glycerin, Glycine, Glyceryl monostearate, Glyceryl behenate, Hydroxy propyl cellulose, Hydroxyl propyl methyl cellulose, Hypromellose, HPMC Pthalate, Iron oxides or ferric oxide, Iron oxide yellow, Iron oxide red or ferric oxide, Lactose (hydrous or anhydrous or monohydrate or spray dried), Magnesium stearate, Microcrystalline cellulose, Mannitol, Methyl cellulose, Magnesium carbonate, Mineral oil, Methacrylic acid copolymer, Magnesium oxide, Methyl paraben, PEG, Polysorbate 80, Propylene glycol, Polyethylene oxide, Propylene paraben, Polaxamer 407 or 188 or plain, Potassium bicarbonate, Potassium sorbate, Potato starch, Phosphoric acid, Polyoxy 140 stearate, Sodium starch glycolate, Starch pregelatinized, Sodium cross-mellose, Sodium lauryl sulfate, Starch, Silicon dioxide, Sodium benzoate, Stearic acid, Sucrose base for medicated confectionery, a granulating agent, Sorbic acid, Sodium carbonate, Saccharin sodium, Sodium alginate, Silica gel, Sorbiton monooleate, Sodium stearyl fumarate, Sodium

chloride, Sodium metabisulfite, Sodium citrate dehydrate, Sodium starch, Sodium carboxy methyl cellulose, Succinic acid, Sodium propionate, Titanium dioxide, Talc, Triacetin, Triethyl citrate.

[0217] Accordingly, in some embodiments of the method of treating a disease as disclosed herein, the method comprises administering to the subject a pharmaceutical composition that is a formulation as disclosed herein. In some embodiments the formulation is a dosage form, which may be, as an example, a solid form such as, for example, a capsule, a tablet, a sachet, or a lozenge; or which may be, as an example, a liquid form such as, for example, a solution, a suspension, an emulsion, or a syrup.

[0218] In some embodiments, the formulation is not comprised in an ingestible device. In some embodiments wherein the formulation is not comprised in an ingestible device, the formulation may be suitable for oral administration. The formulation may be, for example, a solid dosage form or a liquid dosage form as disclosed herein. In some embodiments wherein the formulation is not comprised in an ingestible device, the formulation may be suitable for rectal administration. The formulation may be, for example, a dosage form such as a suppository or an enema. In embodiments where the formulation is not comprised in an ingestible device, the formulation releases the IL-12/IL-23 inhibitor at a location in the gastrointestinal tract of the subject that is proximate to one or more sites of disease. Such localized release may be achieved, for example, with a formulation comprising an enteric coating. Such localized release may be achieved, another example, with a formulation comprising a core comprising one or more polymers suitable for controlled release of an active substance. A non-limiting list of such polymers includes: poly(2-(diethylamino)ethyl methacrylate, 2-(dimethylamino)ethyl methacrylate, poly(ethylene glycol), poly(2-aminoethyl methacrylate), (2-hydroxypropyl)methacrylamide, poly(β -benzyl-L-aspartate), poly(N-isopropylacrylamide), and cellulose derivatives.

[0219] In some embodiments, the formulation is comprised in an ingestible device as disclosed herein. In some embodiments wherein the formulation is comprised in an ingestible device, the formulation may be suitable for oral administration. The formulation may be, for example, a solid dosage form or a liquid dosage form as disclosed herein. In some embodiments the formulation is suitable for introduction and optionally for storage in the device. In some embodiments the formulation is suitable for introduction and optionally for storage in a reservoir comprised in the device. In some embodiments the formulation is suitable for introduction and optionally for storage in a reservoir comprised in the device. Thus, in some embodiments, provided herein is a reservoir comprising a therapeutically effective amount of an IL-12/IL-23 inhibitor, wherein the reservoir is configured to fit into an ingestible device. In some embodiments, the reservoir comprising a therapeutically effective amount of an IL-12/IL-23 inhibitor is attachable to an ingestible device. In some embodiments, the reservoir comprising a therapeutically effective amount of an IL-12/IL-23 inhibitor is capable of anchoring itself to the subject's tissue. As an example, the reservoir capable of anchoring itself to the subject's tissue comprises silicone. As an example, the reservoir capable of anchoring itself to the subject's tissue comprises polyvinyl chloride.

[0220] In some embodiments the formulation is suitable for introduction in a spray catheter, as disclosed herein.

[0221] The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, for example, those with complementary activities that do not adversely affect each other. For instance, the formulation may further comprise another IL-12/IL-23 inhibitor or a chemotherapeutic agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0222] The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly(methylmethacrylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[0223] The formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[0224] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the IL-12/IL-23 inhibitor, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(−)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated IL-12/IL-23 inhibitors remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37° C., resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S—S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[0225] Pharmaceutical formulations may contain one or more IL-12/IL-23 inhibitors. The pharmaceutical formulations may be formulated in any manner known in the art. In some embodiments the formulations include one or more of the following components: a sterile diluent (e.g., sterile water or saline), a fixed oil, polyethylene glycol, glycerin, propylene glycol, or other synthetic solvents, antibacterial or antifungal agents, such as benzyl alcohol or methyl parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like, antioxidants, such as ascorbic acid or sodium bisulfite, chelating agents, such as ethylenediaminetetraacetic acid, buffers, such as acetates, citrates, or phosphates, and isotonic agents, such as sugars (e.g., dextrose), polyalcohols (e.g., mannitol or sorbitol), or salts (e.g.,

sodium chloride), or any combination thereof. Liposomal suspensions can also be used as pharmaceutically acceptable carriers (see, e.g., U.S. Pat. No. 4,522,811, incorporated by reference herein in its entirety). The formulations can be formulated and enclosed in ampules, disposable syringes, or multiple dose vials. Where required, proper fluidity can be maintained by, for example, the use of a coating, such as lecithin, or a surfactant. Controlled release of the IL-12/IL-23 inhibitor can be achieved by implants and microencapsulated delivery systems, which can include biodegradable, biocompatible polymers (e.g., ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid; Alza Corporation and Nova Pharmaceutical, Inc.).

[0226] In some embodiments, the IL-12/IL-23 inhibitor is present in a pharmaceutical formulation within the device.

[0227] In some embodiments, the IL-12/IL-23 inhibitor is present in solution within the device.

[0228] In some embodiments, the IL-12/IL-23 inhibitor is present in a suspension in a liquid medium within the device.

[0229] In some embodiments, the IL-12/IL-23 inhibitor is present as a pure, powder (e.g., lyophilized) form of the IL-12/IL-23 inhibitor.

Definitions

[0230] By “ingestible”, it is meant that the device can be swallowed whole.

[0231] “Gastrointestinal inflammatory disorders” are a group of chronic disorders that cause inflammation and/or ulceration in the mucous membrane. These disorders include, for example, inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, indeterminate colitis and infectious colitis), mucositis (e.g., oral mucositis, gastrointestinal mucositis, nasal mucositis and proctitis), necrotizing enterocolitis and esophagitis.

[0232] “Inflammatory Bowel Disease” or “IBD” is a chronic inflammatory autoimmune condition of the gastrointestinal (GI) tract. The GI tract can be divided into four main different sections, the oesophagus, stomach, small intestine and large intestine or colon. The small intestine possesses three main subcompartments: the duodenum, jejunum and ileum. Similarly, the large intestine consists of six sections: the cecum, ascending colon, transverse colon, ascending colon, sigmoid colon, and the rectum. The small intestine is about 6 m long, its diameter is 2.5 to 3 cm and the transit time through it is typically 3 hours. The duodenum has a C-shape, and is 30 cm long. Due to its direct connection with the stomach, it is physically more stable than the jejunum and ileum, which are sections that can freely move. The jejunum is 2.4 m in length and the ileum is 3.6 m in length and their surface areas are 180 m² and 280 m² respectively. The large intestine is 1.5 m long, its diameter is between 6.3 and 6.5 cm, the transit time through this section is 20 hours and has a reduced surface area of approximately 150 m². The higher surface area of the small intestine enhances its capacity for systemic drug absorption.

[0233] The etiology of IBD is complex, and many aspects of the pathogenesis remain unclear. The treatment of moderate to severe IBD poses significant challenges to treating physicians, because conventional therapy with corticosteroids and immunomodulator therapy (e.g., azathioprine, 6 mercaptopurine, and methotrexate administered via traditional routes such as tablet form, oral suspension, or intravenously) is associated with side effects and intolerance and

has not shown proven benefit in maintenance therapy (steroids). Monoclonal antibodies targeting tumor necrosis factor alpha (TNF- α), such as infliximab (a chimeric antibody) and adalimumab (a fully human antibody), are currently used in the management of CD. Infliximab has also shown efficacy and has been approved for use in UC. However, approximately 10%-20% of patients with CD are primary nonresponders to anti TNF therapy, and another ~20%-30% of CD patients lose response over time (Schnitzler et al., *Gut* 58:492-500 (2009)). Other adverse events (AEs) associated with anti TNFs include elevated rates of bacterial infection, including tuberculosis, and, more rarely, lymphoma and demyelination (Chang et al., *Nat Clin Pract Gastroenterol Hepatology* 3:220 (2006); Hoentjen et al., *World J. Gastroenterol.* 15(17):2067 (2009)). No currently available therapy achieves sustained remission in more than 20%-30% of IBD patients with chronic disease (Hanauer et al, *Lancet* 359: 1541-49 (2002); Sandborn et al, *N Engl J Med* 353: 1912-25 (2005)). In addition, most patients do not achieve sustained steroid-free remission and mucosal healing, clinical outcomes that correlate with true disease modification.

[0234] Although the cause of IBD remains unknown, several factors such as genetic, infectious and immunologic susceptibility have been implicated. IBD is much more common in Caucasians, especially those of Jewish descent. The chronic inflammatory nature of the condition has prompted an intense search for a possible infectious cause. Although agents have been found which stimulate acute inflammation, none has been found to cause the chronic inflammation associated with IBD. The hypothesis that IBD is an autoimmune disease is supported by the previously mentioned extraintestinal manifestation of IBD as joint arthritis, and the known positive response to IBD by treatment with therapeutic agents such as adrenal glucocorticoids, cyclosporine and azathioprine, which are known to suppress immune response. In addition, the GI tract, more than any other organ of the body, is continuously exposed to potential antigenic substances such as proteins from food, bacterial byproducts (LPS), etc.

[0235] A chronic inflammatory autoimmune condition of the gastrointestinal (GI) tract presents clinically as either ulcerative colitis (UC) or Crohn's disease (CD). Both IBD conditions are associated with an increased risk for malignancy of the GI tract.

[0236] "Crohn's disease" ("CD") is a chronic transmural inflammatory disease with the potential to affect any part of the entire GI tract, and UC is a mucosal inflammation of the colon. Both conditions are characterized clinically by frequent bowel motions, malnutrition, and dehydration, with disruption in the activities of daily living.

[0237] CD is frequently complicated by the development of malabsorption, strictures, and fistulae and may require repeated surgery. UC, less frequently, may be complicated by severe bloody diarrhea and toxic megacolon, also requiring surgery. The most prominent feature Crohn's disease is the granular, reddish-purple edematous thickening of the bowel wall. With the development of inflammation, these granulomas often lose their circumscribed borders and integrate with the surrounding tissue. Diarrhea and obstruction of the bowel are the predominant clinical features. As with ulcerative colitis, the course of Crohn's disease may be continuous or relapsing, mild or severe, but unlike ulcerative colitis, Crohn's disease is not curable by resection of the involved segment of bowel. Most patients with Crohn's

disease require surgery at some point, but subsequent relapse is common and continuous medical treatment is usual. Crohn's disease may involve any part of the alimentary tract from the mouth to the anus, although typically it appears in the ileocolic, small-intestinal or colonic-anorectal regions. Histopathologically, the disease manifests by discontinuous granulomas, crypt abscesses, fissures and aphthous ulcers. The inflammatory infiltrate is mixed, consisting of lymphocytes (both T and B cells), plasma cells, macrophages, and neutrophils. There is a disproportionate increase in IgM- and IgG-secreting plasma cells, macrophages and neutrophils.

[0238] To date, the primary outcome measure in Crohn's Disease clinical trials is the Crohn's Disease Activity Index (CDAI), which has served as the basis for approval of multiple drug treatments, including for example, vedolizumab and natalizumab. The CDAI was developed by regressing clinician global assessment of disease activity on eighteen potential items representing patient reported outcomes (PROs) (i.e. abdominal pain, pain awakening patient from sleep, appetite), physical signs (i.e. average daily temperature, abdominal mass), medication use (i.e. loperamide or opiate use for diarrhea) and a laboratory test (i.e. hematocrit). Backward stepwise regression analysis identified eight independent predictors which are the number of liquid or soft stools, severity of abdominal pain, general well-being, occurrence of extra-intestinal symptoms, need for anti diarrheal drugs, presence of an abdominal mass, hematocrit, and body weight. The final score is a composite of these eight items, adjusted using regression coefficients and standardization to construct an overall CDAI score, ranging from 0 to 600 with higher score indicating greater disease activity. Widely used benchmarks are: CDAI<150 is defined as clinical remission, 150 to 219 is defined as mildly active disease, 220 to 450 is defined as moderately active disease, and above 450 is defined as very severe disease (Best W R, et al., *Gastroenterology* 77:843-6, 1979). Vedolizumab and natalizumab have been approved on the basis of demonstrated clinical remission, i.e. CDAI<150.

[0239] Although the CDAI has been in use for over 40 years, and has served as the basis for drug approval, it has several limitations as an outcome measure for clinical trials. For example, most of the overall score comes from the patient diary card items (pain, number of liquid bowel movements, and general well-being), which are vaguely defined and not standardized terms (Sandler et al., *J. Clin. Epidemiol* 41:451-8, 1988; Thia et al., *Inflamm Bowel Dis* 17: 105-11, 2011). In addition, measurement of pain is based on a four-point scale rather than an updated seven-point scale. The remaining 5 index items contribute very little to identifying an efficacy signal and may be a source of measurement noise. Furthermore, concerns have been raised about poor criterion validity for the CDAI, a reported lack of correlation between the CDAI and endoscopic measures of inflammation (which may render the CDAI as a poor discriminator of active CD and irritable bowel syndrome) and high reported placebo rates (Korzenik et al., *N Engl J Med.* 352:2193-201, 2005; Sandborn W J, et al., *N Engl J Med* 353: 1912-25, 2005; Sandborn W J, et al., *Ann Intern Med* 146:829-38, 2007, Epub 2007 April 30; Kim et al., *Gastroenterology* 146: (5 supplement 1) S-368, 2014).

[0240] It is, thus, generally recognized that additional or alternative measures of CD symptoms are needed, such as new PRO tools or adaptations of the CDAI to derive a new

PRO. The PRO2 and PRO3 tools are such adaptations of the CDAI and have been recently described in Khanna et al., *Aliment Pharmacol. Ther.* 41: 77-86, 2015. The PRO2 evaluates the frequency of loose/liquid stools and abdominal pain {Id}. These items are derived and weighted accordingly from the CDAI and are the CDAI diary card items, along with general well-being, that contribute most to the observed clinical benefit measured by CDAI (Sandler et al., *J. Clin. Epidemiol* 41:451-8, 1988; Thia et al., *Inflamm Bowel Dis* 17: 105-11, 2011; Kim et al., *Gastroenterology* 146: (5 supplement 1) S-368, 2014). The remission score of <11 is the CDAI-weighted sum of the average stool frequency and pain scores in a 7-day period, which yielded optimum sensitivity and specificity for identification of CDAI remission (score of <150) in a retrospective data analysis of ustekinumab induction treatment for moderate to severe CD in a Phase II clinical study (Gasink C, et al., abstract, ACG Annual Meeting 2014). The PRO2 was shown to be sensitive and responsive when used as a continuous outcome measure in a retrospective data analysis of MTX treatment in active CD (Khanna R, et al., *Inflamm Bowel Dis* 20: 1850-61, 2014) measured by CDAI. Additional outcome measures include the Mayo Clinic Score, the Crohn disease endoscopic index of severity (CDEIS), and the Ulcerative colitis endoscopic index of severity (UCEIS). Additional outcome measures include Clinical remission, Mucosal healing, Histological healing (transmural), MRI or ultrasound for measurement or evaluation of bowel wall thickness, abscesses, fistula and histology.

[0241] An additional means of assessing the extent and severity of Crohn's Disease is endoscopy. Endoscopic lesions typical of Crohn's disease have been described in numerous studies and include, e.g., aphthoid ulcerations, "punched-out ulcers," cobblestoning and stenosis. Endoscopic evaluation of such lesions was used to develop the first validated endoscopic score, the Crohn's Disease Endoscopic Index of Severity (CDEIS) (Mary et al., *Gut* 39:983-9, 1989). More recently, because the CDEIS is time-consuming, complicated and impractical for routine use, a Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) was developed and validated (Daperno et al., *Gastrointest. Endosc.* 60(4):505-12, 2004). The SES-CD consists of four endoscopic variables (size of ulcers, proportion of surface covered by ulcers, proportion of surface with any other lesions (e.g., inflammation), and presence of narrowings [stenosis]) that are scored in five ileocolonic segments, with each variable, or assessment, rated from 0 to 3.

[0242] To date, there is no cure for CD. Accordingly, the current treatment goals for CD are to induce and maintain symptom improvement, induce mucosal healing, avoid surgery, and improve quality of life (Lichtenstein G R, et al., *Am J Gastroenterol* 104:465-83, 2009; Van Assche G, et al., *J Crohns Colitis*. 4:63-101, 2010). The current therapy of IBD usually involves the administration of antiinflammatory or immunosuppressive agents, such as sulfasalazine, corticosteroids, 6-mercaptopurine/azathioprine, or cyclosporine, all of which are not typically delivered by localized release of a drug at the site or location of disease. More recently, biologics like TNF-alpha inhibitors and IL-12/IL-23 blockers, are used to treat IBD. If anti-inflammatory/immunosuppressive/biologic therapies fail, colectomies are the last line of defense. The typical operation for CD not involving the rectum is resection (removal of a diseased segment of

bowel) and anastomosis (reconnection) without an ostomy. Sections of the small or large intestine may be removed. About 30% of CD patients will need surgery within the first year after diagnosis. In the subsequent years, the rate is about 5% per year. Unfortunately, CD is characterized by a high rate of recurrence; about 5% of patients need a second surgery each year after initial surgery.

[0243] Refining a diagnosis of inflammatory bowel disease involves evaluating the progression status of the diseases using standard classification criteria. The classification systems used in IBD include the Truelove and Witts Index (Truelove S. C. and Witts, L. J. *Br Med J.* 1955; 2: 1041-1048), which classifies colitis as mild, moderate, or severe, as well as Lennard-Jones. (Lennard-Jones J E. *Scand J Gastroenterol Suppl* 1989; 170:2-6) and the simple clinical colitis activity index (SCCAI). (Walmsley et. al. *Gut.* 1998; 43:29-32) These systems track such variables as daily bowel movements, rectal bleeding, temperature, heart rate, hemoglobin levels, erythrocyte sedimentation rate, weight, hematocrit score, and the level of serum albumin.

[0244] There is sufficient overlap in the diagnostic criteria for UC and CD that it is sometimes impossible to say which a given patient has; however, the type of lesion typically seen is different, as is the localization. UC mostly appears in the colon, proximal to the rectum, and the characteristic lesion is a superficial ulcer of the mucosa; CD can appear anywhere in the bowel, with occasional involvement of stomach, esophagus and duodenum, and the lesions are usually described as extensive linear fissures.

[0245] In approximately 10-15% of cases, a definitive diagnosis of ulcerative colitis or Crohn's disease cannot be made and such cases are often referred to as "indeterminate colitis." Two antibody detection tests are available that can help the diagnosis, each of which assays for antibodies in the blood. The antibodies are "perinuclear anti-neutrophil antibody" (pANCA) and "anti-*Saccharomyces cerevisiae* antibody" (ASCA). Most patients with ulcerative colitis have the pANCA antibody but not the ASCA antibody, while most patients with Crohn's disease have the ASCA antibody but not the pANCA antibody. However, these two tests have shortcomings as some patients have neither antibody and some Crohn's disease patients may have only the pANCA antibody. A third test, which measures the presence and accumulation of circulating anti-microbial antibodies—particularly flagellin antibodies, has proven to be useful for detecting susceptibility to Crohn's Disease before disease development. See Choung, R. S., et al. "Serologic microbial associated markers can predict Crohn's disease behaviour years before disease diagnosis." *Alimentary pharmacology & therapeutics* 43.12 (2016): 1300-1310.

[0246] "Ulcerative colitis (UC)" afflicts the large intestine. The course of the disease may be continuous or relapsing, mild or severe. The earliest lesion is an inflammatory infiltration with abscess formation at the base of the crypts of Lieberkuhn. Coalescence of these distended and ruptured crypts tends to separate the overlying mucosa from its blood supply, leading to ulceration. Symptoms of the disease include cramping, lower abdominal pain, rectal bleeding, and frequent, loose discharges consisting mainly of blood, pus and mucus with scanty fecal particles. A total colectomy may be required for acute, severe or chronic, unremitting ulcerative colitis.

[0247] The clinical features of UC are highly variable, and the onset may be insidious or abrupt, and may include

diarrhea, tenesmus and relapsing rectal bleeding. With fulminant involvement of the entire colon, toxic megacolon, a life-threatening emergency, may occur. Extraintestinal manifestations include arthritis, pyoderma gangrenosum, uveitis, and erythema nodosum.

[0248] The terms “antibody” and “immunoglobulin” are used interchangeably in the broadest sense and include monoclonal antibodies (for example, full length or intact monoclonal antibodies), polyclonal antibodies, multivalent antibodies, multispecific antibodies (e.g., bispecific, trispecific etc. antibodies so long as they exhibit the desired biological activity) and may also include certain antibody fragments (as described in greater detail herein). An antibody can be human, humanized and/or affinity matured.

[0249] “Antibody fragments” comprise only a portion of an intact antibody, where in certain embodiments, the portion retains at least one, and typically most or all, of the functions normally associated with that portion when present in an intact antibody. In one embodiment, an antibody fragment comprises an antigen binding site of the intact antibody and thus retains the ability to bind antigen. In another embodiment, an antibody fragment, for example one that comprises the Fc region, retains at least one of the biological functions normally associated with the Fc region when present in an intact antibody, such as FcRn binding, antibody half-life modulation, ADCC function and complement binding. In one embodiment, an antibody fragment is a monovalent antibody that has an in vivo half-life substantially similar to an intact antibody. For example, such an antibody fragment may comprise on antigen binding arm linked to an Fc sequence capable of conferring in vivo stability to the fragment.

[0250] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigen. Furthermore, in contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

[0251] The monoclonal antibodies herein specifically include “chimeric” antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; and Morrison et al, Proc. Natl. Acad. Sci. USA 81:6851-6855 (1984)).

[0252] “Treatment regimen” refers to a combination of dosage, frequency of administration, or duration of treatment, with or without addition of a second medication.

[0253] “Effective treatment regimen” refers to a treatment regimen that will offer beneficial response to a patient receiving the treatment.

[0254] “Effective amount” refers to an amount of drug that offers beneficial response to a patient receiving the treatment. For example, an effective amount may be a Human Equivalent Dose (HED).

[0255] “Dispensable”, with reference to any substance, refers to any substance that may be released from an ingestible device as disclosed herein, or from a component of the device such as a reservoir. For example, a dispensable substance may be an IL-12/IL-23 inhibitor, and/or a formulation comprising an IL-12/IL-23 inhibitor.

[0256] “Patient response” or “patient responsiveness” can be assessed using any endpoint indicating a benefit to the patient, including, without limitation, (1) inhibition, to some extent, of disease progression, including slowing down and complete arrest; (2) reduction in the number of disease episodes and/or symptoms; (3) reduction in lesion size; (4) inhibition (i.e., reduction, slowing down or complete stopping) of disease cell infiltration into adjacent peripheral organs and/or tissues; (5) inhibition (i.e., reduction, slowing down or complete stopping) of disease spread; (6) decrease of auto-immune response, which may, but does not have to, result in the regression or ablation of the disease lesion; (7) relief, to some extent, of one or more symptoms associated with the disorder; (8) increase in the length of disease-free presentation following treatment; and/or (9) decreased mortality at a given point of time following treatment. The term “responsiveness” refers to a measurable response, including complete response (CR) and partial response (PR).

[0257] As used herein, “complete response” or “CR” means the disappearance of all signs of inflammation or remission in response to treatment. This does not necessarily mean the disease has been cured.

[0258] “Partial response” or “PR” refers to a decrease of at least 50% in the severity of inflammation, in response to treatment.

[0259] A “beneficial response” of a patient to treatment with a therapeutic agent and similar wording refers to the clinical or therapeutic benefit imparted to a patient at risk for or suffering from a gastrointestinal inflammatory disorder from or as a result of the treatment with the agent. Such benefit includes cellular or biological responses, a complete response, a partial response, a stable disease (without progression or relapse), or a response with a later relapse of the patient from or as a result of the treatment with the agent.

[0260] As used herein, “non-response” or “lack of response” or similar wording means an absence of a complete response, a partial response, or a beneficial response to treatment with a therapeutic agent.

[0261] “A patient maintains responsiveness to a treatment” when the patient’s responsiveness does not decrease with time during the course of a treatment.

[0262] A “symptom” of a disease or disorder (e.g., inflammatory bowel disease, e.g., ulcerative colitis or Crohn’s disease) is any morbid phenomenon or departure from the normal in structure, function, or sensation, experienced by a subject and indicative of disease.

IL-12/IL-23 Inhibitors

[0263] The term “IL-12/IL-23 inhibitors” refers to an agent which decreases IL-12 or IL-23 expression and/or the ability of IL-12 to bind to an IL-12 receptor or the ability of IL-23 to bind to an IL-23 receptor. IL-12 is a heterodimeric cytokine that includes both IL-12A (p35) and IL-12B (p40) polypeptides. IL-23 is a heterodimeric cytokine that includes

both IL-23 (p19) and IL-12B (p40) polypeptides. The receptor for IL-12 is a heterodimeric receptor includes IL-12R β 1 and IL-12R β 2. The receptor for IL-23 receptor is a heterodimeric receptor that includes both IL-12R β 1 and IL-23R.

[0264] In some embodiments, the IL-12/IL-23 inhibitor can decrease the binding of IL-12 to the receptor for IL-12. In some embodiments, the IL-12/IL-23 inhibitor can decrease the binding of IL-23 to the receptor for IL-23. In some embodiments, the IL-12/IL-23 inhibitor decreases the expression of IL-12 or IL-23. In some embodiments, the IL-12/IL-23 inhibitor decreases the expression of a receptor for IL-12. In some embodiments, the IL-12/IL-23 inhibitor decreases the expression of a receptor for IL-23.

[0265] In some embodiments, the IL-12/IL-23 inhibitory agent targets IL-12B (p40) subunit. In some embodiments, the IL-12/IL-23 inhibitory agent targets IL-12A (p35). In some embodiments, the IL-12/IL-23 inhibitory agent targets IL-23 (p19). In some embodiments, the IL-12/IL-23 inhibitory agent targets the receptor for IL-12 (one or both of

IL-12R β 1 or IL-12R β 2). In some embodiments, the IL-12/IL-23 inhibitory agent targets the receptor for IL-23 (one or both of IL-12R β 1 and IL-23R).

[0266] In some embodiments, an IL-12/IL-23 inhibitor can be an inhibitory nucleic acid. In some embodiments, the inhibitory nucleic acid can be an antisense nucleic acid, a ribozyme, and a small interfering RNA (siRNA). Examples of aspects of these different oligonucleotides are described below. Any of the examples of inhibitory nucleic acids that can decrease expression of IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA in a mammalian cell can be synthesized in vitro.

[0267] Inhibitory nucleic acids that can decrease the expression of IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA expression in a mammalian cell include antisense nucleic acid molecules, i.e., nucleic acid molecules whose nucleotide sequence is complementary to all or part of an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA (e.g., complementary to all or a part of any one of SEQ ID NOs: 1-12).

Human IL-12A (p35) mRNA

(SEQ ID NO: 1)

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1  ttctgctttc attttgggcc gagctggagg cggcggggcc gtcccgaac ggctgaggcc
61  gggcaccgcc ggagttaatc cgaaagcgcc gcaagccccc cgggcccggc gcaccgcacg
121  tgtcaccgag aagctgatgt agagagagac acagaaggag acagaaagca agagaccaga
181  gtcccgggaa agtccctcgc cgccctcgga caattataaa aatgtggccc cctgggtcag
241  cctcccagcc accgccctca cctgcccgcc ccacaggtct gcatccagcg gctgcgcctg
301  tgtccctgca gtgccggctc agcatgtgtc cagcgcgcag cctcctcctt gtggctaccc
361  tggctcctct ggaccacctc agtttggcca gaaacctccc cgtggccact ccagaccagc
421  gaatgttccc atgccttcac cactcccaaa acctgctgag ggccgtcagc aacatgctcc
481  agaaggccag acaaaactca gaattttacc cttgcacttc tgaagagatt gatcatgaag
541  atatcacaaa agataaaacc agcacagtgg aggcctgttt accattggaa ttaaccaaga
601  atgagagttg cctaataatc agagagacct ctttcataac taatgggagt tgcctggcct
661  ccagaagacg ctcttttatg atggccctgt gccttagtag tatttatgaa gacttgaaga
721  tgtaccaggt ggagttcaag accatgaatg caaagcttct gatggatcct aagaggcaga
781  tctttctaga tcaaaacatg ctggcagtta ttgatgagct gatgcaggcc ctgaatttca
841  acagtgagac tgtgccacaa aaatcctccc ttgaagaacc ggatttttat aaaactaaaa
901  tcaagctctg catacttctt catgctttca gaattcgggc agtgactatt gatagagtga
961  tgagctatct gaatgcttcc taaaaagcga ggtccctcca aaccgtgtgc atttttataa
1021 aactttgaaa tgaggaaact ttgataggat gtggattaag aactagggag ggggaaagaa
1081 ggatgggact attacatcca catgatacct ctgatcaagt atttttgaca ttactgtgg
1141 ataaattgtt ttaagtttt catgaatgaa ttgctaagaa gggaaaatat ccactctgaa
1201 ggtgtttttc attcacttta atagaagggc aaatatatat aagctatttc tgtaccacaa
1261 tgtttgtgga aacaaacatg taagcataac ttattttaaa atatttatat atataacttg
1321 gtaatcatga aagcatctga gctaacttat atttatttat gttatattta ttaaaattat
1381 tatcaagtgt atttgaaaaa tttttttaag tgttctaaaa ataaaagtat tgaattaaag
1441 tgaaaaaaaaa

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-continued

Human IL-12B (p40) mRNA

(SEQ ID NO: 2)

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1  ctgtttcagg gccattggac tctccgtcct gccagagca agatgtgtca ccagcagttg
61  gtcattctctt ggtttttccct ggtttttctg gcattctccc tcgtggccat atgggaactg
121  aagaaagatg tttatgtcgt agaattggat tggatccgg atgccctgg agaaatggtg
181  gtcctcacct gtgacacccc tgaagaagat ggtatccct ggaccttgga ccagagcagt
241  gaggtcttag gctctggcaa aacctgacc atccaagta aagagtttg agatgctggc
301  cagtacacct gtcacaaagg aggcgagggt ctaagccatt cgtctctgct gcttcacaaa
361  aaggaagatg gaatttggc cactgatatt ttaaaggacc agaaagaacc caaaaataag
421  acctttctaa gatcgaggc caagaattat tctggacgtt tcacctgctg gtggctgacg
481  acaatcagta ctgatttgac attcagtgtc aaaagcagca gaggtcttc tgaccccaa
541  ggggtgacgt gcgagctgc tacactctct gcagagagag tcagagggga caacaaggag
601  tatgagtact cagtggagtg ccaggaggac agtgccctgc cagctgctga ggagagtctg
661  ccattgagg tcatggtgga tgccgttcac aagctcaagt atgaaaacta caccagcagc
721  ttcttcatca gggacatcat caaacctgac ccaccaaga acttgacgt gaagccatta
781  aagaattctc ggcagggtga ggtcagctgg gattaccctg acacctggag tactccacat
841  tctactttc ccctgacatt ctgcgttcag gtccagggca agagcaagag agaaaagaaa
901  gatagagtct tcacggacaa gacctcagcc acggctcatc gccgcaaaaa tgccagcatt
961  agcgtgcggg ccaggaccg ctactatagc tcactcttga gcgaatgggc atctgtgccc
1021  tgcagttagg ttctgatcca ggatgaaaat ttggaggaaa agtggagat attagcaaaa
1081  atgttttaaag acacaacgga atagacccaa aaagataatt tctatctgat ttgctttaa
1141  acgttttttt aggtacacaa tgatatcttt gctgtatttg tatagttaga tgctaaatgc
1201  tcattgaaac aatcagctaa tttatgtata gattttcag ctctcaagtt gccatggggc
1261  ttcattgctat ttaaatattt aagtaattta tgtatttatt agtatattac tgttatttaa
1321  cgtttgtctg ccaggatgta tggaatgttt catactctta tgacctgatc catcaggatc
1381  agtccctatt atgcaaaatg tgaatttaat tttatttgta ctgacaactt tcaagcaag
1441  gctgcaagta catcagtttt atgacaatca ggaagaatgc agtggtctga taccagtgcc
1501  atcatacact tgtgatggat gggaacgcaa gagatactta catggaaacc tgacaatgca
1561  aacctgttga gaagatccag gagaacaaga tgctagtcc catgtctgtg aagacttcct
1621  ggagatggtg ttgataaagc aatttagggc cacttacact tctaagcaag ttaaatcttt
1681  ggatgcctga attttaaaaa ggctagaaaa aaatgattga ccagcctggg aaacataaca
1741  agaccccgct tctacaaaaa aaatttaaaa ttagccaggc gtggtggctc atgcttggtg
1801  tccagctgtc tcaggaggat gaggcaggag gatctcttga gccaggagg tcaaggctat
1861  ggtgagccgt gattgtgcca ctgcatacca gcctagggtg cagaatgaga cctgtctca
1921  aaaaaaaaaa tgattgaaat taaaattcag ctttagcttc catggcagtc ctcaccccca
1981  cctctctaaa agacacagga ggatgacaca gaaacaccgt aagtgtctgg aaggcaaaaa
2041  gatcttaaga ttcaagagag aggacaagta gttatggcta aggacatgaa attgtcagaa
2101  tggcaggtgg cttcttaaca gccctgtgag aagcagacag atgcaagaa aatctggaat
2161  cctttctca ttagcatgaa tgaacctgat acacaattat gaccagaaaa tatggctcca
2221  tgaagggtgt acttttaagt aatgtatgtg cgctctgtaa agtgattaca ttgtttcct

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2281 gtttgtttat ttattttatt atttttgcat tctgaggctg aactaataaa aactcttctt
 2341 tgtaatc

Human IL-23 (p19) mRNA

(SEQ ID NO: 3)

1 aaaacaacag gaagcagctt acaaaactcg tgaacaactg agggaaccaa accagagacg
 61 cgctgaacag agagaatcag gctcaaagca agtggaaagt ggagagatt ccaccaggac
 121 tggtgcaagg cgcagagcca gccagatttg agaagaaggc aaaaagatgc tggggagcag
 181 agctgtaatg ctgctgttgc tgctgccctg gacagctcag ggagagctg tgcctggggg
 241 cagcagccct gcctggactc agtgccagca gctttcacag aagctctgca cactggcctg
 301 gagtgcacat ccactagtgg gacacatgga tctaagagaa gaggagatg aagagactac
 361 aaatgatgtt ccccatatcc agtgtggaga tggctgtgac ccccaaggac tcagggacaa
 421 cagtcagttc tgcttgcaaa ggatccacca gggctctgatt tttatgaga agctgctagg
 481 atcggtatatt ttcacagggg agccttctct gctccctgat agccctgtgg gccagcttca
 541 tgccctccca ctgggccctc gccaaactcct gcagcctgag ggtcaccact gggagactca
 601 gcagattcca agcctcagtc ccagccagcc atggcagcgt ctccttctcc gcttcaaaat
 661 ccttcgcagc ctccaggcct ttgtggctgt agccgcccg gtctttgccc atggagcagc
 721 aaccctgagt ccctaaaggc agcagctcaa ggatggcact cagatctcca tggcccagca
 781 aggccaaagt aaatctacca cccagggcac ctgtgagcca acaggtaat tagtccatta
 841 attttagtgg gactgcata tgttgaaaat taccaatact gactgacatg tgatgctgac
 901 ctatgataag gttgagtatt tattagatgg gaagggaat ttggggatta tttatcctcc
 961 tggggacagt ttggggagga ttatttatgt tatttatatt gaattatga cattttttaa
 1021 taaagtctta tttttgtggc taaaaaaaa

Human IL-12R β 1 mRNA Variant 1

(SEQ ID NO: 4)

1 ctctttcact ttgacttgcc ttagggatgg gctgtgacac ttacttttt ttcttttttc
 61 ttttttttca gtctttttct cttgctcagc ttcaatgtgt tccggagtgg ggacggggtg
 121 gctgaacctc gcaggtggca gagaggctcc cctggggctg tggggctcta cgtggatccg
 181 atggagccgc tgggtgacctg ggtgggtccc ctctctctcc tcttctgct gtccaggcag
 241 ggcgctgcct gcagaaccag tgagtgtgtg ttccaggacc cgcctatccc ggatgcagac
 301 tcaggctcgg cctcgggccc tagggacctg agatgctatc ggatatccag tgatcgttac
 361 gagtgtcctc ggcagtatga ggggtccaca gctggggta gccacttctc gcggtgttgc
 421 cttagctcgg ggcgctgctg ctacttcgcc gccggctcag ccaccaggct gcagttctcc
 481 gaccaggctg ggggtgtctgt gctgtacact gtcacactct ggggtggaatc ctgggcccag
 541 aaccagacag agaagtctcc tgaggtgacc ctgcagctct acaactcagt taaatatgag
 601 cctcctctgg gagacatcaa ggtgtccaag ttggccgggc agctgcgtat ggagtgggag
 661 accccggata accaggttgg tgctgagggt cagttccggc accggacacc cagcagccca
 721 tggaagtggg gcgactgcgg acctoaggat gatgatactg agtccctgcct ctgccccctg
 781 gagatgaatg tggcccagga attccagctc cgacgacggc agctggggag ccaaggaaat
 841 tcttgagca agtgaggcag ccccggtgct gtccccctg aaaaccccc acagcctcag
 901 gtgagattct cgggtggagca gctgggccag gatgggagga ggcggctgac cctgaaagag
 961 cagccaaccc agctggagct tccagaaggc tgtcaagggc tggcgccctg cacggaggct

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1021 acttaccgac tacagctcca catgctgtcc tgcccgtgta aggccaaaggc caccaggacc
 1081 ctgcacctgg ggaagatgcc ctatctctcg ggtgctgect acaacgtggc tgcctctccc
 1141 tcgaaccaat ttggctctgg cctgaaccag acgtggcaca ttctgcccga caccacaca
 1201 gaaccagtgg ctctgaatat cagcgtcgga accaacggga ccaccatgta ttggccagcc
 1261 cgggctcaga gcatgacgta ttgcattgaa tggcagcctg tgggccagga cgggggcctt
 1321 gccacctgca gcctgactgc gccgcaagac ccggatccgg ctggaatggc aacctacagc
 1381 tggagtcgag agtctggggc aatggggcag gaaaagtgtt actacattac catctttgcc
 1441 tctgcgcacc ccgagaagct caccttgtgg tctacggtec tgtccaccta ccactttggg
 1501 ggcaatgcct cagcagctgg gacaccgcac cagctctcgg tgaagaatca tagcttgga
 1561 tctgtgtctg tggactgggc accatccctg ctgagcacct gtcccggcgt cctaaaggag
 1621 tatgttgtcc gctgccgaga tgaagacagc aaacaggtgt cagagcatcc cgtgcagccc
 1681 acagagaccc aagttaacct cagtggcctg cgggctggtg tagcctacac ggtgcaggtg
 1741 cgagcagaca cagcgtggct gaggggtgtc tggagccagc ccagcgcctt cagcatcgaa
 1801 gtgcagggtt ctgattggct catcttcttc gcctccctgg ggagcttccg gacatccctt
 1861 ctctggggcg tccttggtta ccttggcctg aacagggccg caccggcacct gtgcccgcg
 1921 ctgccacac cctgtgccag ctccgccatt gagttccctg gaggggaagga gacttggcag
 1981 tggatcaacc cagtggactt ccaggaagag gcacccctgc aggaggccct ggtggttagg
 2041 atgtctcggg acaaaaggca gaggactgag cctctcgaga agacagagct acctgagggt
 2101 gccctcagc tggccctgga tacagagttg tccttgagg atggagacag gtgcaaggcc
 2161 aagatgtgat cgttgaggct cagagagggt gactgactcg ccgaggcta cgtagcacac
 2221 acaggagtca catttgacc caaataaacc agagctctc caggctccag tgcacctgcc
 2281 tctctctcgc ccctgcctg ttgccaccca tctcggggg gaacctaga tgctgccatg
 2341 aaatggaagc tgctgcaccc tgctgggctt ggcacccgtg gggcaggagc agaccctgcc
 2401 atttacctgt tctggcgtag aatggactgg gaatgggggc aaggggggct cagatggatc
 2461 cctggacctt gggctgggca tccaccccca ggagcactgg atggggagtc tggactcaag
 2521 ggctccctgc agcattgcgg ggtctttag ctggaggat ccaggcatat aggggaaggg
 2581 gctgtaaaact ttgtgggaaa aatgacggtc ctccatccc acccccacc ccaccctcac
 2641 cccctataa aatgggggtg gtgataatga ccttacacag ctgttcaaaa tcatcgtaaa
 2701 tgagctcct cttgggtatt ttttctctgt ttgaagcttg aatgtctgc tcaaaatctc
 2761 aaaacacgag ccttgaatt caaaaaaaaa aaaaaaaaaa

Human IL-12R β 1 mRNA Variant 2

(SEQ ID NO: 5)

1 ctcttttcaat ttgacttgcc ttagggatgg gctgtgacac ttactttttt ttcttttttc
 61 ttttttttca gtctttttctc cttgtctcagc ttcaatgtgt tccggagtgg ggaagggtg
 121 gctgaacctc gcaggtggca gagaggctcc cctggggctg tggggctcta cgtggatccg
 181 atggagccgc tggtagactg ggtggtcocc ctctctctcc tcttctgct gtccaggcag
 241 ggcgctgect gcagaaccag tgagtgtgtt ttccaggacc cgcctatccc ggatgcagac
 301 tcaggctcgg cctcggggcc tagggacctg agatgctatc ggatatccag tgatcgttac
 361 gagtgctect ggcagtatga gggctccaca gctggggctc gccacttctc gcggtgttgc
 421 cttagctccg ggcgctgctg ctacttcgcc gccggctcag ccaccaggct gcagttctcc

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481 gaccaggctg ggggtgtctgt gctgtacact gtcacactct ggggtggaatc ctgggccagg
 541 aaccagacag agaagttctc tgaggtgacc ctgcagctct acaactcagt taaatatgag
 601 cctcctctgg gagacatcaa ggtgtccaag ttggccgggc agctgcgtat ggagtgggag
 661 accccggata accagggttg tgctgaggtg cagttccggc accggacacc cagcagccca
 721 tggaagttag gcgactcgcg acctcaggat gatgatactg agtcctgcct ctgccccctg
 781 gagatgaatg tggccaggga attccagctc cgacgacggc agctggggag ccaaggaagt
 841 tcttgagca agtgaggcag ccccggtgtg gtccccctg aaaaaacccc acagcctcag
 901 gtgagattct cgggtggagca gctgggccag gatgggagga ggcggtgac cctgaaagag
 961 cagccaaccc agctggagct tccagaaggc tgtcaagggc tggcgcttg cagggaggtc
 1021 acttaccgac tacagctcca catgctgtcc tgcccggtga aggccaaagg caccaggacc
 1081 ctgcacctgg ggaagatgcc ctatctctcg ggtgctgcct acaactggc tgctatctcc
 1141 tcgaaccaat ttggtctcgg cctgaaccag acgtggcaca ttctgcccga cccccacaca
 1201 gatggcatga tctcagctca ctgcaacctc cgccttcag attcaagaga ttctcctgct
 1261 tcagcctccc gagtagctgg gattacaggc atctgccacc ataccggct aattttgtat
 1321 ttttagtaga gacggggttt caccacgttg gccaggctgg tctcgaactc ctgacctcaa
 1381 gtgatccacc tgctttggcc tcccaaagtg ttgggattat agcgctgagc caccatgccc
 1441 agcctaattt ttgtattttt agtagagatg gagtttcacc atgttgccca ggctggtctc
 1501 aaactcctgc cctcaggatg tccaccacc tcagcctctc aaagtgtggt gattacaggt
 1561 gtgagccact gtggccgacc tactattttt attatttttg agctagggtc tcagtctggt
 1621 ggcagactgg agtgcaatca tggctcactg cagccttgaa ctcccagact caagtgatcc
 1681 ttccacctca gcctctggag tagctgggac tacagacatg caccaccaca cctggttaat
 1741 tttttatttt tttttttgt agagacaggt gtctctctac gttgccagg ctggtctcga
 1801 actcctgggc tcaagtgate caccatctc cactcccaa agtgctagga ttacaggcgt
 1861 gagccaccgt acccagcctg gtcccatatc atagtgaat ggtgctgta aagctctcag
 1921 cattggcttg gcacatgcag ttggtactca ataaacggct gttgctatcc caaaaaaaaa
 1981 aaaaaaaaaa aaaaaaa

Human IL-12R β 1 mRNA Variant 3

(SEQ ID NO: 6)

1 ctcttttcaat ttgacttgcc ttagggatgg gctgtgacac ttactttttt ttcttttttc
 61 ttttttttca gtctttttctc cttgtctcag tccaatgtgt tccggagtgg ggaagggtg
 121 gctgaacctc gcaggtggca gagaggctcc cctggggctg tggggctcta cgtggatccg
 181 atggagccgc tggtagactg ggtggtcacc ctctcttcc tcttcctgct gtccaggcag
 241 ggcgtgctct gcagaaccag tgagtgtgtg ttccaggacc cgcctatacc ggatgcagac
 301 tcaggctcgg cctcggggccc tagggacctg agatgtatc ggatatccag tgatcgttac
 361 gagtgctctc ggcagtatga ggggtccaca gctgggggtc gccacttctc gcggtgttgc
 421 cttagctccg ggcgtgctg ctacttcgac gccggctcag ccaccaggct gcagttctcc
 481 gaccaggctg ggggtgtctgt gctgtacact gtcacactct ggggtggaatc ctgggccagg
 541 aaccagacag agaagttctc tgaggtgacc ctgcagctct acaactcagt taaatatgag
 601 cctcctctgg gagacatcaa ggtgtccaag ttggccgggc agctgcgtat ggagtgggag
 661 accccggata accagggttg tgctgaggtg cagttccggc accggacacc cagcagccca

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721 tggaagttag gcgactgcgg acctcaggat gatgatactg agtcctgcct ctgccccctg
 781 gagatgaatg tggcccagga attccagctc cgacgacggc agctggggag ccaaggaagt
 841 tcttgagaca agtggagcag ccccggtgtc gtccccctg aaaaaaaaa acagcctcag
 901 gtgagattct cggtaggaca gctgggccag gatgggagga ggaggctgac cctgaaagag
 961 cagccaaccc agctggagct tccagaaggc tgtcaagggc tggcgcttg cagggaggtc
 1021 acttaccgac tacagctcca catgctgtcc tgcccggtga aggccaaagg caccaggacc
 1081 ctgcacctgg ggaagatgcc ctatctctcg ggtgctgcct acaacgtggc tgtcatctcc
 1141 tcgaaccaat ttgtctctgg cctgaaccag acgtggcaca ttctgcccga caccacaca
 1201 gaaccagtgg ctctgaatat cagcgctcga accaacggga ccaccatgta ttggccagcc
 1261 cgggctcaga gcatgacgta ttgcattgaa tggcagcctg tgggccagga cgggggcctt
 1321 gccacctgca gcctgactgc gccgcaagac ccggatccgg ctggaatggc aacctacagc
 1381 tggagtcgag agtctggggc aatggggcag gaaaagtgtt actacattac catctttgcc
 1441 tctgcgcacc ccgagaagct cactttgtgg tctacggctc tgtccacctc ccactttggg
 1501 ggcgaatgct cagcagctgg gacaccgcac cagctctcgg tgaagaatca tagcttgagc
 1561 tctgtgtctg tggactgggc accatccctg ctgagcacct gtcccgccgt cctaaaggag
 1621 tatgttgtcc gctgccgaga tgaagacagc aaacagggtg cagagcatcc cgtgcagccc
 1681 acagagaccc aagtaccctc cagtggcctg cgggctggtg tagcctacac ggtgcagggtg
 1741 cgagcagaca cagcgtggct gaggggtgtc tggagccagc ccagcgctt cagcatcgaa
 1801 gtgcagggtt ctgattggct catcttcttc gcctccctgg ggagcttctt gagcatcctt
 1861 ctgctggggc tccttggtta ccttggcctg aacagggccg cagggcacct gtgcccgcg
 1921 ctgcccacac cctgtgccag ctccgccatt gagttccctg gagggaaagg gacttggcag
 1981 tggatcaacc cagtggactt ccaggaagag gcatccctgc aggaggccct ggtggtagag
 2041 atgtcctggg acaaaggcga gaggactgag cctctcgaga agacagagct acctgagggt
 2101 gccctcgagc tggccctgga tacagagttg tccttggagg atggagacag atgtgatcgt
 2161 tgaggctcag agagggtgag tgactcgccc gaggtctagt agcacacaca ggagtcacat
 2221 ttggacccaa ataaccaga gtcctccag gctccagtgc acctgcctcc tctctgcccc
 2281 gtgcctgttg ccacccatcc tgcgggggaa ccctagatgc tgccatgaaa tggaaagctg
 2341 tgcacctcgc tgggcctggc atccgtgggg caggagcaga cctgcccatt tacctgttct
 2401 ggcgtagaat ggactgggaa tgggggcaag gggggctcag atggatccct ggaccctggg
 2461 ctgggcatcc acccccagga gcaactggat gggagtctgg actcaagggc tcctgcagc
 2521 attgctgggt cttgtagctt ggaggatcca ggcataatag gaagggggct gtaaaacttg
 2581 tgggaaaaat gacggctctc ccacccacc cccacccca cctcaccac cctataaaat
 2641 ggggggtgtg ataataacct tacacagctg ttcaaaatca tcgtaaatga gcctcctctt
 2701 gggatatttt ttctgtttg aagcttgaat gtcctgtctc aaatctcaaa acacgagcct
 2761 tggaattcaa aaaaaaaaa aaaaaaa

Human IL-12R β 1 mRNA Variant 4

(SEQ ID NO: 7)

1 agaacactcc gctgcctctc cagagccagg cacacagcag gcgtccata aatgttcgtt
 61 ggtcttttct cctgtctcag cttcaatgtg ttccggagtg gggacggggt ggctgaacct
 121 cgcagggtggc agagaggctc ccctggggct gtggggctct acgtggatcc gatggagccg

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181 ctggtgacct ggggtgtccc cctcctcttc ctcttctctg tgtccaggca gggcgctgcc
241 tgcagaacca gtgagtgtctg ttttcaggac ccgccatata cggatgcaga ctccaggctcg
301 gcctcggggc ctagggacct gagatgttat cggatatcca gtgatcgta cgagtgtctc
361 tggcagtatg aggtgccac agctggggc agccacttc tgcggtgttg ccttagctcc
421 gggcgctgct gctacttcgc cgcgggtca gccaccaggc tgcagttctc cgaccaggct
481 ggggtgtctg tgctgtacac tgtcacactc tgggtggaat cctgggccag gaaccagaca
541 gagaagtctc ctgaggtgac cctgcagctc tacaactcag ttaaatatga gcctcctctg
601 ggagacatca aggtgtccaa gttggccggg cagctgcgta tggagtggga gaccccgat
661 aaccagggtg gtgtcaggt gcagttccg caccggacac ccagcagccc atggaagttg
721 ggcgactgct gacctcagga tgatgatact gactcctgcc tctgccccct ggagatgaat
781 gtggcccagg aattccagct ccgacgacgg cagctgggga gccaaaggaag ttcttgagc
841 aagtggagca gcccgtgtg cgttccccct gaaaacccc cacagctca ggtgagattc
901 tcggtggagc agctgggcca ggatgggagg aggcggctga ccctgaaaga gcagccaacc
961 cagctggagc ttccagaagg ctgtcaaggg ctggcgctg gcacggaggt cacttaccga
1021 ctacagctcc acatgtgtc ctgcccgtgt aaggccaagg ccaccaggac cctgcacctg
1081 ggggaagatgc cctatctctc ggggtgtgcc tacaactggg ctgtcatctc ctggaaccaa
1141 ttggctcctg gcctgaacca gacgtggcac attcctgccc acaccacac agaaccagtg
1201 gctctgaata tcagcgtcgg aaccaacggg accaccatgt attggccagc ccgggctcag
1261 agcatgacgt attgcattga atggcagcct gtgggcccagg acgggggcct tgccacctgc
1321 agcctgactg cgcgcgaaga cccggatccg gctggaatgg caacctacag ctggagtcca
1381 gagtctgggg caatggggca ggaaaagtgt tactacatta ccattcttgc ctctgcgcac
1441 cccgagaagc tcacctgtg gtctacggtc ctgtccacct accactttgg gggcaatgcc
1501 tcagcagctg ggacaccgca ccacgtctcg gtgaagaatc atagcttgga ctctgtgtct
1561 gtggagtggg caccatccct gctgagcacc tgtcccgcg tctaaagga gtatgttgc
1621 cgctgccgag atgaagacag caaacagggt tcagagcatc ccgtgcagcc cacagagacc
1681 caagttaccc tcagtggcct gcgggctggt gtagcctaca cggtgcaagt gcgagcagac
1741 acagcgtggc tgaggggtgt ctggagccag cccagcgcct tcagcatcga agtgacaggtt
1801 tctgattggc tcattctctt cgcctccctg gggagcttcc tgagcatcct tctcgtgggc
1861 gtccttggtc accttgacct gaacagggc gcacggcacc tgtgcccgcc gctgcccaca
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1981 ccagtggact tccaggaaga ggcattccctg caggaggccc tgggtgtaga gatgtcctgg
2041 gacaaaggcg agaggactga gcctctcgag aagacagagc tacctgaggg tgcccctgag
2101 ctggccctgg atacagagtt gtccttgag gatggagaca ggtgcaaggc caagatgtga
2161 tcgttgagc tcagagaggg tgagtgtct gcccgaggct acgtagcaca cacaggagtc
2221 acatttgga ccaaataacc cagagctcct ccaggctcca gtgcacctgc ctctctctg
2281 ccccgctgct gttccaccc atcctgcggg ggaaccctag atgctgcat gaaatggaag
2341 ctgctgcacc ctgctgggcc tggcatccgt ggggcaggag cagacctgc catttaacctg
2401 ttctggcgta gaatggactg ggaatggggg caaggggggc tcagatggat cctggaccc
2461 tgggctgggc atccaccccc aggagcactg gatggggagt ctggactcaa gggctccctg

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2521 cagcattgcg gggctcttga gcttggagga tccaggcata tagggaaggg ggctgtaaac
 2581 tttgtgggaa aaatgacggt cctcccatcc cccccccac cccacctca cccccctata
 2641 aaatgggggt ggtgataatg acctacaca gctgttcaaa atcatcgtaa atgagcctcc
 2701 tcttgggtat ttttttctg tttgaagctt gaatgtcctg ctcaaatctt caaaacacga
 2761 gccttggaat tcaaaaaaaaa aaaaaaaaaa a

Human IL-12R β 2 mRNA Variant 1

(SEQ ID NO: 8)

1 tgcagagcac agagaaagga catctgcgag gaaagttccc tgatggctgt caacaaagtg
 61 ccacgtctct atggctgtga acgctgagca cagattttaa tcgcgctat catatcttgg
 121 tgcataaacg cacctcacct cggccaaccc ttgctccgtc ttatgagaca ggctttatta
 181 tccgcatctt atatgagggg aaactgacgg tggagagaga attatcttgc tcaaggcgac
 241 acagcagagc ccacaggtgg cagaatccca cccgagcccg cttcgacccg cgggggtggaa
 301 accacgggag cccgcccggc tgcgcttcca gagctgaact gagaagcgag tcctctccgc
 361 cctgcgggcca cgcgccagcc ccgacccccc ccccgggccc atcctcaact gccgccagct
 421 ccccgcgccc accccggagt tgggtggcga gaggcgggag gcggagcgcg gagggcgggc
 481 gctggcaccg ggaacgcccc agcgccggca gagagcgcg agagcgcgac acgtgcggcc
 541 cagagcaccg gggccacccg gtccccgcag gcccgggacc gcgccgctg gcaggcgaca
 601 cgtggaagaa tacggagttc tataccagag ttgattgttg atggcacata ctttagagg
 661 atgctcattg gcatttatgt ttataatcac gtggctgttg attaaagcaa aaatagatgc
 721 gtgcaagaga ggcgatgtga ctgtgaagcc ttcccatgta atttacttg gatccactgt
 781 caatattaca tgctctttga agcccagaca aggtgcttt cactattcca gacgtaacaa
 841 gttaatcctg tacaagttg acagaagaat caattttcac catggccact ccctcaatte
 901 tcaagtcaaa ggtcttcccc ttgttacaac ctgtttgtc tgcaactgg cctgtatcaa
 961 tagtgatgaa attcaaatat gtggagcaga gatcttcgtt ggtgttgctc cagaacagcc
 1021 tcaaaattta tcctgcatac agaagggaga acaggggact gtggcctgca cctgggaaag
 1081 aggacgagac cccacttat aactgagta tactctacag ctaagtggac caaaaaattt
 1141 aacctggcag aagcaatgta aagacattta ttgtactat ttggactttg gaatcaacct
 1201 cccccctgaa tcacctgaat ccaatttcac agccaaggtt actgctgtca atagtcttgg
 1261 aagctcctct tcaattccat ccacattcac attcttgga atagtggagc ctcttcctcc
 1321 gtgggacatt agaatacaat ttcaaaaggc ttctgtgagc agatgtaccc tttattggag
 1381 agatgagggg atgtactgac ttaatcgact cagatatcgg ccagtaaca gcaggctctg
 1441 gaatatggtt aatgttaca aggccaaagg aagacatgat ttgctggatc tgaaccatt
 1501 tacagaatat gaatttcaga tttctctaa gctacatctt tataaggga gttggagtga
 1561 ttggagtga tcatagag cacaacacc agaagaagag cctactggga tgttagatgt
 1621 ctggtacatg aaacggcaca ttgactacag tagacaacag atttctctt tctggaagaa
 1681 tctgagtgtc tcagaggcaa gaggaataat tctccactat caggtgacct tgcaggagct
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 1801 tctagaacc ggaattggg ctgtggctgt gtctgcagca aattcaaaag gcagttctct
 1861 gccactcgt attaacataa tgaacctgtg tgaggcaggg ttgctggctc ctgccagggt
 1921 ctctgcaaac tcagagggca tggacaacat tctggtgact tggcagcctc ccaggaaaga

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1981 tccctctgct gttcaggagt acgtggtgga atggagagag ctccatccag ggggtgacac
 2041 acagggtccct ctaaaactggc tacggagtcg accctacaat gtgtctgctc tgatttcaga
 2101 gaacataaaa tcctacatct gttatgaaat ccgtgtgtat gcactctcag gggatcaagg
 2161 aggatgcagc tccatcctgg gtaactctaa gcacaaagca ccactgagtg gccccacat
 2221 taatgcatc acagaggaaa aggggagcat tttaatttca tggaacagca ttcagttcca
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 2581 gcaaaagggtg tttgttctcc tagcagccct cagacctcag tgggtgtagca gagaaattcc
 2641 agatccagca aatagcactt gcgctaagaa atatccatt gcagaggaga agacacagct
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 3181 gctgactctg gatcagttaa agatgagggtg tgactccctc atgctctgag tggtagaggct
 3241 tcaagcctta aagtcagtgt gccctcaacc agcacagcct gcccacattc cccagcccc
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 3721 cacattggct gttaatcact tggaatgtgt ttagcttgac tgaggaatta aattttgatt
 3781 gtaaatata atcgccacac atggctagtgt gctactgtat tggagtgcac agctctagat
 3841 ggctcctaga ttattgagag ccttcaaac aaatcaacct agttctatag atgaagacat
 3901 aaaagacact ggtaaacacc aaggtaaaag ggcccccaag gtggtcatga ctggtctcat
 3961 ttgcagaagt ctaagaatgt acctttttct ggccgggcgt ggtagctcat gcctgtaac
 4021 ccagcacttt gggaggctga

Human IL-12R β 2 mRNA Variant 2

(SEQ ID NO: 9)

1 tgcagagcac agagaaagga catctgcgag gaaagttccc tgatggctgt caacaaagtg
 61 ccacgtctct atggctgtga acgctgagca cagatttata tcgcgcctat catatcttgg
 121 tgcataaacg cacctcacct cggtaacccc ttgctccgtc ttatgagaca ggctttatta

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181 tccgcatttt atatgagggg aaactgacgg tggagagaga attatcttgc tcaaggcgac
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301 accacggggc cccgcccggc tgcgcttcca gagctgaact gagaagcgag tcctctccgc
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421 ccccgcgccc accccggagt tgggtggcgca gaggcgggag gcggaggcgg gagggcgggc
481 gctggcaccg ggaacgcccc agcgccggca gagagcggg agagcgcgac acgtgcggcc
541 cagagcaccg gggccacccc gtccccgcag gcccgggacc gcgcccgtg gcaggcgaca
601 cgtggtcacg gtgatccatt tgtaaagtcg ggaataaatg acctctgaag tgttgtctgt
661 atattgatct gctaccagta aaacatatct ctgaagaata cggagttcta taccagagtt
721 gattgttgat ggcacatact tttagaggat gctcattggc atttatgttt ataatacgt
781 ggctgttgat taaagcaaaa atagatgcgt gcaagagagg cgatgtgact gtgaagcctt
841 cccatgtaat tttacttga tccactgtca atattacatg ctctttgaag ccagacaag
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961 attttcacca tggccactcc ctcaattctc aagtcacagg tcttcccctt ggtacaacct
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1081 tcttcgttgg tgttgctcca gaacagcctc aaaatttate ctgcatacag aagggagaac
1141 aggggactgt ggctgcacc tgggaaagag gacgagacac ccacttatac actgagtata
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1261 gtgactatth ggactttgga atcaacctca ccctgaatc acctgaatcc aatttcacag
1321 ccaaggttac tgctgtcaat agtcttgga gctcctcttc acttccatcc acattcacat
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1561 gacatgattt gctggatctg aaaccattta cagaatatga atttcagatt tcctctaagc
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1681 aagaagagcc tactgggatg ttagatgtct ggtacatgaa acggcacatt gactacagta
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1921 ctgcagcaaa ttcaaaaggc agttctctgc ccaactgtat taacataatg aacctgtgtg
1981 aggcagggtt gctggctcct cgccaggtct ctgcaaacac agagggcagc gacaacatc
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2281 acaaagcacc actgagtggc cccacacatta atgccatcac agaggaaaag gggagcattt
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2401 tatactggaa ggaacgggac tccaactccc agcctcagct ctgtgaaatt ccctacagag
2461 tctcccaaaa ttcacatcca ataaacagcc tgcagccccc agtgacatat gtctgtgga

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 2641 tgggcatttt ctcaacgcac tacttccagc aaaagagaag acacagctgc ccttgacag
 2701 gctcctgata gactggccca cgctgaaga tctgaaccg ctggtcatca gtgaagtcct
 2761 tcatcaagtg accccagttt tcagacatcc cccctgtccc aactggccac aaagggaaaa
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 3241 gtcagtgtgc cctcaaccag cacagcctgc cccaattccc ccagcccctg cccagcagc
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 3601 gctacacagc aggtgtgtaca cagcagatca gtactgttca acagaacttc ctgagatgat
 3661 ggaaatgttc tacctctgca ctcaactgtc agtacattag acactaggca cattggctgt
 3721 taatcacttg gaatgtgttt agcttgactg aggaattaaa ttttgattgt aaatttaaat
 3781 cgccacacat ggctagtggc tactgtattg gagtgacag ctctagatgg ctctagatt
 3841 attgagagcc ttcaaaacaa atcaacctag ttctatagat gaagacataa aagacactgg
 3901 taaacaccaa ggtaaaaggg cccccaagggt ggtcatgact ggtctcattt gcagaagtct
 3961 aagaatgtac ctttttctgg ccgggctgg tagctcatgc ctgtaatccc agcactttgg
 4021 gaggtga

Human IL-12R β 2 mRNA Variant 3

(SEQ ID NO: 10)

1 tgcagagcac agagaaagga catctgcgag gaaagttccc tgatggctgt caacaaagtg
 61 ccacgtctct atggtgtgtga acgctgagca cagattttaa tcgcgcctat catatcttgg
 121 tgcataaacg cacctcacct cggtaacccc ttgctccgtc ttatgagaca ggctttatta
 181 tccgcatttt atatgagggg aaactgacgg tggagagaga attatcttgc tcaaggcgac
 241 acagcagagc ccacaggtgg cagaatccca cccgagcccg cttcgaccgg cggggtggaa
 301 accacgggag cccgcccggc tgcgcttcca gagctgaact gagaagcgag tcctctccgc
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 421 ccccgcgccc accccggagt tggtggcgca gaggcgggag gcggaggcgg gagggcgggc
 481 gctggcaccg ggaacgcccg agcgccggca gagagcggg agagcggac acgtgcggcc
 541 cagagcaccg gggccacccc gtccccgacg gcccgggacc gcgcccgtg gcaggcgaca
 601 cgtggaagaa tacggagttc tataccagag ttgattgttg atggcacata ctttttaggg
 661 atgctcattg gcatttatgt ttataatcac gtggctgttg attaaagcaa aaatagatgc

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721 gtgcaagaga ggcgatgtga ctgtgaagcc ttcccatgta attttacttg gatccactgt
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2521 agtgacccca gttttcagac atccccctg ctccaactgg ccacaaaggg aaaaaggaaat
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 3661 ccaaggtaaa agggccccc aagtggtcat gactggtctc atttgcagaa gtctaagaat
 3721 gtaccttttt ctggccgggc gtggtagctc atgctgttaa tcccagcact ttgggaggct
 3781 ga

Human IL-12R β 2 mRNA Variant 4

(SEQ ID NO: 11)

1 tgcagagcac agagaaagga catctgcgag gaaagttccc tgatggctgt caacaaagtg
 61 ccacgtctct atggctgtga acgctgagca cagattttta tcgcgcctat catatcttgg
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 421 ccccgcgccc accccggagt tgggtggcga gaggcgggag gcggaggcgg gagggcgggc
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 541 cagagcaccg gggccacccc gtccccgcag gcccgggacc gcgccgctg gcaggcgaca
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 3241 agggccttaa aattacatcc ttcactgtgt ggacctagag actccaactt gaattcctag
 3301 taactttctt ggtatgctgg ccagaaaggg aaatgaggag gagagtagaa accacagctc
 3361 ttagtagtaa tggcatacag tctagaggac cattcatgca atgactattt ctaagccac
 3421 tgctacacag caggctgtac acagcagatc agtactgttc aacagaactt cctgagatga
 3481 tggaaatgtt ctacctctgc actcactgtc cagtacatta gacactaggc acattggctg
 3541 ttaatcactt ggaatgtgtt tagcttgact gaggaattaa attttgattg taaatttaa
 3601 tgcacacaa tggctagtgg ctactgtatt ggagtgcaca gctctagatg gctcctagat
 3661 tattgagagc cttcaaaaca aatcaaccta gttctataga tgaagacata aaagacactg
 3721 gtaaacacca aggtaaaagg gcccacaagg tggctcatgac tggctctcatt tgcagaagtc

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3781 taagaatgta cctttttctg gccgggctg gtagctcatg cctgtaatcc cagcactttg

3841 ggaggctga

Human IL-23R mRNA

(SEQ ID NO: 12)

1 acaagggttg cagcctggct ctgaagtgga attatgtgct tcaaacaggt tgaaagaggg
 61 aaacagtctt ttctgcttc cagacatgaa tcaggtcact attcaatggg atgcagtaat
 121 agccctttac atactcttca gctgggtgtca tggaggaatt acaaataaa actgctctgg
 181 ccacatctgg gtagaaccag ccacaatctt taagatgggt atgaatatct ctatatattg
 241 ccaagcagca attaagaact gccaccaag gaaacttcatt tttataaaa atggcatcaa
 301 agaaagattt caaatcaca ggattaataa aacaacagct cggctttggg ataaaaactt
 361 tctggaacca catgcttcta tgtactgcac tgcagaatgt cccaaacatt ttcaagagac
 421 actgatattg ggaaaagaca ttctctctgg ataccgccca gatattcctg atgaagtaac
 481 ctgtgtcatt tatgaatatt caggcaacat gacttgacc tggaatgctg ggaagtcac
 541 ctacatagac acaaaatcag tgggtacatg gaagagtta gagacagaag aagagcaaca
 601 gtatctcacc tcaagctata ttaacatctc cactgattca ttacaagggt gcaagaagta
 661 cttggtttgg gtccaagcag caaacgcact aggcattgaa gagtcaaaac aactgcaaat
 721 tcacctggat gatatagtga taccttctgc agccgtcatt tccagggtg agactataaa
 781 tgcacagtg cccaagacca taatttattg ggatagtcaa acaacaattg aaaaggtttc
 841 ctgtgaaatg agatacaagg ctacaacaaa ccaaacttgg aatgttaaag aatttgacac
 901 caattttaca tatgtgcaac agtcagaatt ctacttgag ccaaacatta agtacgtatt
 961 tcaagtgaga tgtcaagaaa caggcaaaag gtactggcag ccttgagatt caccgttttt
 1021 tcataaaaca cctgaaacag ttccccagg caccataaaa gcattccaac atgacacatg
 1081 gaattctggg ctaacagttg cttccatctc tacagggcac ctacttctg acaacagagg
 1141 agacattgga cttttattgg gaatgatcgt ctttgctgtt atgttgtcaa ttctttcttt
 1201 gattgggata ttttaacagat cattccgaac tgggattaaa agaaggatct tattgttaat
 1261 accaaagtgg cttttatgaag atattcctaa tatgaaaaac agcaatgttg tgaaaatgct
 1321 acaggaaaaat agtgaactta tgaataataa ttccagttag caggtcctat atgttgatcc
 1381 catgattaca gagataaaag aaatcttcat ccagaacac aagcctacag actacaagaa
 1441 ggagaataca ggaccctcgg agacaagaga ctaccgcga aactcgctat tcgacaatac
 1501 tacagtgtga tatattcctg atctcaacac tggatataaa ccccaaattt caaattttct
 1561 gcctgagggg agccatctca gcaataataa tgaaattact tccttaacac ttaaaccacc
 1621 agttgattcc ttagactcag gaaataatcc caggttaca aagcatccta attttgcttt
 1681 ttctgtttca agtgtaatt cactaagcaa cacaatattt cttggagaat taagcctcat
 1741 attaaatcaa ggagaatgca gttctcctga cataaaaaa tcagtagagg aggaaaccac
 1801 catgcttttg gaaaatgatt caccagtgga aactattcca gaacagacc tgcttctctga
 1861 tgaatttgct tcctgtttgg ggatcgtgaa tgaggagtgt ccacttatta atacttattt
 1921 tccacaaaat tttttggaaa gccacttcaa taggatttca ctcttggaag agtagagctg
 1981 tgtgggtcaaa atcaatatga gaaagctgcc ttgcaatctg aacttggttt ttccctgcaa
 2041 tagaaattga attctgcctc tttttgaaaa aaatgtattc acatacaaat cttcacatgg
 2101 acacatgttt tcatttccct tggataaata cctaggtagg ggattgctgg gccatatgat
 2161 aagcatatgt ttcagttcta ccaatcttgt ttccagagta gtgacatttc tgtgctccta

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2221 ccataccat gtaagaattc cgggagctc catgcctttt taatttttagc cattcttctg
2281 cctcatttct taaaattaga gaattaaggt ccgaaggtg gaacatgctt catggtcaca
2341 catacaggca caaaacagc attatgtgga cgcctcatgt attttttata gagtcaacta
2401 tttcctcttt attttccctc attgaaagat gcaaacagc tctctattgt gtacagaaag
2461 ggtaataaat gcaaaatacc tggtagtaaa ataaatgctg aaaattttcc tttaaaatag
2521 aatcattagg ccaggcgtgg tggtcatgc ttgtaatccc agcactttgg taggctgagg
2581 tgggtggatc acctgaggtc aggagttcga gtccagcctg gccaatatgc tgaaacctg
2641 tctctactaa aattacaaaa attagccggc catggtggca ggtgcttgta atcccagcta
2701 cttgggaggg tgaggcagga gaatcacttg aaccaggaag gcagaggttg cactgagctg
2761 agattgtgcc actgcactcc agcctgggca acaagagcaa aactctgtct ggaaaaaaaa
2821 aaaaaa

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[0268] An antisense nucleic acid molecule can be complementary to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein. Non-coding regions (5' and 3' untranslated regions) are the 5' and 3' sequences that flank the coding region in a gene and are not translated into amino acids.

[0269] Based upon the sequences disclosed herein, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense nucleic acids to target a nucleic acid encoding an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein described herein. Antisense nucleic acids targeting a nucleic acid encoding an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein can be designed using the software available at the Integrated DNA Technologies website.

[0270] An antisense nucleic acid can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides or more in length. An antisense oligonucleotide can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used.

[0271] Examples of modified nucleotides which can be used to generate an antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil,

4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methyl-ester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest).

[0272] The antisense nucleic acid molecules described herein can be prepared in vitro and administered to a mammal, e.g., a human. Alternatively, they can be generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein to thereby inhibit expression, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarities to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. The antisense nucleic acid molecules can be delivered to a mammalian cell using a vector (e.g., a lentivirus, a retrovirus, or an adenovirus vector).

[0273] An antisense nucleic acid can be an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual, β -units, the strands run parallel to each other (Gaultier et al., *Nucleic Acids Res.* 15:6625-6641, 1987). The antisense nucleic acid can also comprise a 2'-O-methylribonucleotide (Inoue et al., *Nucleic Acids Res.* 15:6131-6148, 1987) or a chimeric RNA-DNA analog (Inoue et al., *FEBS Lett.* 215:327-330, 1987). Non-limiting examples of antisense nucleic acids are described in Vaknin-Dembinsky et al., *J. Immunol.* 176(12): 7768-7774, 2006.

[0274] Another example of an inhibitory nucleic acid is a ribozyme that has specificity for a nucleic acid encoding an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein (e.g., specificity for an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA, e.g., specificity for any one of SEQ ID NOs: 1-12). Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-

stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach, *Nature* 334:585-591, 1988)) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA can be designed based upon the nucleotide sequence of any of the IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, and IL-23R mRNA sequences disclosed herein. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA (see, e.g., U.S. Pat. Nos. 4,987,071 and 5,116,742). Alternatively, an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel et al., *Science* 261:1411-1418, 1993.

[0275] An inhibitor nucleic acid can also be a nucleic acid molecule that forms triple helical structures. For example, expression of an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein (e.g., the promoter and/or enhancer, e.g., a sequence that is at least 1 kb, 2 kb, 3 kb, 4 kb, or 5 kb upstream of the transcription initiation start state) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene, *Anticancer Drug Des.* 6(6):569-84, 1991; Helene, *Ann. N. Y. Acad. Sci.* 660:27-36, 1992; and Maher, *Bioassays* 14(12):807-15, 1992.

[0276] In various embodiments, inhibitory nucleic acids can be modified at the base moiety, sugar moiety, or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see, e.g., Hyrup et al., *Bioorganic Medicinal Chem.* 4(1):5-23, 1996). Peptide nucleic acids (PNAs) are nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs allows for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols (see, e.g., Perry-O'Keefe et al., *Proc. Natl. Acad. Sci. U.S.A.* 93:14670-675, 1996). PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication.

[0277] PNAs can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity.

PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation.

[0278] The synthesis of PNA-DNA chimeras can be performed as described in Finn et al., *Nucleic Acids Res.* 24:3357-63, 1996. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al., *Nucleic Acids Res.* 17:5973-88, 1989). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al., *Nucleic Acids Res.* 24:3357-63, 1996). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser et al., *Bioorganic Med. Chem. Lett.* 5:1119-1124, 1975).

[0279] In some embodiments, the inhibitory nucleic acids can include other appended groups such as peptides, or agents facilitating transport across the cell membrane (see, Letsinger et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556, 1989; Lemaitre et al., *Proc. Natl. Acad. Sci. U.S.A.* 84:648-652, 1989; and WO 88/09810). In addition, the inhibitory nucleic acids can be modified with hybridization-triggered cleavage agents (see, e.g., Krol et al., *Bio/Techniques* 6:958-976, 1988) or intercalating agents (see, e.g., Zon, *Pharm. Res.* 5:539-549, 1988). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[0280] Another means by which expression of an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA can be decreased in a mammalian cell is by RNA interference (RNAi). RNAi is a process in which mRNA is degraded in host cells. To inhibit an mRNA, double-stranded RNA (dsRNA) corresponding to a portion of the gene to be silenced (e.g., a gene encoding an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R protein) is introduced into a mammalian cell. The dsRNA is digested into 21-23 nucleotide-long duplexes called short interfering RNAs (or siRNAs), which bind to a nuclease complex to form what is known as the RNA-induced silencing complex (or RISC). The RISC targets the homologous transcript by base pairing interactions between one of the siRNA strands and the endogenous mRNA. It then cleaves the mRNA about 12 nucleotides from the 3' terminus of the siRNA (see Sharp et al., *Genes Dev.* 15:485-490, 2001, and Hammond et al., *Nature Rev. Gen.* 2:110-119, 2001).

[0281] RNA-mediated gene silencing can be induced in a mammalian cell in many ways, e.g., by enforcing endogenous expression of RNA hairpins (see, Paddison et al., *Proc. Natl. Acad. Sci. U.S.A.* 99:1443-1448, 2002) or, as noted above, by transfection of small (21-23 nt) dsRNA (reviewed in Caplen, *Trends Biotech.* 20:49-51, 2002). Methods for modulating gene expression with RNAi are described, e.g., in U.S. Pat. No. 6,506,559 and US 2003/0056235, which are hereby incorporated by reference.

[0282] Standard molecular biology techniques can be used to generate siRNAs. Short interfering RNAs can be chemically synthesized, recombinantly produced, e.g., by expressing RNA from a template DNA, such as a plasmid, or obtained from commercial vendors, such as Dharmacon.

The RNA used to mediate RNAi can include synthetic or modified nucleotides, such as phosphorothioate nucleotides. Methods of transfecting cells with siRNA or with plasmids engineered to make siRNA are routine in the art.

[0283] The siRNA molecules used to decrease expression of an IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA can vary in a number of ways. For example, they can include a 3' hydroxyl group and strands of 21, 22, or 23 consecutive nucleotides. They can be blunt ended or include an overhanging end at either the 3' end, the 5' end, or both ends. For example, at least one strand of the RNA molecule can have a 3' overhang from about 1 to about 6 nucleotides (e.g., 1-5, 1-3, 2-4 or 3-5 nucleotides (whether pyrimidine or purine nucleotides) in length. Where both strands include an overhang, the length of the overhangs may be the same or different for each strand.

[0284] To further enhance the stability of the RNA duplexes, the 3' overhangs can be stabilized against degradation (by, e.g., including purine nucleotides, such as adenosine or guanosine nucleotides or replacing pyrimidine nucleotides by modified analogues (e.g., substitution of uridine 2-nucleotide 3' overhangs by 2'-deoxythymidine is tolerated and does not affect the efficiency of RNAi). Any siRNA can be used in the methods of decreasing IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R mRNA, provided it has sufficient homology to the target of interest (e.g., a sequence present in any one of SEQ ID NOs: 1-15, e.g., a target sequence encompassing the translation start site or the first exon of the mRNA). There is no upper limit on the length of the siRNA that can be used (e.g., the siRNA can range from about 21 base pairs of the gene to the full length of the gene or more (e.g., about 20 to about 30 base pairs, about 50 to about 60 base pairs, about 60 to about 70 base pairs, about 70 to about 80 base pairs, about 80 to about 90 base pairs, or about 90 to about 100 base pairs).

[0285] Non-limiting examples of siRNAs targeting IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R are described in Tan et al., *J. Alzheimers Dis.* 38(3): 633-646, 2014; Niimi et al., *J. Neuroimmunol.* 254(1-2):39-45, 2013. Non-limiting examples of short hairpin RNA (shRNA) targeting IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R are described in Bak et al., *BMC Dermatol.* 11:5, 2011.

[0286] Non-limiting examples of inhibitory nucleic acids are microRNAs (e.g., microRNA-29 (Brain et al., *Immunity* 39(3):521-536, 2013), miR-10a (Xue et al., *J. Immunol.* 187(11):5879-5886, 2011), microRNA-155 (Podsiad et al., *Am. J. Physiol. Lung Cell Mol. Physiol.* 310(5):L465-75, 2016).

[0287] In some embodiments, a therapeutically effective amount of an inhibitory nucleic acid targeting IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R can be administered to a subject (e.g., a human subject) in need thereof.

[0288] In some embodiments, the inhibitory nucleic acid can be about 10 nucleotides to about 40 nucleotides (e.g., about 10 to about 30 nucleotides, about 10 to about 25 nucleotides, about 10 to about 20 nucleotides, about 10 to about 15 nucleotides, 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23

nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, 30 nucleotides, 31 nucleotides, 32 nucleotides, 33 nucleotides, 34 nucleotides, 35 nucleotides, 36 nucleotides, 37 nucleotides, 38 nucleotides, 39 nucleotides, or 40 nucleotides) in length. One skilled in the art will appreciate that inhibitory nucleic acids may comprise at least one modified nucleic acid at either the 5' or 3' end of DNA or RNA.

[0289] Any of the inhibitor nucleic acids described herein can be formulated for administration to the gastrointestinal tract. See, e.g., the formulation methods described in US 2016/0090598 and Schoellhammer et al., *Gastroenterology*, doi: 10.1053/j.gastro.2017.01.002, 2017.

[0290] As is known in the art, the term "thermal melting point (T_m)" refers to the temperature, under defined ionic strength, pH, and inhibitory nucleic acid concentration, at which 50% of the inhibitory nucleic acids complementary to the target sequence hybridize to the target sequence at equilibrium. In some embodiments, an inhibitory nucleic acid can bind specifically to a target nucleic acid under stringent conditions, e.g., those in which the salt concentration is at least about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30° C. for short oligonucleotides (e.g., 10 to 50 nucleotide). Stringent conditions can also be achieved with the addition of destabilizing agents such as formamide.

[0291] In some embodiments of any of the inhibitory nucleic acids described herein, the inhibitory nucleic acid binds to a target nucleic acid (e.g., a nucleic acid encoding any one of IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R) with a T_m of greater than 20° C., greater than 22° C., greater than 24° C., greater than 26° C., greater than 28° C., greater than 30° C., greater than 32° C., greater than 34° C., greater than 36° C., greater than 38° C., greater than 40° C., greater than 42° C., greater than 44° C., greater than 46° C., greater than 48° C., greater than 50° C., greater than 52° C., greater than 54° C., greater than 56° C., greater than 58° C., greater than 60° C., greater than 62° C., greater than 64° C., greater than 66° C., greater than 68° C., greater than 70° C., greater than 72° C., greater than 74° C., greater than 76° C., greater than 78° C., or greater than 80° C., e.g., as measured in phosphate buffered saline using a UV spectrophotometer.

[0292] In some embodiments of any of the inhibitor nucleic acids described herein, the inhibitory nucleic acid binds to a target nucleic acid (e.g., a nucleic acid encoding any one of IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R) with a T_m of about 20° C. to about 80° C., about 78° C., about 76° C., about 74° C., about 72° C., about 70° C., about 68° C., about 66° C., about 64° C., about 62° C., about 60° C., about 58° C., about 56° C., about 54° C., about 52° C., about 50° C., about 48° C., about 46° C., about 44° C., about 42° C., about 40° C., about 38° C., about 36° C., about 34° C., about 32° C., about 30° C., about 28° C., about 26° C., about 24° C., or about 22° C. (inclusive); about 22° C. to about 80° C., about 78° C., about 76° C., about 74° C., about 72° C., about 70° C., about 68° C., about 66° C., about 64° C., about 62° C., about 60° C., about 58° C., about 56° C., about 54° C., about 52° C., about 50° C., about 48° C., about 46° C., about 44° C., about 42° C., about 40° C., about 38° C., about 36° C., about 34° C., about 32° C., about 30° C., about 28° C., about 26° C., or about 24° C. (inclusive); about 24° C. to about 80° C., about 78° C., about 76° C., about 74° C., about 72° C., about 70° C.

[illegible][illegible]

[0293] In some embodiments, the inhibitory nucleic acid can be formulated in a nanoparticle (e.g., a nanoparticle including one or more synthetic polymers, e.g., Patil et al., *Pharmaceutical Nanotechnol.* 367:195-203, 2009; Yang et al., *ACS Appl. Mater. Interfaces*, doi: 10.1021/acsaami.6b16556, 2017; Perepeluk et al., *Mol. Ther. Nucleic Acids* 6:259-268, 2017). In some embodiments, the nanoparticle can be a mucoadhesive particle (e.g., nanoparticles having a positively-charged exterior surface) (Andersen et al., *Methods Mol. Biol.* 555:77-86, 2009). In some embodiments, the nanoparticle can have a neutrally-charged exterior surface.

[0294] In some embodiments, the inhibitory nucleic acid can be formulated, e.g., as a liposome (Buyens et al., *J Control Release* 158(3): 362-370, 2012; Scarabel et al., *Expert Opin. Drug Deliv.* 17:1-14, 2017), a micelle (e.g., a mixed micelle) (Tangsangsakrati et al., *BioMacromolecules* 17:246-255, 2016; Wu et al., *Nanotechnology*, doi: 10.1088/1361-6528/aa6519, 2017), a microemulsion (WO 11/004395), a nanoemulsion, or a solid lipid nanoparticle (Sahay et al., *Nature Biotechnol.* 31:653-658, 2013; and Lin et al., *Nanomedicine* 9(1):105-120, 2014). Additional exem-

plary structural features of inhibitory nucleic acids and formulations of inhibitory nucleic acids are described in US 2016/0090598.

[0295] In some embodiments, a pharmaceutical composition can include a sterile saline solution and one or more inhibitory nucleic acid (e.g., any of the inhibitory nucleic acids described herein). In some examples, a pharmaceutical composition consists of a sterile saline solution and one or more inhibitory nucleic acid (e.g., any of the inhibitory nucleic acids described herein). In certain embodiments, the sterile saline is a pharmaceutical grade saline. In certain embodiments, a pharmaceutical composition can include one or more inhibitory nucleic acid (e.g., any of the inhibitory nucleic acids described herein) and sterile water. In certain embodiments, a pharmaceutical composition consists of one or more inhibitory nucleic acid (e.g., any of the inhibitory nucleic acids described herein) and sterile water. In certain embodiments, a pharmaceutical composition includes one or more inhibitory nucleic acid (e.g., any of the inhibitory nucleic acids described herein) and phosphate-buffered saline (PBS). In certain embodiments, a pharmaceutical composition consists of one or more inhibitory nucleic acids (e.g., any of the inhibitory nucleic acids described herein) and sterile phosphate-buffered saline (PBS). In some examples, the sterile saline is a pharmaceutical grade PBS.

[0296] In certain embodiments, one or more inhibitory nucleic acids (e.g., any of the inhibitory nucleic acids described herein) may be admixed with pharmaceutically acceptable active and/or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions depend on a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

[0297] Pharmaceutical compositions including one or more inhibitory nucleic acids encompass any pharmaceutically acceptable salts, esters, or salts of such esters. Non-limiting examples of pharmaceutical compositions include pharmaceutically acceptable salts of inhibitory nucleic acids. Suitable pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts.

[0298] Also provided herein are prodrugs that can include additional nucleosides at one or both ends of an inhibitory nucleic acid which are cleaved by endogenous nucleases within the body, to form the active inhibitory nucleic acid.

[0299] Lipid moieties can be used to formulate an inhibitory nucleic acid. In certain such methods, the inhibitory nucleic acid is introduced into preformed liposomes or lipoplexes made of mixtures of cationic lipids and neutral lipids. In certain methods, inhibitory nucleic acid complexes with mono- or poly-cationic lipids are formed without the presence of a neutral lipid. In certain embodiments, a lipid moiety is selected to increase distribution of an inhibitory nucleic acid to a particular cell or tissue in a mammal. In some examples, a lipid moiety is selected to increase distribution of an inhibitory nucleic acid to fat tissue in a mammal. In certain embodiments, a lipid moiety is selected to increase distribution of an inhibitory nucleic acid to muscle tissue.

[0300] In certain embodiments, pharmaceutical compositions provided herein comprise one or more inhibitory nucleic acid and one or more excipients. In certain such embodiments, excipients are selected from water, salt solu-

tions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

[0301] In some examples, a pharmaceutical composition provided herein includes liposomes and emulsions. Liposomes and emulsions can be used to formulate hydrophobic compounds. In some examples, certain organic solvents such as dimethylsulfoxide are used.

[0302] In some examples, a pharmaceutical composition provided herein includes one or more tissue-specific delivery molecules designed to deliver one or more inhibitory nucleic acids to specific tissues or cell types in a mammal. For example, a pharmaceutical composition can include liposomes coated with a tissue-specific antibody.

[0303] In some embodiments, a pharmaceutical composition provided herein can include a co-solvent system. Examples of such co-solvent systems include benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™ and 65% w/v polyethylene glycol 300. As can be appreciated, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0304] In some examples, a pharmaceutical composition can be formulated for oral administration. In some examples, pharmaceutical compositions are formulated for buccal administration.

[0305] In some examples, a pharmaceutical composition is formulated for administration by injection (e.g., intravenous, subcutaneous, intramuscular, etc.). In some of these embodiments, a pharmaceutical composition includes a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In some examples, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In some examples, injectable suspensions are prepared using appropriate liquid carriers, suspending agents, and the like. Some pharmaceutical compositions for injection are formulated in unit dosage form, e.g., in ampoules or in multi-dose containers. Some pharmaceutical compositions for injection are suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, and/or dispersing agents. Solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes.

Antibodies

[0306] In some embodiments, the IL-12/IL-23 inhibitor is an antibody or an antigen-binding fragment thereof (e.g., a Fab or a scFv). In some embodiments, an antibody or antigen-binding fragment described herein binds specifically to any one of IL-12A (p35), IL-12B (p40), IL-23 (p19), IL-12R β 1, IL-12R β 2, or IL-23R, or a combination thereof.

[0307] In some embodiments, the antibody can be a humanized antibody, a chimeric antibody, a multivalent antibody, or a fragment thereof. In some embodiments, an

antibody can be a scFv-Fc, a V_H -H domain, a V_{NAR} domain, a (scFv)₂, a minibody, or a BiTE. In some embodiments, an antibody can be a DVD-Ig, and a dual-affinity re-targeting antibody (DART), a triomab, kih IgG with a common LC, a crossmab, an ortho-Fab IgG, a 2-in-1-IgG, IgG-ScFv, scFv₂-Fc, a bi-nanobody, tandem antibody, a DART-Fc, a scFv-HAS-scFv, DNL-Fab3, DAF (two-in-one or four-in-one), DutaMab, DT-IgG, knobs-in-holes common LC, knobs-in-holes assembly, charge pair antibody, Fab-arm exchange antibody, SEEDbody, Triomab, LUZ-Y, Fcab, k λ -body, orthogonal Fab, DVD-IgG, IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)-IgG, IgG(L,H)-Fc, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFv, 2scFv-IgG, IgG-2scFv, scFv4-Ig, Zyboby, DVI-IgG, nanobody, nanobody-HSA, a diabody, a TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, Triple Body, miniantibody, minibody, TriBi minibody, scFv-CH3 KIH, Fab-scFv, scFv-CH-CL-scFv, F(ab')₂-scFv₂, scFv-KIH, Fab-scFv-Fc, tetravalent HCAB, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, intrabody, dock and lock bispecific antibody, ImmTAC, HSAbody, scDiabody-HAS, tandem scFv, IgG-IgG, Cov-X-Body, and scFv1-PEG-scFv2.

[0308] Non-limiting examples of an antigen-binding fragment of an antibody include an Fv fragment, a Fab fragment, a F(ab')₂ fragment, and a Fab' fragment. Additional examples of an antigen-binding fragment of an antibody is an antigen-binding fragment of an IgG (e.g., an antigen-binding fragment of IgG1, IgG2, IgG3, or IgG4) (e.g., an antigen-binding fragment of a human or humanized IgG, e.g., human or humanized IgG1, IgG2, IgG3, or IgG4); an antigen-binding fragment of an IgA (e.g., an antigen-binding fragment of IgA1 or IgA2) (e.g., an antigen-binding fragment of a human or humanized IgA, e.g., a human or humanized IgA1 or IgA2); an antigen-binding fragment of an IgD (e.g., an antigen-binding fragment of a human or humanized IgD); an antigen-binding fragment of an IgE (e.g., an antigen-binding fragment of a human or humanized IgE); or an antigen-binding fragment of an IgM (e.g., an antigen-binding fragment of a human or humanized IgM).

[0309] In some embodiments, the antibody is a humanized antibody, a chimeric antibody, a multivalent antibody, or a fragment thereof. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a humanized monoclonal antibody. See e.g., Hunter & Jones, *Nat. Immunol.* 16:448-457, 2015; Heo et al., *Oncotarget* 7(13):15460-15473, 2016. Additional examples of antibodies and antigen-binding fragments thereof are described in U.S. Pat. Nos. 8,440,196; 7,842,144; 8,034,344; and 8,529,895; US 2013/0317203; US 2014/0322239; US 2015/0166666; US 2016/0152714; and US 2017/0002082, each of which is incorporated by reference in its entirety.

[0310] In some embodiments, the antibody is ustekinumab (CNTO 1275, Stelara®) or a variant thereof (Krueger et al., *N. Engl. J. Med.* 356(6):580-592, 2007; Kauffman et al., *J. Invest. Dermatol.* 123(6):1037-1044, 2004; Gottlieb et al., *Curr. Med. Res. Opin.* 23(5):1081-1092, 2007; Leonardi et al., *Lancet* 371(9625):1665-1674, 2008; Papp et al., *Lancet* 371(9625):1675-1684, 2008). In some embodiments, the antibody is briakinumab (ABT-874, J-695) or a variant thereof (Gordon et al., *J. Invest. Dermatol.* 132(2):304-314, 2012; Kimball et al., *Arch Dermatol.* 144(2): 200-207, 2008).

[0311] In some embodiments, the antibody is guselkumab (CNTO-1959) (Callis-Duffin et al., *J. Am. Acad. Dermatol.*

70(5 Suppl 1), 2014); AB162 (Sofen et al., *J. Allergy Clin. Immunol.* 133: 1032-40, 2014); tildrakizumab (MK-3222, SCH900222) (Papp et al. (2015) *Br. J. Dermatol.* 2015); Langley et al., Oral Presentation at: American Academy of Dermatology, March 21-25, Denver Colo., 2014); AMG 139 (MEDI2070, brazikumab) (Gomollon, *Gastroenterol. Hepatol.* 38(Suppl. 1):13-19, 2015; Kock et al., *Br. J. Pharmacol.* 172(1):159-172, 2015); FM-202 (Tang et al., *Immunology* 135(2): 112-124, 2012); FM-303 (Tang et al., *Immunology* 135(2): 112-124, 2012); ADC-1012 (Tang et al., *Immunology* 135(2):112-124, 2012); LY-2525623 (Gaffen et al., *Nat. Rev. Immunol.* 14:585-600, 2014; Sands, *Gastroenterol. Hepatol.* 12(12):784-786, 2016), LY-3074828 (Coskun et al., *Trends Pharmacol. Sci.* 38(2):127-142, 2017), BI-655066 (risankizumab) (Singh et al., *MAbs* 7(4):778-791, 2015; Krueger et al., *J. Allergy Clin. Immunol.* 136(1): 116-124, 2015) or a variant thereof.

[0312] See e.g., Tang et al., *Immunology* 135(2):112-124, 2012. Further teachings of IL-12/IL-23 antibodies and antigen-binding fragments thereof are described in U.S. Pat. Nos. 6,902,734; 7,247,711; 7,252,971; and 7,491,391; US 2012/0288494; and US 2013/0302343, each of which is incorporated by reference in its entirety.

[0313] In some embodiments, the IL-12/IL-23 inhibitor is PTG-200, an IL-23R inhibitor currently in preclinical development by Protagonist Therapeutics.

[0314] In some embodiments, the IL-12/IL-23 inhibitor is Mirikizumab (LY 3074828), an IL-23R inhibitor currently in clinical development (Phase II) by Eli Lilly.

[0315] In some embodiments, the IL-12/IL-23 inhibitor is AK-101 (Akeso Biopharma Inc), a monoclonal antibody.

[0316] In some embodiments, the inhibitor is one of the following:

Common Name	Brand name	Company
ustekinumab (CNTO 1275)	Stelara	Janssen
brazikumab (AMG 139, MEDI2070)		AZ licensed to Allergan
risankizumab (BI-655066)		Abbvie & BI collaboration
briakinumab (ABT-874, J-695)		Abbvie
guselkumab (CNTO-1959)		Janssen (from MorphoSys)
tildrakizumab (MK-3222, SCH900222)		Sun Pharmaceuticals
LY-2525623		Eli Lilly
Mirikizumab (LY 3074828)		Eli Lilly
FM-303		Femta
AK-101	TBD	Akeso Biopharma Inc

In some embodiments, the inhibitor is:

STA-5326 (apilimod) or a variant thereof (Keino et al., *Arthritis Res. Ther.* 10: R122, 2008; Wada et al., *Blood* 109(3):1156-1164, 2007; Sands et al., *Inflamm. Bowel Dis.* 16(7):1209-1218, 2010).

[0317] In some embodiments, any of the antibodies or antigen-binding fragments described herein has a dissociation constant (K_D) of less than 1×10^{-5} M (e.g., less than 0.5×10^{-5} M, less than 1×10^{-6} M, less than 0.5×10^{-6} M, less than 1×10^{-7} M, less than 0.5×10^{-7} M, less than 1×10^{-8} M,

less than 0.5×10^{-8} M, less than 1×10^{-9} M, less than 0.5×10^{-9} M, less than 1×10^{-10} M, less than 0.5×10^{-10} M, less than 1×10^{-11} M, less than 0.5×10^{-11} M, or less than 1×10^{-12} M), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

[0318] In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_D of about 1×10^{-12} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, about 1×10^{-9} M, about 0.5×10^{-9} M, about 1×10^{-10} M, about 0.5×10^{-10} M, about 1×10^{-11} M, or about 0.5×10^{-11} M (inclusive); about 0.5×10^{-11} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, about 1×10^{-9} M, about 0.5×10^{-9} M, about 1×10^{-10} M, or about 0.5×10^{-10} M (inclusive); about 1×10^{-11} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, about 1×10^{-9} M, about 0.5×10^{-9} M, about 1×10^{-10} M, or about 0.5×10^{-10} M (inclusive); about 0.5×10^{-10} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, about 1×10^{-9} M, about 0.5×10^{-9} M, or about 1×10^{-10} M (inclusive); about 1×10^{-10} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, about 1×10^{-9} M, or about 0.5×10^{-9} M (inclusive); about 0.5×10^{-9} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, about 0.5×10^{-8} M, or about 0.5×10^{-9} M (inclusive); about 1×10^{-9} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, about 1×10^{-8} M, or about 0.5×10^{-8} M (inclusive); about 0.5×10^{-8} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, about 0.5×10^{-7} M, or about 0.5×10^{-8} M (inclusive); about 0.5×10^{-8} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, about 1×10^{-7} M, or about 0.5×10^{-7} M (inclusive); about 0.5×10^{-7} M to about 1×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, about 0.5×10^{-6} M, or about 1×10^{-7} M (inclusive); about 1×10^{-7} M to about 0.5×10^{-5} M, about 0.5×10^{-5} M, about 1×10^{-6} M, or about 0.5×10^{-6} M (inclusive); about 0.5×10^{-6} M to about 1×10^{-5} M, about 0.5×10^{-5} M, or about 1×10^{-6} M (inclusive); about 1×10^{-6} M to about 1×10^{-5} M or about 0.5×10^{-5} M (inclusive); or about 0.5×10^{-5} M to about 1×10^{-5} M (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

[0319] In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_{off} of about 1×10^{-6} s⁻¹ to about 1×10^{-3} s⁻¹, about 0.5×10^{-3} s⁻¹, about 1×10^{-4} s⁻¹, about 0.5×10^{-4} s⁻¹, about 1×10^{-5} s⁻¹, or about 0.5×10^{-5} s⁻¹ (inclusive); about 0.5×10^{-5} s⁻¹ to about 1×10^{-3} s⁻¹, about 0.5×10^{-3} s⁻¹, about 1×10^{-4} s⁻¹, about 0.5×10^{-4} s⁻¹, or about 1×10^{-5} s⁻¹ (inclusive); about 1×10^{-5} s⁻¹ to about 1×10^{-3} s⁻¹, about 0.5×10^{-3} s⁻¹, about 1×10^{-4} s⁻¹, about 0.5×10^{-4} s⁻¹, or about 0.5×10^{-5} s⁻¹ (inclusive); about 0.5×10^{-5} s⁻¹ to about 1×10^{-3} s⁻¹, about 0.5×10^{-3} s⁻¹, or about 1×10^{-4} s⁻¹ (inclusive); about 1×10^{-4} s⁻¹ to about 1×10^{-3} s⁻¹, or about 0.5×10^{-3} s⁻¹ (inclusive); or about 0.5×10^{-5} s⁻¹ to about 1×10^{-3} s⁻¹ (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

[0320] In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_{on} of about 1×10^2 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, about 0.5×10^6 M⁻¹s⁻¹, about 1×10^5 M⁻¹s⁻¹, about 0.5×10^5 M⁻¹s⁻¹, about 1×10^4 M⁻¹s⁻¹, about 0.5×10^4 M⁻¹s⁻¹, about 1×10^3 M⁻¹s⁻¹, or about 0.5×10^3 M⁻¹s⁻¹ (inclusive); about 0.5×10^3 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, about 0.5×10^6 M⁻¹s⁻¹, about 1×10^5 M⁻¹s⁻¹, about 0.5×10^5 M⁻¹s⁻¹, about 1×10^4 M⁻¹s⁻¹, about 0.5×10^4 M⁻¹s⁻¹, or about 1×10^3 M⁻¹s⁻¹ (inclusive); about 1×10^3 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, about 0.5×10^6 M⁻¹s⁻¹, about 1×10^5 M⁻¹s⁻¹, about 0.5×10^5 M⁻¹s⁻¹, about 1×10^4 M⁻¹s⁻¹, or about 0.5×10^4 M⁻¹s⁻¹ (inclusive); about 0.5×10^4 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, about 0.5×10^6 M⁻¹s⁻¹, about 1×10^5 M⁻¹s⁻¹, about 0.5×10^5 M⁻¹s⁻¹, or about 1×10^4 M⁻¹s⁻¹ (inclusive); about 1×10^4 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, about 0.5×10^6 M⁻¹s⁻¹, about 1×10^5 M⁻¹s⁻¹, about 0.5×10^5 M⁻¹s⁻¹, or about 1×10^4 M⁻¹s⁻¹ (inclusive); about 0.5×10^5 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, about 0.5×10^6 M⁻¹s⁻¹, or about 1×10^5 M⁻¹s⁻¹ (inclusive); about 1×10^5 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, about 0.5×10^6 M⁻¹s⁻¹, or about 1×10^5 M⁻¹s⁻¹ (inclusive); about 1×10^5 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹, or about 0.5×10^6 M⁻¹s⁻¹ (inclusive); or about 0.5×10^6 M⁻¹s⁻¹ to about 1×10^6 M⁻¹s⁻¹ (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

Fusion Proteins

[0321] In some embodiments, the IL-12/IL-23 inhibitor is a fusion protein, a soluble antagonist, or an antimicrobial peptide. In some embodiments, the fusion protein comprises a soluble fragment of a receptor of IL-12 or a soluble fragment of a receptor of IL-23. In some embodiments, the fusion protein comprises an extracellular domain of a receptor of IL-12 or an extracellular domain of a receptor of IL-23.

[0322] In some embodiments, the fusion protein is adnectin or a variant thereof (Tang et al., *Immunology* 135(2): 112-124, 2012). In some embodiments, the soluble antagonist is a human IL-23Ra-chain mRNA transcript (Raymond et al., *J. Immunol.* 185(12):7302-7308, 2010). In some embodiments, the IL-12/IL-23 is an antimicrobial peptide (e.g., MP-196 (Wenzel et al., *PNAS* 111(14):E1409-E1418, 2014)).

Small Molecules

[0323] In some embodiments, the IL-12/IL-23 inhibitor is a small molecule. In some embodiments, the small molecule is STA-5326 (apilimod) or a variant thereof (Keino et al., *Arthritis Res. Ther.* 10: R122, 2008; Wada et al., *Blood* 109(3):1156-1164, 2007; Sands et al., *Inflamm. Bowel Dis.* 16(7): 1209-1218, 2010).

[0324] Endoscopes, Ingestible Devices, and Reservoirs

[0325] As discussed herein, in some embodiments, a method of treating a disease of the gastrointestinal tract comprises administering to the subject a pharmaceutical formulation wherein the pharmaceutical formulation is delivered proximate to one or more sites of disease by one of various methods. For example, the pharmaceutical formulation may be delivered via a medical device such as an endoscope, ingestible device, or reservoir; the pharmaceutical formulation may be a solid dosage form, a liquid dosage form, a suppository or an enema for rectal administration with different types of release such as sustained or delayed release.

[0326] In one embodiment, the pharmaceutical formulation is delivered proximate to one or more sites of disease by an endoscope, ingestible device, or reservoir containing the pharmaceutical formulation.

[0327] The GI tract can be imaged using endoscopes, or more recently, by ingestible devices that are swallowed. Direct visualization of the GI mucosa is useful to detect subtle mucosal alterations, as in inflammatory bowel diseases, as well as any flat or sessile lesions.

[0328] As discussed herein, in some embodiments, the method of treating a disease of the gastrointestinal tract comprises administering to the subject a pharmaceutical formulation. In some embodiments, the pharmaceutical formulation is delivered proximate to one or more sites of disease by one of various methods. For example, the pharmaceutical formulation may be delivered via a medical device such as an endoscope, ingestible device, or reservoir; the pharmaceutical formulation may be a solid dosage form, a liquid dosage form, a suppository or an enema for rectal administration with different types of release such as sustained or delayed release.

[0329] In one embodiment, the pharmaceutical formulation is delivered proximate to one or more sites of disease by an endoscope, ingestible device, or reservoir containing the pharmaceutical formulation.

[0330] The technology behind standard colonoscopy consists of a long, semi-rigid insertion tube with a steerable tip (stiff if compared to the colon), which is pushed by the physician from the outside. However, invasiveness, patient discomfort, fear of pain, and—more often than not—the need for conscious sedation limit the take-up of screening colonoscopy. Diagnosis and treatment in the GI tract are dominated by the use of flexible endoscopes. A few large companies, namely Olympus Medical Systems Co. (Tokyo, Japan), Pentax Medical Co. (Montvale, N.J., USA), Fujinon, Inc. (Wayne, N.J., USA) and Karl Storz GmbH & Co. KG (Tutlingen, Germany), cover the majority of the market in flexible GI endoscopy.

[0331] Endoscopes may comprise a catheter. As an example, the catheter may be a spray catheter. As an example, a spray catheter may be used to deliver dyes for diagnostic purposes. As an example, a spray catheter may be used to deliver a therapeutic agent at the site of disease in the GI tract. For example, the Olympus PW-205V is a ready-to-use spray catheter that enables efficient spraying for maximal differentiation of tissue structures during endoscopy, but may also be used to deliver drugs diseased tissue.

[0332] In a review of robotic endoscopic capsules, Journal of Micro-Bio Robotics 11.1-4 (2016): 1-18, Ciuti et al. state that progress in micro-electromechanical systems (MEMS) technologies have led to the development of new endoscopic capsules with enhanced diagnostic capabilities, in addition to traditional visualization of mucosa (embedding, e.g. pressure, pH, blood detection and temperature sensors).

[0333] Endoscopic capsules, however, do not have the capability of accurately locating a site autonomously. They require doctor oversight over a period of hours in order to manually determine the location. Autonomous ingestible devices are advantageous in that regard.

[0334] Ingestible devices are also advantageous over spray catheters in that they are less invasive, thereby allowing for regular dosing more frequently than spray catheters. Another advantage of ingestible devices is the greater ease with which they can access, relative to a catheter, certain

sections of the GI tract such as the ascending colon, the cecum, and all portions of the small intestine.

Methods and Mechanisms for Localization

[0335] In addition to, or as an alternative, to directly visualizing the GI tract, one or more different mechanisms can be used to determine the location of an ingestible device within the GI tract. Various implementations may be used for localization of ingestible devices within the GI tract.

[0336] For example, certain implementations can include one or more electromagnetic sensor coils, magnetic fields, electromagnetic waves, electric potential values, ultrasound positioning systems, gamma scintigraphy techniques or other radio-tracker technology have been described by others. Alternatively, imaging can be used to localize, for example, using anatomical landmarks or more complex algorithms for 3D reconstruction based on multiple images. Other technologies rely on radio frequency, which relies on sensors placed externally on the body to receive the strength of signals emitted by the capsule. Ingestible devices may also be localized based on reflected light in the medium surrounding the device; pH; temperature; time following ingestion; and/or acoustic signals.

[0337] The disclosure provides an ingestible device, as well as related systems and methods that provide for determining the position of the ingestible device within the GI tract of a subject with very high accuracy. In some embodiments, the ingestible device can autonomously determine its position within the GI tract of the subject.

[0338] Typically, the ingestible device includes one or more processing devices, and one more machine readable hardware storage devices. In some embodiments, the one or more machine readable hardware storage devices store instructions that are executable by the one or more processing devices to determine the location of the ingestible device in a portion of a GI tract of the subject. In certain embodiments, the one or more machine readable hardware storage devices store instructions that are executable by the one or more processing devices to transmit data to an external device (e.g., a base station external to the subject, such as a base station carried on an article worn by the subject) capable of implementing the data to determine the location of the device within the GI tract of the subject.

[0339] In some embodiments, the location of the ingestible device within the GI tract of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%. In some embodiments, the location of the ingestible device within the GI tract of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%. In such embodiments, the portion of the GI tract of the subject can include, for example, the esophagus, the stomach, duodenum, the jejunum, and/or the terminal ileum, cecum and colon. An exemplary and non-limiting embodiment is provided below in Example 13.

[0340] In certain embodiments, the location of the ingestible device within the esophagus of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%. An exemplary and non-limiting embodiment is provided below in Example 13.

[0341] In some embodiments, the location of the ingestible device within the stomach of the subject can be deter-

mined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%. An exemplary and non-limiting embodiment is provided below in Example 13.

[0342] In certain embodiments, the location of the ingestible device within the duodenum of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%. An exemplary and non-limiting embodiment is provided below in Example 13.

[0343] In some embodiments, the location of the ingestible device within the jejunum of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%. An exemplary and non-limiting embodiment is provided below in Example 13.

[0344] In certain embodiments, the location of the ingestible device within the terminal ileum, cecum and colon of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%.

[0345] In some embodiments, the location of the ingestible device within the cecum of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%. An exemplary and non-limiting embodiment is provided below in Example 13. In such embodiments, the portion of the GI tract of the subject can include, for example, the esophagus, the stomach, duodenum, the jejunum, and/or the terminal ileum, cecum and colon.

[0346] In certain embodiments, the location of the ingestible device within the esophagus of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%.

[0347] In some embodiments, the location of the ingestible device within the stomach of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%.

[0348] In certain embodiments, the location of the ingestible device within the duodenum of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%.

[0349] In some embodiments, the location of the ingestible device within the jejunum of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%.

[0350] In certain embodiments, the location of the ingestible device within the terminal ileum, cecum and colon of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%.

[0351] In some embodiments, the location of the ingestible device within the cecum of the subject can be determined to an accuracy of at least 85%, e.g., at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, 100%.

[0352] As used herein, the term “reflectance” refers to a value derived from light emitted by the device, reflected back to the device, and received by a detector in or on the device. For example, in some embodiments this refers to light emitted by the device, wherein a portion of the light is reflected by a surface external to the device, and the light is received by a detector located in or on the device.

[0353] As used herein, the term “illumination” refers to any electromagnetic emission. In some embodiments, an

illumination may be within the range of Infrared Light (IR), the visible spectrum and ultraviolet light (UV), and an illumination may have a majority of its power centered at a particular wavelength in the range of 100 nm to 1000 nm. In some embodiments, it may be advantageous to use an illumination with a majority of its power limited to one of the infrared (750 nm-1000 nm), red (600 nm-750 nm), green (495 nm-600 nm), blue (400 nm-495 nm), or ultraviolet (100 nm-400 nm) spectrums. In some embodiments a plurality of illuminations with different wavelengths may be used. For illustrative purposes, the embodiments described herein may refer to the use of green or blue spectrums of light. However, it is understood that these embodiments may use any suitable light having a wavelength that is substantially or approximately within the green or blue spectra defined above, and the localization systems and methods described herein may use any suitable spectra of light.

[0354] Referring now to FIG. 1, shown therein is a view of an example embodiment of an ingestible device **100**, which may be used to identify a location within a gastrointestinal (GI) tract. In some embodiments, ingestible device **100** may be configured to autonomously determine whether it is located in the stomach, a particular portion of the small intestine such as a duodenum, jejunum, or ileum, or the large intestine by utilizing sensors operating with different wavelengths of light. Additionally, ingestible device **100** may be configured to autonomously determine whether it is located within certain portions of the small intestine or large intestine, such as the duodenum, the jejunum, the cecum, or the colon.

[0355] Ingestible device **100** may have a housing **102** shaped similar to a pill or capsule. The housing **102** of ingestible device **100** may have a first end portion **104**, and a second end portion **106**. The first end portion **104** may include a first wall portion **108**, and second end portion **106** may include a second wall portion **110**. In some embodiments, first end portion **104** and second end portion **106** of ingestible device **100** may be manufactured separately, and may be affixed together by a connecting portion **112**.

[0356] In some embodiments, ingestible device **100** may include an optically transparent window **114**. Optically transparent window **114** may be transparent to various types of illumination in the visible spectrum, infrared spectrum, or ultraviolet light spectrum, and ingestible device **100** may have various sensors and illuminators located within the housing **102**, and behind the transparent window **114**. This may allow ingestible device **100** to be configured to transmit illumination at different wavelengths through transparent window **114** to an environment external to housing **102** of ingestible device **100**, and to detect a reflectance from a portion of the illumination that is reflected back through transparent window **114** from the environment external to housing **102**. Ingestible device **100** may then use the detected level of reflectance in order to determine a location of ingestible device **100** within a GI tract. In some embodiments, optically transparent window **114** may be of any shape and size, and may wrap around the circumference of ingestible device **100**. In this case, ingestible device **100** may have multiple sets of sensors and illuminators positioned at different locations azimuthally behind window **114**.

[0357] In some embodiments, ingestible device **100** may optionally include an opening **116** in the second wall portion **110**. In some embodiments, the second wall portion **110** may be configured to rotate around the longitudinal axis of

ingestible device **100** (e.g., by means of a suitable motor or other actuator housed within ingestible device **100**). This may allow ingestible device **100** to obtain a fluid sample from the GI tract, or release a substance into the GI tract, through opening **116**.

[0358] FIG. 2 shows an exploded view of ingestible device **100**. In some embodiments, ingestible device **100** may optionally include a rotation assembly **118**. Optional rotation assembly **118** may include a motor **118-1** driven by a microcontroller (e.g., a microcontroller coupled to printed circuit board **120**), a rotation position sensing ring **118-2**, and a storage sub-unit **118-3** configured to fit snugly within the second end portion **104**. In some embodiments, rotation assembly **118** may cause second end portion **104**, and opening **116**, to rotate relative to the storage sub-unit **118-3**. In some embodiments, there may be cavities on the side of storage sub-unit **118-3** that function as storage chambers. When the opening **116** is aligned with a cavity on the side of the storage sub-unit **118-3**, the cavity on the side of the storage sub-unit **118-3** may be exposed to the environment external to the housing **102** of ingestible device **100**. In some embodiments, the storage sub-unit **118-3** may be loaded with a medicament or other substance prior to the ingestible device **100** being administered to a subject. In this case, the medicament or other substance may be released from the ingestible device **100** by aligning opening **116** with the cavity within storage sub-unit **118-3**. In some embodiments, the storage sub-unit **118-3** may be configured to hold a fluid sample obtained from the GI tract. For example, ingestible device **100** may be configured to align opening **116** with the cavity within storage sub-unit **118-3**, thus allowing a fluid sample from the GI tract to enter the cavity within storage sub-unit **118-3**. Afterwards, ingestible device **100** may be configured to seal the fluid sample within storage sub-unit **118-3** by further rotating the second end portion **106** relative to storage sub-unit **118-3**. In some embodiments, storage sub-unit **118-3** may also contain a hydrophilic sponge, which may enable ingestible device **100** to better draw certain types of fluid samples into ingestible device **100**. In some embodiments, ingestible device **100** may be configured to either obtain a sample from within the GI tract, or to release a substance into the GI tract, in response to determining that ingestible device **100** has reached a predetermined location within the GI tract. For example, ingestible device **100** may be configured to obtain a fluid sample from the GI tract in response to determining that the ingestible device has entered the jejunum portion of the small intestine (e.g., as determined by process **900** discussed in relation to FIG. 9). Other ingestible devices capable of obtaining samples or releasing substances are discussed in commonly-assigned PCT Application No. PCT/CA2013/000133 filed Feb. 15, 2013, commonly-assigned U.S. Provisional Application No. 62/385,553, and commonly-assigned U.S. Provisional Application No. 62/376,688, which each are hereby incorporated by reference herein in their entirety. It is understood that any suitable method of obtaining samples or releasing substances may be incorporated into some of the embodiments of the ingestible devices disclosed herein, and that the systems and methods for determining a location of an ingestible device may be incorporated into any suitable type of ingestible device.

[0359] Ingestible device **100** may include a printed circuit board (PCB) **120**, and a battery **128** configured to power PCB **120**. PCB **120** may include a programmable micro-

controller, and control and memory circuitry for holding and executing firmware or software for coordinating the operation of ingestible device **100**, and the various components of ingestible device **100**. For example, PCB **120** may include memory circuitry for storing data, such as data sets of measurements collected by sensing sub-unit **126**, or instructions to be executed by control circuitry to implement a localization process, such as, for example, one or more of the processes, discussed herein, including those discussed below in connection with one or more of the associated flow charts. PCB **120** may include a detector **122** and an illuminator **124**, which together form sensing sub-unit **126**. In some embodiments, control circuitry within PCB **120** may include processing units, communication circuitry, or any other suitable type of circuitry for operating ingestible device **100**. For illustrative purposes, only a single detector **122** and a single illuminator **124** forming a single sensing sub-unit **126** are shown. However, it is understood that in some embodiments there may be multiple sensing sub-units, each with a separate illuminator and detector, within ingestible device **100**. For example, there may be several sensing sub-units spaced azimuthally around the circumference of the PCB **120**, which may enable ingestible device **100** to transmit illumination and detect reflectances or ambient light in all directions around the circumference of the device. In some embodiments, sensing sub-unit **126** may be configured to generate an illumination using illuminator **124**, which is directed through the window **114** in a radial direction away from ingestible device **100**. This illumination may reflect off of the environment external to ingestible device **100**, and the reflected light coming back into ingestible device **100** through window **114** may be detected as a reflectance by detector **122**.

[0360] In some embodiments, window **114** may be of any suitable shape and size. For example, window **114** may extend around a full circumference of ingestible device **100**. In some embodiments there may be a plurality of sensing sub-units (e.g., similar to sensing sub-unit **126**) located at different positions behind the window. For example, three sensing sub-units may be positioned behind the window at the same longitudinal location, but spaced 120 degrees apart azimuthally. This may enable ingestible device **100** to transmit illuminations in all directions radially around ingestible device **100**, and to measure each of the corresponding reflectances.

[0361] In some embodiments, illuminator **124** may be capable of producing illumination at a variety of different wavelengths in the ultraviolet, infrared, or visible spectrum. For example, illuminator **124** may be implemented by using Red-Green-Blue Light-Emitting diode packages (RGB-LED). These types of RGB-LED packages are able to transmit red, blue, or green illumination, or combinations of red, blue, or green illumination. Similarly, detector **122** may be configured to sense reflected light of the same wavelengths as the illumination produced by illuminator **124**. For example, if illuminator **124** is configured to produce red, blue, or green illumination, detector **122** may be configured to detect different reflectances produced by red, blue, or green illumination (e.g., through the use of an appropriately configured photodiode). These detected reflectances may be stored by ingestible device **100** (e.g., within memory circuitry of PCB **120**), and may then be used by ingestible device **100** in determining a location of ingestible device

100 within the GI tract (e.g., through the use of process 500 (FIG. 5), process 600 (FIG. 6), or process 900 (FIG. 9)).

[0362] It is understood that ingestible device 100 is intended to be illustrative, and not limiting. It will be understood that modifications to the general shape and structure of the various devices and mechanisms described in relation to FIG. 1 and FIG. 2 may be made without significantly changing the functions and operations of the devices and mechanisms. For example, ingestible device 100 may have a housing formed from a single piece of molded plastic, rather than being divided into a first end portion 104 and a second end portion 106. As an alternate example, the location of window 114 within ingestible device 100 may be moved to some other location, such as the center of ingestible device 100, or to one of the ends of ingestible device 100. Moreover, the systems and methods discussed in relation to FIGS. 1-10 may be implemented on any suitable type of ingestible device, provided that the ingestible device is capable of detecting reflectances or levels of illumination in some capacity. For example, in some embodiments ingestible device 100 may be modified to replace detector 122 with an image sensor, and the ingestible device may be configured to measure relative levels of red, blue, or green light by decomposing a recorded image into its individual spectral components. Other examples of ingestible devices with localization capabilities, which may be utilized in order to implement the systems and methods discussed in relation to FIG. 1-11, are discussed in co-owned PCT Application No. PCT/US2015/052500 filed on Sep. 25, 2015, which is hereby incorporated by reference herein in its entirety. Furthermore, it should be noted that the features and limitations described in any one embodiment may be applied to any other embodiment herein, and the descriptions and examples relating to one embodiment may be combined with any other embodiment in a suitable manner.

[0363] FIG. 3 is a diagram of an ingestible device during an example transit through a gastrointestinal (GI) tract, in accordance with some embodiments of the disclosure. Ingestible device 300 may include any portion of any other ingestible device discussed in this disclosure (e.g., ingestible device 100 (FIG. 1)), and may be any suitable type of ingestible device with localization capabilities. For example, ingestible device 300 may be one embodiment of ingestible device 100 without the optional opening 116 (FIG. 1) or optional rotation assembly 118 (FIG. 2)). In some embodiments, ingestible device 300 may be ingested by a subject, and as ingestible device 300 traverses the GI tract, ingestible device 300 may be configured to determine its location within the GI tract. For example, the movement of ingestible device 300 and the amount of light detected by ingestible device 300 (e.g., via detector 122 (FIG. 2)) may vary substantially depending on the location of ingestible device 300 within the GI tract, and ingestible device 300 may be configured to use this information to determine a location of ingestible device 300 within the GI tract. For instance, ingestible device 300 may detect ambient light from the surrounding environment, or reflectances based on illumination generated by ingestible device 300 (e.g., generated by illuminator 124 (FIG. 1)), and use this information to determine a location of ingestible device 300 through processes, such as described herein. The current location of ingestible device 300, and the time that ingestible device 300 detected each transition between the various portions of the

GI tract, may then be stored by ingestible device 300 (e.g., in memory circuitry of PCB 120 (FIG. 2)), and may be used for any suitable purpose.

[0364] Shortly after ingestible device 300 is ingested, ingestible device will traverse the esophagus 302, which may connect the subject's mouth to a stomach 306. In some embodiments, ingestible device 300 may be configured to determine that it has entered the esophagus portion GI tract by measuring the amount and type of light (e.g., via detector 122 (FIG. 2)) in the environment surrounding the ingestible device 300. For instance, ingestible device 300 may detect higher levels of light in the visible spectrum (e.g., via detector 122 (FIG. 2)) while outside the subject's body, as compared to the levels of light detected while within the GI tract. In some embodiments, ingestible device 300 may have previously stored data (e.g., on memory circuitry of PCB 120 (FIG. 2)) indicating a typical level of light detected when outside of the body, and the ingestible device 300 may be configured to determine that entry to the body has occurred when a detected level of light (e.g., detected via detector 122 (FIG. 2)) has been reduced beyond a threshold level (e.g., at least a 20-30% reduction) for a sufficient period of time (e.g., 5.0 seconds).

[0365] In some embodiments, ingestible device 300 may be configured to detect a transition from esophagus 302 to stomach 306 by passing through sphincter 304. In some embodiments, ingestible device 300 may be configured to determine whether it has entered stomach 306 based at least in part on a plurality of parameters, such as but not limited to the use of light or temperature measurements (e.g., via detector 122 (FIG. 2) or via a thermometer within ingestible device 300), pH measurements (e.g., via a pH meter within ingestible device 300), time measurements (e.g., as detected through the use of clock circuitry included within PCB 120 (FIG. 2)), or any other suitable information. For instance, ingestible device 300 may be configured to determine that ingestible device 300 has entered stomach 306 after detecting that a measured temperature of ingestible device 300 exceeds 31 degrees Celsius. Additionally, or alternately, ingestible device 300 may be configured to automatically determine it has entered stomach 306 after one minute (or another pre-set time duration parameter, 80 seconds, 90 seconds, etc.) has elapsed from the time that ingestible device 300 was ingested, or one minute (or another pre-set time duration parameter, 80 seconds, 90 seconds, etc.) from the time that ingestible device 300 detected that it has entered the GI tract.

[0366] Stomach 306 is a relatively large, open, and cavernous organ, and therefore ingestible device 300 may have a relatively large range of motion. By comparison, the motion of ingestible device 300 is relatively restricted within the tube-like structure of the duodenum 310, the jejunum 314, and the ileum (not shown), all of which collectively form the small intestine. Additionally, the interior of stomach 306 has distinct optical properties from duodenum 310 and jejunum 314, which may enable ingestible device 300 to detect a transition from stomach 306 to duodenum 310 through the appropriate use of measured reflectances (e.g., through the use of reflectances measured by detector 122 (FIG. 2)), as used in conjunction with process 600 (FIG. 6)).

[0367] In some embodiments, ingestible device 300 may be configured to detect a pyloric transition from stomach 306 to duodenum 310 through the pylorus 308. For instance, in some embodiments, ingestible device 300 may be con-

figured to periodically generate illumination in the green and blue wavelengths (e.g., via illuminator 124 (FIG. 2)), and measure the resulting reflectances (e.g., via detector 122 (FIG. 2)). Ingestible device 300 may be configured to then use a ratio of the detected green reflectance to the detected blue reflectance to determine whether ingestible device 300 is located within the stomach 306, or duodenum 310 (e.g., via process 600 (FIG. 6)). In turn, this may enable ingestible device 300 to detect a pyloric transition from stomach 306 to duodenum 310, an example of which is discussed in relation to FIG. 6.

[0368] Similarly, in some embodiments, ingestible device 300 may be configured to detect a reverse pyloric transition from duodenum 310 to stomach 306. Ingestible device 300 will typically transition naturally from stomach 306 to duodenum 310, and onward to jejunum 314 and the remainder of the GI tract. However, similar to other ingested substances, ingestible device 300 may occasionally transition from duodenum 310 back to stomach 306 as a result of motion of the subject, or due to the natural behavior of the organs with the GI tract. To accommodate this possibility, ingestible device 300 may be configured to continue to periodically generate illumination in the green and blue wavelengths (e.g., via illuminator 124 (FIG. 2)), and measure the resulting reflectances (e.g., via detector 122 (FIG. 2)) to detect whether or not ingestible device 300 has returned to stomach 306. An exemplary detection process is described in additional detail in relation to FIG. 6.

[0369] After entering duodenum 310, ingestible device 300 may be configured to detect a transition to the jejunum 314 through the duodenojejunal flexure 312. For example, ingestible device 300 may be configured to use reflectances to detect peristaltic waves within the jejunum 314, caused by the contraction of the smooth muscle tissue lining the walls of the jejunum 314. In particular, ingestible device 300 may be configured to begin periodically transmitting illumination (and measuring the resulting reflectances (e.g., via detector 122 and illuminator 124 of sensing sub-unit 126 (FIG. 2)) at a sufficiently high frequency in order to detect muscle contractions within the jejunum 314. Ingestible device 300 may then determine that it has entered the jejunum 314 in response to having detected either a first muscle contraction, or a predetermined number of muscle contractions (e.g., after having detected three muscle contractions in sequence). The interaction of ingestible device 300 with the walls of jejunum 314 is also discussed in relation to FIG. 4, and an example of this detection process is described in additional detail in relation to FIG. 9.

[0370] FIG. 4 is a diagram of an ingestible device during an example transit through a jejunum, in accordance with some embodiments of the disclosure. Diagrams 410, 420, 430, and 440 depict ingestible device 400 as it traverses through a jejunum (e.g., jejunum 314), and how ingestible device 400 interacts with peristaltic waves formed by walls 406A and 406B (collectively, walls 406) of the jejunum. In some implementations, ingestible device 400 may include any portion of any other ingestible device discussed in this disclosure (e.g., ingestible device 100 (FIG. 1) or ingestible device 300 (FIG. 3)), and may be any suitable type of ingestible device with localization capabilities. For example, ingestible device 400 may be substantially similar to the ingestible device 300 (FIG. 3) or ingestible device 100 (FIG.

1), with window 404 being the same as window 114 (FIG. 1), and sensing sub-unit 402 being the same as sensing sub-unit 126 (FIG. 2).

[0371] Diagram 410 depicts ingestible device 400 within the jejunum, when the walls 406 of the jejunum are relaxed. In some embodiments, the confined tube-like structure of the jejunum naturally causes ingestible device 400 to be oriented longitudinally along the length of the jejunum, with window 404 facing walls 406. In this orientation, ingestible device 400 may use sensing sub-unit 402 to generate illumination (e.g., via illuminator 124 (FIG. 2)) oriented towards walls 406, and to detect the resulting reflectances (e.g., via detector 122 (FIG. 2)) from the portion of the illumination reflected off of walls 406 and back through window 404. In some embodiments, ingestible device 400 may be configured to use sensing sub-unit 402 to generate illumination and measure the resulting reflectance with sufficient frequency to detect peristaltic waves within the jejunum. For instance, in a healthy human subject, peristaltic waves may occur at a rate of approximately 0.1 Hz to 0.2 Hz. Therefore, the ingestible device 400 may be configured to generate illumination and measure the resulting reflectance at least once every 2.5 seconds (i.e., the minimum rate necessary to detect a 0.2 Hz signal), and preferably at a higher rate, such as once every 0.5 seconds, which may improve the overall reliability of the detection process due to more data points being available. It is understood that the ingestible device 400 need not gather measurements at precise intervals, and in some embodiments the ingestible device 400 may be adapted to analyze data gathered at more irregular intervals, provided that there are still a sufficient number of appropriately spaced data points to detect 0.1 Hz to 0.2 Hz signals.

[0372] Diagram 420 depicts ingestible device 400 within the jejunum, when the walls 406 of the jejunum begin to contract and form a peristaltic wave. Diagram 420 depicts contracting portion 408A of wall 406A and contracting portion 408B of wall 406B (collectively, contracting portion 408 of wall 406) that form a peristaltic wave within the jejunum. The peristaltic wave proceeds along the length of the jejunum as different portions of wall 406 contract and relax, causing it to appear as if contracting portions 408 of wall 406 proceed along the length of the jejunum (i.e., as depicted by contracting portions 408 proceeding from left to right in diagrams 410-430). While in this position, ingestible device 400 may detect a similar level of reflectance (e.g., through the use of illuminator 124 and detector 122 of sensing sub-unit 126 (FIG. 2)) as detected when there is no peristaltic wave occurring (e.g., as detected when ingestible device 400 is in the position indicated in diagram 410).

[0373] Diagram 430 depicts ingestible device 400 within the jejunum, when the walls 406 of the jejunum continue to contract, squeezing around ingestible device 400. As the peristaltic wave proceeds along the length of the jejunum, contracting portions 408 of wall 406 may squeeze tightly around ingestible device 400, bringing the inner surface of wall 406 into contact with window 404. While in this position, ingestible device 400 may detect a change in a reflectance detected as a result of illumination produced by sensing sub-unit 402. The absolute value of the change in the measured reflectance may depend on several factors, such as the optical properties of the window 404, the spectral components of the illumination, and the optical properties of the walls 406. However, ingestible device 400 may be

configured to store a data set with the reflectance values over time, and search for periodic changes in the data set consistent with the frequency of the peristaltic waves (e.g., by analyzing the data set in the frequency domain, and searching for peaks between 0.1 Hz to 0.2 Hz). This may enable ingestible device 400 to detect muscle contractions due to peristaltic waves without foreknowledge of the exact changes in reflectance signal amplitude that may occur as a result of detecting the muscle contractions of the peristaltic wave. An example procedure for detecting muscle contractions is discussed further in relation to FIG. 9, and an example of a reflectance data set gathered while ingestible device 400 is located within the jejunum is discussed in relation to FIG. 10.

[0374] Diagram 440 depicts ingestible device 400 within the jejunum, when the peristaltic wave has moved past ingestible device 400. Diagram 440 depicts contracting portions 408 that form the peristaltic wave within the jejunum having moved past the end of ingestible device 400. The peristaltic wave proceeds along the length of the jejunum as different portions of wall 406 contract and relax, causing it to appear as if contracting portions 408 of wall 406 proceed along the length of the jejunum (i.e., as depicted by contracting portions 408 proceeding from left to right in diagrams 410-430). While in this position, ingestible device 400 may detect a similar level of reflectance (e.g., through the use of illuminator 124 and detector 122 of sensing sub-unit 126 (FIG. 2)) as detected when there is no peristaltic wave occurring (e.g., as detected when ingestible device 400 is in the position indicated in diagram 410, or diagram 420).

[0375] Depending on the species of the subject, peristaltic waves may occur with relatively predictable regularity. After the peristaltic wave has passed over ingestible device 400 (e.g., as depicted in diagram 440), the walls 406 of the jejunum may relax again (e.g., as depicted in diagram 410), until the next peristaltic wave begins to form. In some embodiments, ingestible device 400 may be configured to continue to gather reflectance value data while it is within the GI tract, and may store a data set with the reflectance values over time. This may allow ingestible device 400 to detect each of the muscle contractions as the peristaltic wave passes over ingestible device 400 (e.g., as depicted in diagram 430), and may enable ingestible device 400 to both count the number of muscle contractions that occur, and to determine that a current location of the ingestible device 400 is within the jejunum. For example, ingestible device 400 may be configured to monitor for possible muscle contractions while is inside either the stomach or the duodenum, and may determine that ingestible device 400 has moved to the jejunum in response to detecting a muscle contraction consistent with a peristaltic wave.

[0376] FIG. 5 is a flowchart illustrating some aspects of a localization process used by the ingestible device. Although FIG. 5 may be described in connection with the ingestible device 100 for illustrative purposes, this is not intended to be limiting, and either portions or the entirety of the localization procedure 500 described in FIG. 5 may be applied to any device discussed in this application (e.g., the ingestible devices 100, 300, and 400), and any of the ingestible devices may be used to perform one or more parts of the process described in FIG. 5. Furthermore, the features of FIG. 5 may be combined with any other systems, methods or processes described in this application. For example, portions of the

process in FIG. 5 may be integrated into or combined with the pyloric transition detection procedure described by FIG. 6, or the jejunum detection process described by FIG. 9.

[0377] At 502, the ingestible device (e.g., ingestible device 100, 300, or 400) gathers measurements (e.g., through detector 122 (FIG. 2)) of ambient light. For example, ingestible device 100 may be configured to periodically measure (e.g., through detector 122 (FIG. 2)) the level of ambient light in the environment surrounding ingestible device 100. In some embodiments, the type of ambient light being measured may depend on the configuration of detector 122 within ingestible device 100. For example, if detector 122 is configured to measure red, green, and blue wavelengths of light, ingestible device 100 may be configured to measure the ambient amount of red, green, and blue light from the surrounding environment. In some embodiments, the amount of ambient light measured by ingestible device 100 will be larger in the area external to the body (e.g., a well-lit room where ingestible device 100 is being administered to a subject) and in the oral cavity of the subject, as compared to the ambient level of light measured by ingestible device 100 when inside of an esophagus, stomach, or other portion of the GI tract (e.g., esophagus 302, stomach 306, duodenum 310, or jejunum 314 (FIG. 3)).

[0378] At 504, the ingestible device (e.g., ingestible device 100, 300, or 400) determines (e.g., via control circuitry within PCB 120 (FIG. 2)) whether the ingestible device has detected entry into the GI tract. For example, ingestible device 100 may be configured to determine when the most recent measurement of ambient light (e.g., the measurement gathered at 502) indicates that the ingestible device has entered the GI tract. For instance, the first time that ingestible device 100 gathers a measurement of ambient light at 502, ingestible device 100 may store that measurement (e.g., via storage circuitry within PCB 120 (FIG. 2)) as a typical level of ambient light external to the body. Ingestible device 100 may be configured to then compare the most recent measurement of ambient light to the typical level of ambient light external to the body (e.g., via control circuitry within PCB 120 (FIG. 2)), and determine that ingestible device 100 has entered the GI tract when the most recent measurement of ambient light is substantially smaller than the typical level of ambient light external to the body. For example, ingestible device 100 may be configured to detect that it has entered the GI tract in response to determining that the most recent measurement of ambient light is less than or equal to 20% of the typical level of ambient light external to the body. If ingestible device 100 determines that it has detected entry into the GI tract (e.g., that ingestible device 100 has entered at least the esophagus 302 (FIG. 3)), process 500 proceeds to 506. Alternately, if ingestible device 100 determines that it has not detected entry into the GI tract (e.g., as a result of the most recent measurement being similar to the typical level of ambient light external to the body), process 500 proceeds back to 502 where the ingestible device 100 gathers further measurements. For instance, ingestible device 100 may be configured to wait a predetermined amount of time (e.g., five seconds, ten seconds, etc.), and then gather another measurement of the level of ambient light from the environment surrounding ingestible device 100.

[0379] At 506, the ingestible device (e.g., ingestible device 100, 300, or 400) waits for a transition from the esophagus to the stomach (e.g., from esophagus 302 to

stomach 306 (FIG. 3)). For example, ingestible device 100 may be configured to determine that it has entered the stomach (e.g., stomach 306 (FIG. 3)) after waiting a predetermined period of time after having entered the GI tract. For instance, a typical esophageal transit time in a human patient may be on the order of 15-30 seconds. In this case, after having detected that ingestible device 100 has entered the GI tract at 504 (i.e., after detecting that ingestible device 100 has reached at least esophagus 302 (FIG. 3)), ingestible device 100 may be configured to wait one minute, or a similar amount of time longer than the typical esophageal transit time (e.g., ninety-seconds), before automatically determining that ingestible device 100 has entered at least the stomach (e.g., stomach 306 (FIG. 3)).

[0380] In some embodiments, the ingestible device (e.g., ingestible device 100, 300, or 400) may also determine it has entered the stomach based on measurements of pH or temperature. For example, ingestible device 100 may be configured to determine that it has entered the stomach if a temperature of ingestible device has increased to at least 31 degrees Celsius (i.e., consistent with the temperature inside the stomach), or if a measured pH of the environment surrounding ingestible device 100 is sufficiently acidic (i.e., consistent with the acidic nature of gastric juices that may be found inside the stomach).

[0381] At 508, the ingestible device (e.g., ingestible device 100, 300, or 400) stores data indicating the ingestible device has entered the stomach (e.g., stomach 306 (FIG. 3)). For example, after having waited a sufficient amount of time at 506, ingestible device 100 may store data (e.g., within storage circuitry of PCB 120 (FIG. 2)) indicative of ingestible device 100 having entered at least the stomach. Once ingestible device 100 reaches at least the stomach, process 500 proceeds to 510 where ingestible device 100 may be configured to gather data to detect entry into the duodenum (e.g., duodenum 310 (FIG. 3)).

[0382] In some embodiments, process 500 may also simultaneously proceed from 508 to 520, where ingestible device 100 may be configured to gather data in order to detect muscle contractions and detect entry into the jejunum (e.g., jejunum 314 (FIG. 3)). In some embodiments, ingestible device 100 may be configured to simultaneously monitor for entry into the duodenum at 516-518, as well as detect for entry into the jejunum at 520-524. This may allow ingestible device 100 to determine when it has entered the jejunum (e.g., as a result of detecting muscle contractions), even when it fails to first detect entry into the duodenum (e.g., as a result of very quick transit times of the ingestible device through the duodenum).

[0383] At 510, the ingestible device (e.g., ingestible device 100, 300, or 400) gathers measurements of green and blue reflectance levels (e.g., through the use of illuminator 124 and detector 122 of sensing sub-unit 126 (FIG. 2)) while in the stomach (e.g., stomach 306 (FIG. 3)). For example, ingestible device 100 may be configured to periodically gather measurements of green and blue reflectance levels while in the stomach. For instance, ingestible device 100 may be configured to transmit a green illumination and a blue illumination (e.g., via illuminator 124 (FIG. 2)) every five to fifteen seconds, and measure the resulting reflectance (e.g., via detector 122 (FIG. 2)). Every time that ingestible device 100 gathers a new set of measurements, the measurements may be added to a stored data set (e.g., stored within memory circuitry of PCB 120 (FIG. 2)). The ingest-

ible device 100 may then use this data set to determine whether or not ingestible device 100 is still within a stomach (e.g., stomach 306 (FIG. 3)), or a duodenum (e.g., duodenum 310 (FIG. 3)).

[0384] In some embodiments, the ingestible device (e.g., ingestible device 100, 300, or 400) may be configured to detect a first reflectance based on generating an illumination of a first wavelength in approximately the green spectrum of light (between 495-600 nm), and detecting a second reflectance based on generating an illumination of the second wavelength in approximately the blue spectrum of light (between 400-495 nm). In some embodiments, the ingestible device may ensure that the illumination in the green spectrum and the illumination in the blue spectrum have wavelengths separated by at least 50 nm. This may enable ingestible device 100 to sufficiently distinguish between the two wavelengths when detecting the reflectances (e.g., via detector 122 (FIG. 2)). It is understood that the separation of 50 nm is intended to be illustrative, and not limiting, and depending on the accuracy of the detectors within ingestible device 100, smaller separations may be possible to be used.

[0385] At 512, the ingestible device (e.g., ingestible device 100, 300, or 400) determines (e.g., using control circuitry within PCB 120 (FIG. 2)) whether the ingestible device has detected a transition from the stomach (e.g., stomach 306 (FIG. 3)) to a duodenum (e.g., duodenum 310 (FIG. 3)) based on a ratio of green and blue (G/B) reflectance levels. For example, ingestible device 100 may obtain (e.g., from memory circuitry of PCB 120 (FIG. 2)) a data set containing historical data for the respective ratio of the green reflectance to the blue reflectance as measured at a respective time. Generally speaking, a duodenum (e.g., duodenum 310 (FIG. 3)) of a human subject reflects a higher ratio of green light to blue light, as compared to the ratio of green light to blue light that is reflected by a stomach (e.g., stomach 306 (FIG. 3)). Based on this, ingestible device 100 may be configured to take a first set of ratios from the data set, representing the result of recent measurements, and compare them to a second set of ratios from the data set, representing the results of past measurements. When the ingestible device 100 determines that the mean value of the first set of ratios is substantially larger than the mean value of the second set of ratios (i.e., that the ratio of reflected green light to reflected blue light has increased), the ingestible device 100 may determine that it has entered the duodenum (e.g., duodenum 310 (FIG. 3)) from the stomach (e.g., stomach 306 (FIG. 3)). If the ingestible device 100 detects a transition from the stomach (e.g., stomach 306 (FIG. 3)) to a duodenum (e.g., duodenum 310 (FIG. 3)), process 500 proceeds to 514, where ingestible device 100 stores data indicating that the ingestible device 100 has entered the duodenum (e.g., duodenum 310 (FIG. 3)). Alternatively, if the ingestible device determines that the ingestible device has not transitioned from the stomach (e.g., stomach 306 (FIG. 3)) to the duodenum (e.g., duodenum 310 (FIG. 3)), process 500 proceeds back to 510 to gather more measurements of green and blue reflectance levels while still in the stomach (e.g., stomach 306 (FIG. 3)). An example procedure for using measurements of green and blue reflectances to monitor for transitions between the stomach and the duodenum is discussed in greater detail in relation to FIG. 6.

[0386] In some embodiments, the first time that ingestible device 100 detects a transition from the stomach (e.g.,

stomach 306 (FIG. 3)) to the duodenum (e.g., duodenum 310 (FIG. 3)), ingestible device 100 may be configured to take a mean of the second set of data, (e.g., the set of data previously recorded while in stomach 306 (FIG. 3)) and store this as a typical ratio of green light to blue light detected within the stomach (e.g., stomach 306 (FIG. 3)) (e.g., within memory circuitry of PCB 120 (FIG. 2)). This stored information may later be used by ingestible device 100 to determine when ingestible device 100 re-enters the stomach (e.g., stomach 306 (FIG. 3)) from the duodenum (e.g., duodenum 310 (FIG. 3)) as a result of a reverse pyloric transition.

[0387] At 514, the ingestible device (e.g., ingestible device 100, 300, or 400) stores data indicating that the ingestible device has entered the duodenum (e.g., duodenum 310 (FIG. 3)). For example, ingestible device 100 may store a flag within local memory (e.g., memory circuitry of PCB 120) indicating that the ingestible device 100 is currently in the duodenum. In some embodiments, the ingestible device 100 may also store a timestamp indicating the time when ingestible device 100 entered the duodenum. Once ingestible device 100 reaches the duodenum, process 500 proceeds to 520 where ingestible device 100 may be configured to gather data in order to detect muscle contractions and detect entry into the jejunum (e.g., jejunum 314 (FIG. 3)). Process 500 also proceeds from 514 to 516, where ingestible device 100 may be configured to gather data additional data in order to detect re-entry into the stomach (e.g., stomach 306 (FIG. 3)) from the duodenum (e.g., duodenum 310 (FIG. 3)).

[0388] At 516, the ingestible device (e.g., ingestible device 100, 300, or 400) gathers measurements (e.g., via sensing sub-unit 126 (FIG. 2)) of green and blue reflectance levels while in the duodenum (e.g., duodenum 310 (FIG. 3)). For example, ingestible device 100 may be configured to periodically gather measurements (e.g., via sensing sub-unit 126 (FIG. 2)) of green and blue reflectance levels while in the duodenum, similar to the measurements made at 510 while in the stomach. For instance, ingestible device 100 may be configured to transmit a green illumination and a blue illumination (e.g., via illuminator 124 (FIG. 2)) every five to fifteen seconds, and measure the resulting reflectance (e.g., via detector 122 (FIG. 2)). Every time that ingestible device 100 gathers a new set of measurements, the measurements may be added to a stored data set (e.g., stored within memory circuitry of PCB 120 (FIG. 2)). The ingestible device 100 may then use this data set to determine whether or not ingestible device 100 is still within the duodenum (e.g., duodenum 310 (FIG. 3)), or if the ingestible device 100 has transitioned back into the stomach (e.g., stomach 306 (FIG. 3)).

[0389] At 518, the ingestible device (e.g., ingestible device 100, 300, or 400) determines a transition from the duodenum (e.g., duodenum 310 (FIG. 3)) to the stomach (e.g., stomach 306 (FIG. 3)) based on a ratio of the measured green reflectance levels to the measured blue reflectance levels. In some embodiments, ingestible device 100 may compare the ratio of the measured green reflectance levels to the measured blue reflectance levels recently gathered by ingestible device 100 (e.g., measurements gathered at 516), and determine whether or not the ratio of the measured green reflectance levels to the measured blue reflectance levels is similar to the average ratio of the measured green reflectance levels to the measured blue reflectance levels seen in the stomach (e.g., stomach 306 (FIG. 3)). For instance, ingest-

ible device 100 may retrieve data (e.g., from memory circuitry of PCB 120 (FIG. 2)) indicative of the average ratio of the measured green reflectance levels to the measured blue reflectance levels seen in the stomach, and determine that ingestible device 100 has transitioned back to the stomach if the recently measured ratio of the measured green reflectance levels to the measured blue reflectance levels is sufficiently similar to the average level in the stomach (e.g., within 20% of the average ratio of the measured green reflectance levels to the measured blue reflectance levels seen in the stomach, or within any other suitable threshold level). If the ingestible device detects a transition from the duodenum (e.g., duodenum 310 (FIG. 3)) to the stomach (e.g., stomach 306 (FIG. 3)), process 500 proceeds to 508 to store data indicating the ingestible device has entered the stomach (e.g., stomach 306 (FIG. 3)), and continues to monitor for further transitions. Alternatively, if the ingestible device does not detect a transition from the duodenum (e.g., duodenum 310 (FIG. 3)) to the stomach (e.g., stomach 306 (FIG. 3)), process 500 proceeds to 516 to gather additional measurements of green and blue reflectance levels while in the duodenum (e.g., duodenum 310 (FIG. 3)), which may be used to continuously monitor for possible transitions back into the stomach. An example procedure for using measurements of green and blue reflectances to monitor for transitions between the stomach and the duodenum is discussed in greater detail in relation to FIG. 6.

[0390] At 520, the ingestible device (e.g., ingestible device 100, 300, or 400) gathers periodic measurements of the reflectance levels (e.g., via sensing sub-unit 126 (FIG. 2)) while in the duodenum (e.g., duodenum 310 (FIG. 3)). In some embodiments, the ingestible device (e.g., ingestible device 100, 300, or 400) may gather similar periodic measurements while in the stomach as well. In some embodiments, these periodic measurements may enable ingestible device 100 to detect muscle contractions (e.g., muscle contractions due to a peristaltic wave as discussed in relation to FIG. 4), which may be indicative of entry into a jejunum (e.g., jejunum 314 (FIG. 3)). Ingestible device 100 may be configured to gather periodic measurements using any suitable wavelength of illumination (e.g., by generating illumination using illuminator 124, and detecting the resulting reflectance using detector 122 (FIG. 2)), or combinations of wavelengths of illumination. For example, in some embodiments, ingestible device 100 may be configured to generate red, green, and blue illumination, store separate data sets indicative of red, green, and blue illumination, and analyze each of the data sets separately to search for frequency components in the recorded data indicative of detected muscle contractions. In some embodiments, the measurements gathered by ingestible device 100 at 520 may be sufficiently fast as to detect peristaltic waves in a subject. For instance, in a healthy human subject, peristaltic waves may occur at a rate of approximately 0.1 Hz to 0.2 Hz. Therefore, the ingestible device 400 may be configured to generate illumination and measure the resulting reflectance at least once every 2.5 seconds (i.e., the minimum rate necessary to detect a 0.2 Hz signal), and preferably at a higher rate, such as once every 0.5 seconds or faster, and store values indicative of the resulting reflectances in a data set (e.g., within memory circuitry of PCB 120 (FIG. 2)). After gathering additional data (e.g., after gathering one new data point, or a predetermined number of new data points), process 500

proceeds to **522**, where ingestible device **100** determines whether or not a muscle contraction has been detected.

[0391] At **522**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines (e.g., via control circuitry within PCB **120** (FIG. 0.2)) whether the ingestible device detects a muscle contraction based on the measurements of reflectance levels (e.g., as gathered by sensing sub-unit **126** (FIG. 2)). For example, ingestible device **100** may obtain a fixed amount of data stored as a result of measurements made at **520** (e.g., retrieve the past minute of data from memory circuitry within PCB **120** (FIG. 2)). Ingestible device **100** may then convert the obtained data into the frequency domain, and search for peaks in a frequency range that would be consistent with peristaltic waves. For example, in a healthy human subject, peristaltic waves may occur at a rate of approximately 0.1 Hz to 0.2 Hz, and an ingestible device **100** may be configured to search for peaks in the frequency domain representation of the data between 0.1 Hz and 0.2 Hz above a threshold value. If the ingestible device **100** detects a contraction based on the reflectance levels (e.g., based on detecting peaks in the frequency domain representation of the data between 0.1 Hz and 0.2 Hz), process **500** proceeds to **524** to store data indicating that the device has entered the jejunum. Alternatively, if the ingestible device **100** does not detect a muscle contraction, process **500** proceeds to **520** to gather periodic measurements of the reflectance levels while in the duodenum (e.g., duodenum **310** (FIG. 3)). In some embodiments, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) may store data (e.g., within memory circuitry of PCB **120** (FIG. 2)) indicating that a muscle contraction was detected, and process **500** will not proceed from **522** to **524** until a sufficient number of muscle contractions have been detected.

[0392] At **524**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) stores data (e.g., within memory circuitry of PCB **120** (FIG. 2)) indicating that the device has entered the jejunum (e.g., jejunum **314** (FIG. 3)). For example, in response to detecting that muscle contraction has occurred at **522**, ingestible device **100** may determine that it has entered the jejunum **314**, and is no longer inside of the duodenum (e.g., duodenum **310** (FIG. 3)) or the stomach (e.g., stomach **306** (FIG. 3)). In some embodiments, the ingestible device **100** may continue to measure muscle contractions while in the jejunum, and may store data indicative of the frequency, number, or strength of the muscle contractions over time (e.g., within memory circuitry of PCB **120** (FIG. 2)). In some embodiments, the ingestible device **100** may also be configured to monitor for one or more transitions. Such transitions can include a transition from the jejunum to the ileum, an ileocecal transition from the ileum to the cecum, a transition from the cecum to the colon, or detect exit from the body (e.g., by measuring reflectances, temperature, or levels of ambient light).

[0393] In some embodiments, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) may also determine that it has entered the jejunum (e.g., jejunum **314** (FIG. 3)) after a pre-determined amount of time has passed after having detected entry into the duodenum (e.g., duodenum **310** (FIG. 3)). For example, barring a reverse pyloric transition from the duodenum (e.g., duodenum **310** (FIG. 3)) back to the stomach (e.g., stomach **306** (FIG. 3)), the typical transit time for an ingestible device to reach the jejunum from the duodenum in a healthy human subject is less than three

minutes. In some embodiments, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) may therefore be configured to automatically determine that it has entered the jejunum after spending at least three minutes within the duodenum. This determination may be made separately from the determination made based on measured muscle contractions (e.g., the determination made at **522**), and in some embodiments, ingestible device **100** may determine that it has entered the jejunum in response to either detecting muscle contractions, or after three minutes has elapsed from having entered the duodenum (e.g., as determined by storing data at **514** indicative of the time that ingestible device entered the duodenum).

[0394] For illustrative purposes, **512-518** of process **500** describe the ingestible device (e.g., ingestible device **100**, **300**, or **400**) measuring green reflectances and blue reflectances, calculating a ratio of the two reflectances, and using this information to determine when the ingestible device has transitioned between the duodenum and stomach. However, in some embodiments, other wavelengths of light may be used other than green and blue, provided that the wavelengths of light chosen have different reflective properties within the stomach and the duodenum (e.g., as a result of different reflection coefficients of the stomach tissue and the tissue of the duodenum).

[0395] It will be understood that the steps and descriptions of the flowcharts of this disclosure, including FIG. 5, are merely illustrative. Any of the steps and descriptions of the flowcharts, including FIG. 5, may be modified, omitted, rearranged, and performed in alternate orders or in parallel, two or more of the steps may be combined, or any additional steps may be added, without departing from the scope of the present disclosure. For example, the ingestible device **100** may calculate the mean and the standard deviation of multiple data sets in parallel in order to speed up the overall computation time. As another example, ingestible device **100** may gather data periodic measurements and detect possible muscle contractions (e.g., at **520-522**) while simultaneously gathering green and blue reflectance levels to determine transitions to and from the stomach and duodenum (e.g., at **510-518**). Furthermore, it should be noted that the steps and descriptions of FIG. 5 may be combined with any other system, device, or method described in this application, including processes **600** (FIG. 6) and **900** (FIG. 9), and any of the ingestible devices or systems discussed in this application (e.g., ingestible devices **100**, **300**, or **400**) could be used to perform one or more of the steps in FIG. 5.

[0396] FIG. 6 is a flowchart illustrating some aspects of a process for detecting transitions from a stomach to a duodenum and from a duodenum back to a stomach, which may be used when determining a location of an ingestible device as it transits through a gastrointestinal (GI) tract, in accordance with some embodiments of the disclosure. In some embodiments, process **600** may begin when an ingestible device first detects that it has entered the stomach, and will continue as long as the ingestible device determines that it is within the stomach or the duodenum. In some embodiments, process **600** may only be terminated when an ingestible device determines that it has entered the jejunum, or otherwise progressed past the duodenum and the stomach. Although FIG. 6 may be described in connection with the ingestible device **100** for illustrative purposes, this is not intended to be limiting, and either portions or the entirety of

the duodenum detection process 600 described in FIG. 6 may be applied to any device discussed in this application (e.g., the ingestible devices 100, 300, or 400), and any of the ingestible devices may be used to perform one or more parts of the process described in FIG. 6. Furthermore, the features of FIG. 6 may be combined with any other systems, methods or processes described in this application. For example, portions of the process described by the process in FIG. 6 may be integrated into process 500 discussed in relation to FIG. 5.

[0397] At 602, the ingestible device (e.g., ingestible device 100, 300, or 400) retrieves a data set (e.g., from memory circuitry within PCB 120 (FIG. 2)) with ratios of the measured green reflectance levels to the measured blue reflectance levels over time. For example, ingestible device 100 may retrieve a data set from PCB 120 containing recently recorded ratios of the measured green reflectance levels to the measured blue reflectance levels (e.g., as recorded at 510 or 516 of process 500 (FIG. 5)). In some embodiments, the retrieved data set may include the ratios of the measured green reflectance levels to the measured blue reflectance levels over time. Example plots of data sets of ratios of the measured green reflectance levels to the measured blue reflectance levels are discussed further in relation to FIG. 7 and FIG. 8.

[0398] At 604, the ingestible device (e.g., ingestible device 100, 300, or 400) includes a new measurement (e.g., as made with sensing sub-unit 126 (FIG. 2)) of a ratio of the measured green reflectance level to the measured blue reflectance level in the data set. For example, ingestible device 100 may be configured to occasionally record new data by transmitting green and blue illumination (e.g., via illuminator 124 (FIG. 2)), detecting the amount of reflectance received due to the green and blue illumination (e.g., via detector 122 (FIG. 2)), and storing data indicative of the amount of the received reflectance (e.g., in memory circuitry of PCB 120 (FIG. 2)). The ingestible device 100 may be configured to record new data every five to fifteen seconds, or at any other convenient interval of time. For illustrative purposes, ingestible device 100 is described as storing and retrieving the ratio of the measured green reflectance levels to the measured blue reflectance levels (e.g., if the amount of detected green reflectance was identical to the amount of detected blue reflectance at a given time, the ratio of the green and blue reflectances would be "1.0" at that given time); however, it is understood that the green reflectance data and the blue reflectance data may be stored separately within the memory of ingestible device 100 (e.g., stored as two separate data sets within memory circuitry of PCB 120 (FIG. 2)).

[0399] At 606, the ingestible device (e.g., ingestible device 100, 300, or 400) retrieves a first subset of recent data by applying a first sliding window filter to the data set. For example, ingestible device 100 may use a sliding window filter to obtain a predetermined amount of the most recent data within the data set, which may include any new values of the ratio of the measured green reflectance level to the measured blue reflectance level obtained at 604. For instance, the ingestible device may be configured to select between ten and forty data points from the data set, or ingestible device 100 may be configured to select a predetermined range of data values between fifteen seconds of data and five minutes of data. In some embodiments, other ranges of data may be selected, depending on how fre-

quently measurements are recorded, and the particular application at hand. For instance, any suitable amount of data may be selected in the sliding window, provided that it is sufficient to detect statistically significant differences between the data selected in a second sliding window (e.g., the second subset of data selected at 614).

[0400] In some embodiments, the ingestible device (e.g., ingestible device 100, 300, or 400) may also be configured to remove outliers from the data set, or to smooth out unwanted noise in the data set. For example, ingestible device 100 may select the first subset of data, or any other subset of data, by first obtaining a raw set of values by applying a window filter to the data set (e.g., selecting a particular range of data to be included). Ingestible device 100 may then be configured to identify outliers in the raw set of values; for instance, by identifying data points that are over three standard deviations away from the mean value of the raw set of values, or any other suitable threshold. Ingestible device 100 may then determine the subset of data by removing outliers from the raw set of values. This may enable ingestible device 100 to avoid spurious information when determining whether or not it is located within the stomach or the duodenum.

[0401] At 608, the ingestible device (e.g., ingestible device 100, 300, or 400) determines whether the most recently detected location was the duodenum (e.g., duodenum 310 (FIG. 3)). In some embodiments, ingestible device 100 may store a data flag (e.g., within memory circuitry of PCB 120 (FIG. 2)) indicating the most recent portion of the GI tract that the ingestible device 100 detected itself to be within. For instance, every time ingestible device 100 detects entry to the stomach (e.g., detects entry into stomach 306 (FIG. 3) as a result of the decision made at 610), a flag is stored in memory indicating the ingestible device 100 is in the stomach (e.g., as part of storing data at 612). If ingestible device 100 subsequently detects entry into the duodenum (e.g., detects entry into duodenum 310 (FIG. 3) as a result of a decision made at 624), another different flag is stored in memory indicating that the ingestible device 100 is in the duodenum (e.g., as part of storing data at 624). In this case, ingestible device 100 may retrieve the most recently stored flag at 608, and determine whether or not the flag indicates that the ingestible device 100 was most recently within the duodenum. If ingestible device 100 detects that it was most recently in the duodenum, process 600 proceeds to 610 where the ingestible device compares the recent measurements of the ratios of the measured green reflectance levels to the measured blue reflectance levels (e.g., measurements that include the recent measurement made at 606) to the typical ratios measured within the stomach, and uses this information to determine whether a reverse pyloric transition from the duodenum back to the stomach has occurred. Alternately, if ingestible device 100 detects that it was not most recently in the duodenum (e.g., because it was in the stomach instead), process 600 proceeds to 614 where the ingestible device compares the recent measurements of the ratios of the measured green reflectance levels to the measured blue reflectance levels (e.g., measurements that include the recent measurement made at 606) to past measurements, and uses this information to determine whether a pyloric transition from the stomach to the duodenum has occurred.

[0402] Process 600 proceeds from 608 to 610 when the ingestible device determined that it was most recently in the

duodenum. At **610**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines (e.g., via control circuitry within PCB **120** (FIG. 2)) whether the current G/B signal is similar to a recorded average G/B signal in the stomach. For example, ingestible device **100** may be configured to have previously stored data (e.g., within memory circuitry of PCB **120** (FIG. 2)) indicative of the average ratio of the measured green reflectance levels to the measured blue reflectance levels measured in the stomach. Ingestible device **100** may then retrieve this stored data indicative of the average ratio of the measured green reflectance levels to the measured blue reflectance levels in the stomach, and compare this against the recent measurements in order to determine whether or not ingestible device **100** has returned back to the stomach from the duodenum. For instance, ingestible device **100** may determine if the mean value of the first subset of recent data (i.e., the average value of the recently measured ratios of the measured green reflectance levels to the measured blue reflectance levels) is less than the average ratio of the measured green reflectance levels to the measured blue reflectance levels within the stomach, or less than the average ratio measured within the stomach plus a predetermined number times the standard deviation of the ratios measured within the stomach. For instance, if the average ratio of the measured green reflectance levels to the measured blue reflectance levels in the stomach was “1,” with a standard deviation of “0.2,” ingestible device **100** may determine whether or not the mean value of the first subset of data is less than “ $1.0 + k \cdot 0.2$,” where “k” is a number between zero and five. It is understood that, in some embodiments, the ingestible device **100** may be configured to use a different threshold level to determine whether or not the mean value of the first subset of recent data is sufficiently similar to the average ratio of the measured green reflectance levels to the measured blue reflectance levels within the stomach. In response to determining that the recent ratio of the measured green reflectance levels to the measured blue reflectance levels is similar to the average ratio of measured green and blue reflectance levels seen in the stomach, process **600** proceeds to **612** where ingestible device **100** stores data indicating that it has re-entered the stomach from the duodenum. Alternately, in response to determining that the recent ratio of measured green and blue reflectance levels is sufficiently different from the average ratio of measured green and blue reflectance levels seen in the stomach, ingestible device **100** proceeds directly to **604**, and continues to obtain new data on an ongoing basis.

[0403] At **612**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) stores data indicating a reverse pyloric transition from the duodenum to the stomach was detected. For example, ingestible device **100** may store a data flag (e.g., within memory circuitry of PCB **120** (FIG. 2)) indicating that the ingestible device **100** most recently detected itself to be within the stomach portion of the GI tract (e.g., stomach **306** (FIG. 3)). In some embodiments, ingestible device **100** may also store data (e.g., within memory circuitry of PCB **120** (FIG. 2)) indicating a time that ingestible device **100** detected the reverse pyloric transition from the duodenum to the stomach. This information may be used by ingestible device **100** at **608**, and as a result process **600** may proceed from **608** to **614**, rather than proceeding from **618** to **610**. After ingestible device **100** stores the data indicating a reverse pyloric transition from the duodenum to the stomach was detected, process **600**

proceeds to **604** where ingestible device **100** continues to gather additional measurements, and continues to monitor for further transitions between the stomach and the duodenum.

[0404] Process **600** proceeds from **608** to **614** when the ingestible device determined that it was not most recently in the duodenum (e.g., as a result of having most recently been in the stomach instead). At **614**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) retrieves a second subset of previous data by applying a second sliding window filter to the data set. For example, ingestible device **100** may use a sliding window filter to obtain a predetermined amount of older data from a past time range, which may be separated from recent time range used to select the first subset of data gathered at **606** by a predetermined period of time. In some embodiments, any suitable amount of data may be selected by the first and second window filters, and the first and second window filters may be separated by any appropriate predetermined amount of time. For example, in some embodiments, the first window filter and the second window filter may each be configured to select a predetermined range of data values from the data set, the predetermined range being between fifteen seconds of data and five minutes of data. In some embodiments, the recent measurements and the past measurements may then be separated by a predetermined period of time that is between one to five times the predetermined range of data values. For instance, ingestible device **100** may select the first subset of data and the second subset of data to each be one minute of data selected from the dataset (i.e., selected to have a predetermined range of one minute), and the first subset of data and the second subset of data are selected from recorded measurements that are at least two minutes apart (i.e., the predetermined period of time is two minutes, which is twice the range used to select the subsets of data using the window filters). As another example, ingestible device **100** may select the first subset of data and the second subset of data to each be five minutes of data selected from the dataset (i.e., selected to have a predetermined range of five minutes), and the first subset of data and the second subset of data are selected from recorded measurements that are at least 10 minutes apart (i.e., the predetermined period of time is two minutes, which is twice the range used to select the subsets of data using the window filters).

[0405] In some embodiments, if ingestible device **100** recently transitioned to the stomach from the duodenum (e.g., as determined by checking for recent data stored within ingestible device **100** at **612**), ingestible device **100** may select the second subset of data at **614** from a time frame when ingestible device **100** is known to be within the stomach. In some embodiments, ingestible device **100** may alternately select a previously recorded average and standard deviation for ratios of green reflectances and blue reflectances within the stomach (e.g., an average and standard deviation typical of data recorded within the stomach, as previously recorded within memory circuitry of PCB **120** at **620**) in place of the second subset of data. In this case, ingestible device **100** may simply use the previously recorded average and previously recorded standard deviation when making a determination at **616**, rather than expending resources to calculate the mean and standard deviation of the second subset.

[0406] At **616**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines whether the difference

between the mean of the second subset and the mean of the first subset is greater than a predetermined multiple of the standard deviation of the first subset. For example, ingestible device **100** may compute a difference between a mean of the first subset of recent data and a mean of a second subset of past data, and determine whether this difference is greater than three times the standard deviation of the second subset of past data. In some embodiments, it is understood that any convenient threshold level may be used other than three times the standard deviation, such as any value between one and five times the standard deviation. Also, in some embodiments, the ingestible device may instead set the threshold level based on the standard deviation of the second subset instead of the first subset. In response to determining that the difference between the mean of the first subset and the mean of the second subset is greater than a predetermined multiple of the standard deviation of the second subset, process **600** proceeds to **618**. Otherwise, process **600** proceeds back to **604**, where the ingestible device **604** continues to gather new data to be used in monitoring for transitions between the stomach (e.g., stomach **306** (FIG. 3)) and the duodenum (e.g., duodenum **310** (FIG. 3)).

[**0407**] At **618**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines (e.g., via control circuitry within PCB **120** (FIG. 2)) whether the determination made at **616** is the first time that the difference between the mean of the first subset of recent data and the mean of the second subset of past data is calculated to be greater than the standard deviation of the second subset. If the ingestible device determines that this is the first time that the difference between the mean of the first subset and the mean of the second subset is calculated to be greater than the standard deviation of the second subset, process **600** proceeds to **620** to store the mean of the second subset of past data as an average G/B signal in the stomach. Alternatively, if the ingestible device determines that the immediately preceding determination made at **616** is not the first time that the difference between the mean of the first subset of recent data and the mean of the second subset of past data is calculated to be greater than the standard deviation of the second subset, process **600** proceeds directly to **622**.

[**0408**] At **620**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) stores the mean of the second subset as an average G/B signal in the stomach. For example, ingestible device **100** may be configured to store the mean of the second subset of past data (e.g., store within memory circuitry of PCB **120** (FIG. 2)) as the average ratio of the measured green reflectance levels to the measured blue reflectance levels measured in the stomach. In some embodiments, ingestible device **100** may also store the standard deviation of the second subset of past data as a typical standard deviation of the ratios of the measured green reflectance levels to the measured blue reflectance levels detected within the stomach. This stored information may be used by the ingestible device later on (e.g., at **610**) to compare against future data, which may enable the ingestible device to detect reverse pyloric transitions from the duodenum (e.g., duodenum **310** (FIG. 3)) back to the stomach (e.g., stomach **306** (FIG. 3)), and may generally be used in place of other experimental data gathered from the stomach (e.g., in place of the second subset of data at **616**). After storing the mean of the second subset as an average G/B signal in the stomach, process **600** proceeds to **622**.

[**0409**] At **622**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines whether a difference of the mean of the first subset of recent data to the mean of the second subset of past data is greater than a predetermined threshold, “M”. In some embodiments, the predetermined threshold, “M,” will be sufficiently large to ensure that the mean of the first subset is substantially larger than the mean of the second subset, and may enable ingestible device **100** to ensure that it detected an actual transition to the duodenum. This may be particularly advantageous when the determination made at **616** is potentially unreliable due to the standard deviation of the second subset of past data being abnormally small. For example, a typical value of the predetermined threshold “M,” may be on the order of 0.1 to 0.5. If ingestible device **100** determines that the difference of the mean of the first subset of recent data to the second subset of past data is greater than a predetermined threshold, process **600** proceeds to **624** to store data indicating that a pyloric transition from the stomach to the duodenum (e.g., from stomach **306** to duodenum **310** (FIG. 3)) was detected. Alternatively, if the ingestible device determines that the ratio of the mean of the first subset to the second subset is less than or equal to the predetermined threshold, “M” (i.e., determines that a transition to the duodenum has not occurred), process **600** proceeds directly to **604** where ingestible device **100** continues to make new measurements and monitor for possible transitions between the stomach and the duodenum.

[**0410**] In some embodiments, instead of using a difference of the mean of the first subset of recent data to the mean of the second subset of past data, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines whether the ratio of the mean of the first subset of recent data to the mean of the second subset of past data is greater than a predetermined threshold, “M”. In some embodiments, the predetermined threshold, “M,” will be sufficiently large to ensure that the mean of the first subset is substantially larger than the mean of the second subset, and may enable ingestible device **100** to ensure that it detected an actual transition to the duodenum. This may be particularly advantageous when the determination made at **616** is potentially unreliable due to the standard deviation of the second subset of past data being abnormally small. For example, a typical value of the predetermined threshold “M,” may be on the order of 1.2 to 2.0. It is understood any convenient type of threshold or calculation may be used to determine whether or not the first subset of data and the second subset of data are both statistically distinct from one another, and also substantially different from one another in terms of overall average value.

[**0411**] At **624**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) stores data indicating a pyloric transition from the stomach to the duodenum was detected. For example ingestible device **100** may store a data flag (e.g., within memory circuitry of PCB **120** (FIG. 2)) indicating that the ingestible device **100** most recently detected itself to be within the duodenum portion of the GI tract (e.g., duodenum **310** (FIG. 3)). In some embodiments, ingestible device **100** may also store data (e.g., within memory circuitry of PCB **120** (FIG. 2)) indicating a time that ingestible device **100** detected the pyloric transition from the stomach to the duodenum. This information may be used by ingestible device **100** at **608**, and as a result process **600** may proceed from **608** to **610**, rather than proceeding from **618** to **614**. After ingestible device **100** stores the data indicating

a pyloric transition from the stomach to the duodenum was detected, process 600 proceeds to 604 where ingestible device 100 continues to gather additional measurements, and continues to monitor for further transitions between the stomach and the duodenum.

[0412] It will be understood that the steps and descriptions of the flowcharts of this disclosure, including FIG. 6, are merely illustrative. Any of the steps and descriptions of the flowcharts, including FIG. 6, may be modified, omitted, rearranged, and performed in alternate orders or in parallel, two or more of the steps may be combined, or any additional steps may be added, without departing from the scope of the present disclosure. For example, the ingestible device 100 may calculate the mean and the standard deviation of multiple data sets in parallel in order to speed up the overall computation time. Furthermore, it should be noted that the steps and descriptions of FIG. 6 may be combined with any other system, device, or method described in this application, and any of the ingestible devices or systems discussed in this application could be used to perform one or more of the steps in FIG. 6. For example, portions of process 600 may be incorporated into 508-516 of process 500 (FIG. 5), and may be part of a more general process for determining a location of the ingestible device. As another example, the ratio of detected blue and green light (e.g., as measured and added to the data set at 604) may continue even outside of the stomach or duodenum, and similar information may be recorded by the ingestible device throughout its transit in the GI tract. Example plots of data sets of ratios of measured green and blue reflectance levels, which may be gathered throughout the GI tract, are discussed further in relation to FIG. 7 and FIG. 8 below.

[0413] FIG. 7 is a plot illustrating data collected during an example operation of an ingestible device (e.g., ingestible device 100, 300, or 400), which may be used when determining a location of an ingestible device as it transits through a gastrointestinal (GI) tract, in accordance with some embodiments of the disclosure.

[0414] Although FIG. 7 may be described in connection with ingestible device 100 for illustrative purposes, this is not intended to be limiting, and plot 700 and data set 702 may be typical of data gathered by any device discussed in this application. Plot 700 depicts the ratios of the measured green reflectance levels to the measured blue reflectance levels over time. For example, ingestible device 100 may have computed the value for each point in the data set 702 by transmitting green and blue illumination at a given time (e.g., via illuminator 124 (FIG. 2)), measuring the resulting green and blue reflectances (e.g., via detector 122 (FIG. 2)), calculating the ratio of the resulting reflectances, and storing the ratio in the data set along with a timestamp indicating the time that the reflectances were gathered.

[0415] At 704, shortly after ingestible device 100 begins operation, ingestible device 100 determines that it has reached at least the stomach (e.g., as a result of making a determination similar to the determination discussed in relation to 506 in process 500 (FIG. 5)). Ingestible device 100 continues to gather additional measurements of green and blue reflectance levels, and at 706 ingestible device 100 determines that a pyloric transition has occurred from the stomach to the duodenum (e.g., as a result of making a determination similar to the determinations discussed in relation to 616-624 of process 600 (FIG. 6)). Notably, the values in data set 702 around 706 jump up precipitously,

which is indicative of the higher ratios of measured green reflectance levels to measured blue reflectance levels typical of the duodenum.

[0416] The remainder of the data set 702 depicts the ratios of the measured green reflectance levels to the measured blue reflectance levels throughout the remainder of the GI tract. At 708, ingestible device 100 has reached the jejunum (e.g., as determined through measurements of muscle contractions, as discussed in relation to FIG. 9), and by 710, ingestible device 100 has reached the cecum. It is understood that, in some embodiments, the overall character and appearance of data set 702 changes within the small intestine (i.e., the duodenum, jejunum, and ileum) versus the cecum. Within the jejunum and ileum, there may typically be a wide variation in the ratios of the measured green reflectance levels to the measured blue reflectance levels, resulting in relatively noisy data with a high standard deviation. By comparison, within the cecum ingestible device 100 may measure a relatively stable ratio of the measured green reflectance levels to the measured blue reflectance levels. In some embodiments, ingestible device 100 may be configured to determine transitions from the small intestine to the cecum based on these differences. For example, ingestible device 100 may compare recent windows of data to past windows of data, and detect a transition to the cecum in response to determining that the standard deviation of the ratios in the recent window of data is substantially less than the standard deviation of the ratios in the past window of data.

[0417] FIG. 8 is another plot illustrating data collected during an example operation of an ingestible device, which may be used when determining a location of an ingestible device as it transits through a gastrointestinal (GI) tract, in accordance with some embodiments of the disclosure. Similar to FIG. 7, FIG. 8 may be described in connection with the ingestible device 100 for illustrative purposes. However, this is not intended to be limiting, and plot 800 and data set 802 may be typical of data gathered by any device discussed in this application.

[0418] At 804, shortly after ingestible device 100 begins operation, ingestible device 100 determines that it has reached at least the stomach (e.g., as a result of making a determination similar to the determination discussed in relation to 506 in process 500 (FIG. 5)). Ingestible device 100 continues to gather additional measurements of green and blue reflectance levels (e.g., via sensing sub-unit 126 (FIG. 2)), and at 806 ingestible device 100 determines that a pyloric transition has occurred from the stomach to the duodenum (e.g., as a result of making a determination similar to the determinations discussed in relation to 616-624 of process 600 (FIG. 6)). Notably, the values in data set 802 around 806 jump up precipitously, which is indicative of the higher ratios of measured green reflectance levels to measured blue reflectance levels typical of the duodenum, before falling shortly thereafter. As a result of the reduced values in data set 802, ingestible device 100 determines that a reverse pyloric transition has occurred from the duodenum back to the stomach at 808 (e.g., as a result of making a determination similar to the determinations discussed in relation to 610-612 of process 600 (FIG. 6)). At 810, as a result of the values in data set 802 increasing again, ingestible device 100 determines that another pyloric transition

has occurred from the stomach to the duodenum, and shortly thereafter ingestible device 100 proceeds onwards to the jejunum, ileum, and cecum.

[0419] The remainder of the data set 802 depicts the ratios of the measured green reflectance levels to the measured blue reflectance levels throughout the remainder of the GI tract. Notably, at 812, ingestible device reaches the transition point between the ileum and the cecum. As discussed above in relation to FIG. 7, the transition to the cecum is marked by a reduced standard deviation in the ratios of measured green reflectances and measured blue reflectances over time, and ingestible device 100 may be configured to detect a transition to the cecum based on determining that the standard deviation of a recent set of measurements is substantially smaller than the standard deviation of past measurements taken from the jejunum or ileum.

[0420] FIG. 9 is a flowchart of illustrative steps for detecting a transition from a duodenum to a jejunum, which may be used when determining a location of an ingestible device as it transits through a gastrointestinal (GI) tract, in accordance with some embodiments of the disclosure. Although FIG. 9 may be described in connection with the ingestible device 100 for illustrative purposes, this is not intended to be limiting, and either portions or the entirety of process 900 described in FIG. 9 may be applied to any device discussed in this application (e.g., the ingestible devices 100, 300, and 400), and any of these ingestible devices may be used to perform one or more parts of the process described in FIG. 9. Furthermore, the features of FIG. 9 may be combined with any other systems, methods or processes described in this application. For example, portions of the process described by the process in FIG. 9 may be integrated into the localization process described by FIG. 5 (e.g., as part of 520-524 of process 500 (FIG. 5)). In some embodiments, an ingestible device 100 may perform process 900 while in the duodenum, or in response to detecting entry to the duodenum. In other embodiments, an ingestible device 100 may perform process 900 while in the stomach, or in response to detecting entry into the GI tract. It is also understood that process 900 may be performed in parallel with any other process described in this disclosure (e.g., process 600 (FIG. 6)), which may enable ingestible device 100 to detect entry into various portions of the GI tract, without necessarily detecting entry into a preceding portion of the GI tract.

[0421] For illustrative purposes, FIG. 9 may be discussed in terms of ingestible device 100 generating and making determinations based on a single set of reflectance levels generated at a single wavelength by a single sensing sub-unit (e.g., sensing sub-unit 126 (FIG. 2)). However, it is understood that ingestible device 100 may generate multiple wavelengths of illumination from multiple different sensing sub-units positioned around the circumference of ingestible device (e.g., multiple sensing sub-units positioned at different locations behind window 114 of ingestible device 100 (FIG. 1), and each of the resulting reflectances may be stored as a separate data set. Moreover, each of these sets of reflectance levels may be used to detect muscle contractions by running multiple versions of process 900, each one of which processes data for a different set of reflectances corresponding to data sets obtained from measurements of different wavelengths or measurements made by different sensing sub-units.

[0422] At 902, the ingestible device (e.g., ingestible device 100, 300, or 400) retrieves a set of reflectance levels.

For example, ingestible device 100 may retrieve a data set of previously recorded reflectance levels from memory (e.g., from memory circuitry of PCB 120 (FIG. 2)). Each of the reflectance levels may correspond to reflectances previously detected by ingestible device 100 (e.g., via detector 122 (FIG. 2)) from illumination generated by ingestible device 100 (e.g., via illuminator 124 (FIG. 2)), and may represent a value indicative of an amount of light detected in a given reflectance. However, it is understood that any suitable frequency of light may be used, such as light in the infrared, visible, or ultraviolet spectrums. In some embodiments, the reflectance levels may correspond to reflectances previously detected by ingestible device 100 at periodic intervals.

[0423] At 904, the ingestible device (e.g., ingestible device 100, 300, or 400) includes new measurements of reflectance levels in the data set. For example, ingestible device 100 may be configured to detect a new reflectance (e.g., transmit illumination and detect the resulting reflectance using sensing sub-unit 126 (FIG. 2)) at regular intervals, or with sufficient speed as to detect peristaltic waves. For example, ingestible device 100 may be configured to generate illumination and measure the resulting reflectance once every three seconds (i.e., the minimum rate necessary to detect a 0.17 Hz signal), and preferably at a higher rate, as fast as 0.1 second or even faster. It is understood that the periodic interval between measurements may be adapted as needed based on the species of the subject, and the expected frequency of the peristaltic waves to be measured. Every time ingestible device 100 makes a new reflectance level measurement at 904, the new data is included to the data set (e.g., a data set stored within memory circuitry of PCB 120 (FIG. 2)).

[0424] At 906, the ingestible device (e.g., ingestible device 100, 300, or 400) obtains a first subset of recent data by applying a sliding window filter to the data set. For example, ingestible device 100 may retrieve a one-minute worth of data from the data set. If the data set includes values for reflectances measured every second, this would be approximately 60 data points worth of data. Any suitable type of window size may be used, provided that the size of the window is sufficiently large to detect peristaltic waves (e.g., fluctuations on the order of 0.1 Hz to 0.2 Hz for healthy human subjects). In some embodiments, ingestible device 100 may also clean the data, for example, by removing outliers from the first subset of data obtained through the use of the sliding window filter.

[0425] At 908, the ingestible device (e.g., ingestible device 100, 300, or 400) obtains a second subset of recent data by interpolating the first subset of recent data. For example, ingestible device 100 may interpolate the first subset of data in order to generate a second subset of data with a sufficient number of data points (e.g., data points spaced every 0.5 seconds or greater). In some embodiments, this may enable ingestible device 100 to also replace any outlier data points that may have been removed as part of applying the window filter at 906.

[0426] At 910, the ingestible device (e.g., ingestible device 100, 300, or 400) calculates a normalized frequency spectrum from the second subset of data. For example, ingestible device 100 may be configured to perform a fast Fourier transform to convert the second subset of data from a time domain representation into a frequency domain representation. It is understood that depending on the application being used, and the nature of the subset of data, any

number of suitable procedures (e.g., Fourier transform procedures) may be used to determine a frequency spectrum for the second subset of data. For example, the sampling frequency and size of the second subset of data may be known in advance, and ingestible device **100** may be configured to have pre-stored values of a normalized discrete Fourier transform (DFT) matrix, or the rows of the DFT matrix corresponding to the 0.1 Hz to 0.2 Hz frequency components of interest, within memory (e.g., memory circuitry of PCB **120** (FIG. 2)). In this case, the ingestible device may use matrix multiplication between the DFT matrix and the data set to generate an appropriate frequency spectrum. An example data set and corresponding frequency spectrum that may be obtained by the ingestible device is discussed in greater detail in relation to FIG. 10.

[0427] At **912**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines whether at least a portion of the normalized frequency spectrum is between 0.1 Hz and 0.2 Hz above a threshold value of 0.5 Hz. Peristaltic waves in a healthy human subject occur at a rate between 0.1 Hz and 0.2 Hz, and an ingestible device experiencing peristaltic waves (e.g., ingestible device **400** detecting contractions in walls **406** of the jejunum (FIG. 4)) may detect sinusoidal variations in the amplitude of detected reflectances levels that follow a similar 0.1 Hz to 0.2 Hz frequency. If the ingestible device determines that a portion of the normalized frequency spectrum between 0.1 Hz and 0.2 Hz is above a threshold value of 0.5, this measurement may be consistent with peristaltic waves in a healthy human subject, and process **900** proceeds to **914** where ingestible device **100** stores data indicating a muscle contraction was detected. Alternatively, if the ingestible device determines that no portion of the normalized frequency spectrum between 0.1 Hz and 0.2 Hz above a threshold value of 0.5, process **900** proceeds directly to **904** to make new measurements and to continue to monitor for new muscle contractions. It is understood that a threshold value other than 0.5 may be used, and that the exact threshold may depend on the sampling frequency and type of frequency spectrum used by ingestible device **100**.

[0428] At **914**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) stores data indicating a muscle contraction was detected. For example, ingestible device **100** may store data in memory (e.g., memory circuitry of PCB **120** (FIG. 2)) indicating that a muscle contraction was detected, and indicating the time that the muscle contraction was detected. In some embodiments, ingestible device **100** may also monitor the total number of muscle contractions detected, or the number of muscle contractions detected in a given time frame. In some embodiments, detecting a particular number of muscle contractions may be consistent with ingestible device **100** being within the jejunum (e.g., jejunum **314** (FIG. 3)) of a healthy human subject. After detecting a muscle contraction, process **900** proceeds to **916**.

[0429] At **916**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) determines whether a total number of muscle contractions exceeds a predetermined threshold number. For example, ingestible device **100** may retrieve the total number of muscle contractions detected from memory (e.g., from memory circuitry of PCB **120** (FIG. 2)), and compare the total number to a threshold value. In some embodiments, the threshold value may be one, or any number larger than one. The larger the threshold value, the more muscle contractions need to be detected before ingest-

ible device **100** stores data indicating that it has entered the jejunum. In practice, setting the threshold value as three or higher may prevent the ingestible device from detecting false positives (e.g., due to natural movement of the GI tract organs, or due to movement of the subject). If the total number of contractions exceeds the predetermined threshold number, process **900** proceeds to **918** to store data indicating detection of a transition from the duodenum to the jejunum. Alternatively, if the total number of contractions does not exceed a predetermined threshold number, process **900** proceeds to **904** to include new measurements of reflectance levels in the data set. An example plot of the muscle contractions detected over time is discussed in greater detail in relation to FIG. 11.

[0430] At **918**, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) stores data indicating detection of a transition from the duodenum to the jejunum. For example, ingestible device **100** may store data in memory (e.g., from memory circuitry of PCB **120** (FIG. 2)) indicating that the jejunum has been reached. In some embodiments, if ingestible device **100** is configured to perform all or part of process **900** while in the stomach, ingestible device **100** may store data at **918** indicating detection of a transition from the stomach directly to the jejunum (e.g., as a result of transitioning too quickly through the duodenum for the pyloric transition to be detected using process **600** (FIG. 6)).

[0431] In some embodiments, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) may be configured to obtain a fluid sample from the environment external to a housing of the ingestible device in response to identifying a change in the location of the ingestible device. For example, ingestible device **100** may be configured to obtain a fluid sample from the environment external to the housing of ingestible device **100** (e.g., through the use of optional opening **116** and optional rotating assembly **118** (FIG. 2)) in response to determining that the ingestible device is located within the jejunum (e.g., jejunum **314** (FIG. 3)). In some embodiments, ingestible device **100** may also be equipped with appropriate diagnostics to detect certain medical conditions based on the retrieved fluid sample, such as small intestinal bacterial overgrowth (SIBO).

[0432] In some embodiments, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) may be configured to deliver a dispensable substance that is pre-stored within the ingestible device from the ingestible device into the gastrointestinal tract in response to identifying the change in the location of the ingestible device. For example, ingestible device **100** may have a dispensable substance pre-stored within the ingestible device **100** (e.g., within a storage chamber or cavity on optional storage sub-unit **118-3** (FIG. 2)), and ingestible device **100** may be configured to dispense the substance into the gastrointestinal tract (e.g., through the use of optional opening **116** and optional rotating assembly **118** (FIG. 2)) when the ingestible device **100** detects that the ingestible device **100** is located within the jejunum (e.g., jejunum **314** (FIG. 3)). In some embodiments, this may enable ingestible device **100** to deliver substances (e.g., therapeutics and medicaments) at targeted locations within the GI tract.

[0433] In some embodiments, the ingestible device (e.g., ingestible device **100**, **300**, or **400**) may be configured to perform an action based on the total number of detected muscle contractions. For example, ingestible device **100** may be configured to retrieve data indicative of the total

number of muscle contractions (e.g., from memory circuitry of PCB 120 (FIG. 2)), and compare that to an expected number of muscle contractions in a healthy individual. In response, the ingestible device may either dispense a substance into the gastrointestinal tract (e.g., through the use of optional opening 116 and optional rotating assembly 118 (FIG. 2)), or may obtain a fluid sample from the environment external to the housing of ingestible device 100 (e.g., through the use of optional opening 116 and optional rotating assembly 118 (FIG. 2)). For instance, ingestible device 100 may be configured to obtain a sample in response to determining that a number of detected muscle contractions is abnormal, and differs greatly from the expected number. As another example, ingestible device 100 may be configured to deliver a substance into the GI tract (such as a medicament), in response to determining that the detected muscle contractions are consistent with a functioning GI tract in a healthy individual.

[0434] It will be understood that the steps and descriptions of the flowcharts of this disclosure, including FIG. 9, are merely illustrative. Any of the steps and descriptions of the flowcharts, including FIG. 9, may be modified, omitted, rearranged, performed in alternate orders or in parallel, two or more of the steps may be combined, or any additional steps may be added, without departing from the scope of the present disclosure. For example, the ingestible device 100 may calculate the mean and the standard deviation of multiple data sets in parallel (e.g., multiple data sets, each one corresponding to a different wavelength of reflectance or different sensing sub-unit used to detect the reflectance) in order to speed up the overall computation time. Furthermore, it should be noted that the steps and descriptions of FIG. 9 may be combined with any other system, device, or method described in this application, and any of the ingestible devices or systems discussed in this application could be used to perform one or more of the steps in FIG. 9.

[0435] FIG. 10 is a plot illustrating data collected during an example operation of an ingestible device, which may be used when detecting a transition from a duodenum to a jejunum, in accordance with some embodiments of the disclosure. Diagram 1000 depicts a time domain plot 1002 of a data set of reflectance levels measured by an ingestible device (e.g., the second subset of data discussed in relation to 908 of FIG. 9). In some embodiments, ingestible device 100 may be configured to gather data points at semi-regular intervals approximately 0.5 seconds apart. By comparison, diagram 1050 depicts a frequency domain plot 1004 of the same data set of reflectance levels measured by an ingestible device (e.g., as a result of ingestible device 100 calculating a frequency spectrum at 910 of FIG. 9). In some embodiments, ingestible device 100 may be configured to calculate the frequency spectrum through any convenient means.

[0436] In diagram 1050, the range of frequencies 1006 between 0.1 Hz and 0.2 Hz may be the range of frequencies that ingestible device 100 searches in order to detect muscle contractions. As shown in diagram 1050, there is a strong peak in the frequency domain plot 1004 around 0.14 Hz, which is consistent with the frequency of peristaltic motion in a healthy human individual. In this case, an ingestible device 100 analyzing frequency domain plot 1004 may be configured to determine that the data is consistent with a detected muscle contraction (e.g., using a process similar to 912 of process 900 (FIG. 9)), and may store data (e.g., in memory circuitry of PCB 120 (FIG. 2)) indicating that a

muscle contraction has been detected. Because the muscle contraction was detected from the one-minute window of data ending at 118 minutes, ingestible device 100 may also store data indicating that the muscle contraction was detected at the 118-minute mark (i.e., which may indicate that the ingestible device 100 was turned on and ingested by the subject 118 minutes ago).

[0437] FIG. 11 is a plot illustrating muscle contractions detected by an ingestible device over time, which may be used when determining a location of an ingestible device as it transits through a gastrointestinal (GI) tract, in accordance with some embodiments of the disclosure. In some embodiments, ingestible device 100 may be configured to detect muscle contractions, and store data indicative of when each muscle contraction is detected (e.g., as part of 914 of process 900 (FIG. 9)). Plot 1100 depicts the detected muscle contractions 1106 over time, with each muscle contraction being represented by a vertical line reaching from "0" to "1" on the y-axis.

[0438] At 1102, around the 10-minute mark, ingestible device 100 first enters the duodenum (e.g., as determined by ingestible device 100 performing process 600 (FIG. 6)). Shortly thereafter, at 1108, ingestible device 100 begins to detect several muscle contractions 1106 in quick succession, which may be indicative of the strong peristaltic waves that form in the jejunum (e.g., jejunum 314 (FIG. 3)). Later, around 1110, ingestible device 100 continues to detect intermittent muscle contractions, which may be consistent with an ingestible device 100 within the ileum. Finally, at 1104, ingestible device 100 transitions out of the small intestine, and into the cecum. Notably, ingestible device 100 detects more frequent muscle contractions in the jejunum portion of the small intestine as compared to the ileum portion of the small intestine, and ingestible device 100 does not measure any muscle contractions after having exited the small intestine. In some embodiments, ingestible device 100 may incorporate this information into a localization process. For example, ingestible device 100 may be configured to detect a transition from a jejunum to an ileum in response to determining that a frequency of detected muscle contractions (e.g., the number of muscle contractions measured in a given 10-minute window) has fallen below a threshold number. As another example, ingestible device 100 may be configured to detect a transition from an ileum to a cecum in response to determining that no muscle contractions have been detected for a threshold period of time. It is understood that these examples are intended to be illustrative, and not limiting, and that measurements of muscle contractions may be combined with any of the other processes, systems, or methods discussed in this disclosure.

[0439] FIG. 12 is a flowchart 1200 for certain embodiments for determining a transition of the device from the jejunum to the ileum. It is to be noted that, in general, the jejunum is redder and more vascular than the ileum. Moreover, generally, in comparison to the ileum, the jejunum has a thicker intestine wall with more mesentery fat. These differences between the jejunum and the ileum are expected to result in differences in optical responses in the jejunum relative to the ileum. Optionally, one or more optical signals may be used to investigate the differences in optical responses. For example, the process can include monitoring a change in optical response in reflected red light, blue light, green light, ratio of red light to green light, ratio of red light

to blue light, and/or ratio of green light to blue light. In some embodiments, reflected red light is detected in the process.

[0440] Flowchart 1200 represents a single sliding window process. In step 1210, the jejunum reference signal is determined based on optical reflection. Typically, this signal is as the average signal (e.g., reflected red light) over a period of time since the device was determined to enter the jejunum. The period of time can be, for example, from five minutes to 40 minutes (e.g., from 10 minutes to 30 minutes, from 15 minutes to 25 minutes). In step 1220, the detected signal (e.g., reflected red light) just after the period of time used in step 1210 is normalized to the reference signal determined in step 1210. In step 1230, the signal (e.g., reflected red light) is detected. In step 1240, the mean signal detected based on the single sliding window is compared to a signal threshold. The signal threshold in step 1240 is generally a fraction of the reference signal of the jejunum reference signal determined in step 1210. For example, the signal threshold can be from 60% to 90% (e.g., from 70% to 80%) of the jejunum reference signal. If the mean signal exceeds the signal threshold, then the process determines that the device has entered the ileum at step 1250. If the mean signal does not exceed the signal threshold, then the process returns to step 1230.

[0441] FIG. 13 is a flowchart 1300 for certain embodiments for determining a transition of the device from the jejunum to the ileum using a two sliding window process. In step 1310, the jejunum reference signal is determined based on optical reflection. Typically, this signal is as the average signal (e.g., reflected red light) over a period of time since the device was determined to enter the jejunum. The period of time can be, for example, from five minutes to 40 minutes (e.g., from 10 minutes to 30 minutes, from 15 minutes to 25 minutes). In step 1320, the detected signal (e.g., reflected red light) just after the period of time used in step 1310 is normalized to the reference signal determined in step 1310. In step 1330, the signal (e.g., reflected red light) is detected. In step 1340, the mean difference in the signal detected based on the two sliding windows is compared to a signal threshold. The signal threshold in step 1340 is based on whether the mean difference in the detected signal exceeds a multiple (e.g., from 1.5 times to five times, from two times to four times) of the detected signal of the first window. If signal threshold is exceeded, then the process determines that the device has entered the ileum at step 1350. If the signal threshold is not exceeded, then the process returns to step 1330.

[0442] FIG. 14 is a flowchart 1400 for a process for certain embodiments for determining a transition of the device from the ileum to the cecum. In general, the process involves detecting changes in the reflected optical signal (e.g., red light, blue light, green light, ratio of red light to green light, ratio of red light to blue light, and/or ratio of green light to blue light). In some embodiments, the process includes detecting changes in the ratio of reflected red light to reflected green light, and also detecting changes in the ratio of reflected green light to reflected blue light. Generally, in the process 1400, the sliding window analysis (first and second windows) discussed with respect to process 600 is continued.

[0443] Step 1410 includes setting a first threshold in a detected signal, e.g., ratio of detected red light to detected green light, and setting a second threshold for the coefficient of variation for a detected signal, e.g., the coefficient of

variation for the ratio of detected green light to detected blue light. The first threshold can be set to a fraction (e.g., from 0.5 to 0.9, from 0.6 to 0.8) of the average signal (e.g., ratio of detected red light to detected green light) in the first window, or a fraction (e.g., from 0.4 to 0.8, from 0.5 to 0.7) of the mean difference between the detected signal (e.g., ratio of detected red light to detected green light) in the two windows. The second threshold can be set to 0.1 (e.g., 0.05, 0.02).

[0444] Step 1420 includes detecting the signals in the first and second windows that are to be used for comparing to the first and second thresholds.

[0445] Step 1430 includes comparing the detected signals to the first and second thresholds. If the corresponding value is not below the first threshold or the corresponding value is not below the second threshold, then it is determined that the device has not left the ileum and entered the cecum, and the process returns to step 1420. If the corresponding value is below the first threshold and the corresponding value is below the second threshold, then it is determined that the device has left the ileum and entered the cecum, and the process proceeds to step 1440.

[0446] Step 1450 includes determining whether it is the first time that the device was determined to leave the ileum and enter the cecum. If it is the first time that the device was determined to leave the ileum and enter the cecum, then the process proceeds to step 1460. If it is not the first time that the device has left the ileum and entered the cecum, then the process proceeds to step 1470.

[0447] Step 1460 includes setting a reference signal. In this step the optical signal (e.g., ratio of detected red light to detected green light) as a reference signal.

[0448] Step 1470 includes determining whether the device may have left the cecum and returned to the ileum. The device is determined to have left the cecum and returned to the ileum if the corresponding detected signal (e.g., ratio of detected red light to detected green light) is statistically comparable to the reference signal (determined in step 1460) and the coefficient of variation for the corresponding detected signal (e.g., ratio of detected green light to detected blue light) exceeds the second threshold. If it is determined that the device may have left the cecum and returned to the ileum, the process proceeds to step 1480.

[0449] Step 1480 includes continuing to detect the relevant optical signals for a period of time (e.g., at least one minute, from five minutes to 15 minutes).

[0450] Step 1490 includes determining whether the signals determined in step 1480 indicate (using the methodology discussed in step 1470) that the device re-entered the ileum. If the signals indicate that the device re-entered the ileum, the process proceeds to step 1420. If the signals indicate that the device is in the cecum, the process proceeds to step 1492.

[0451] Step 1492 includes continuing to monitor the relevant optical signals for a period of time (e.g., at least 30 minutes, at least one hour, at least two hours).

[0452] Step 1494 includes determining whether the signals determined in step 1492 indicate (using the methodology discussed in step 1470) that the device re-entered the ileum. If the signals indicate that the device re-entered the ileum, the process proceeds to step 1420. If the signals indicate that the device is in the cecum, the process proceeds to step 1496.