FIG. 1

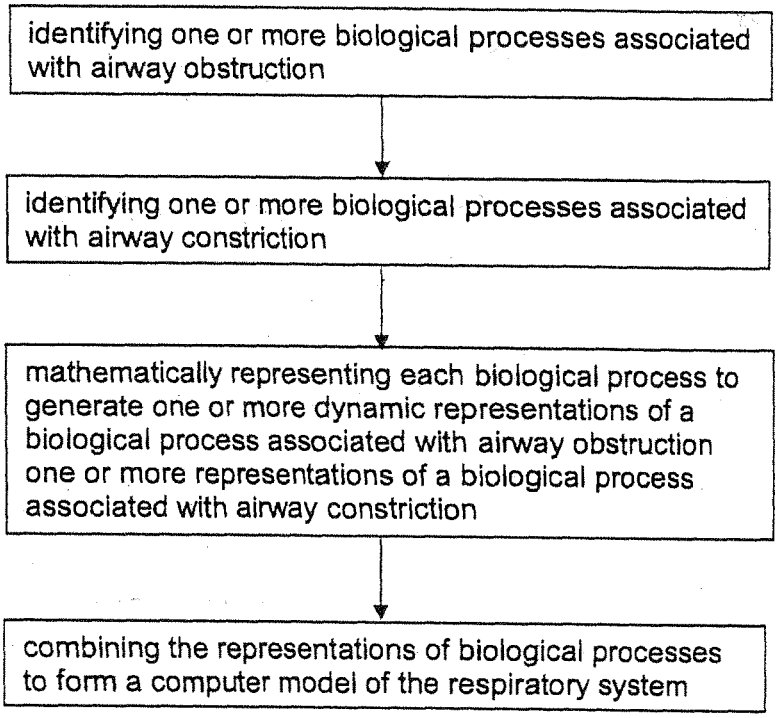
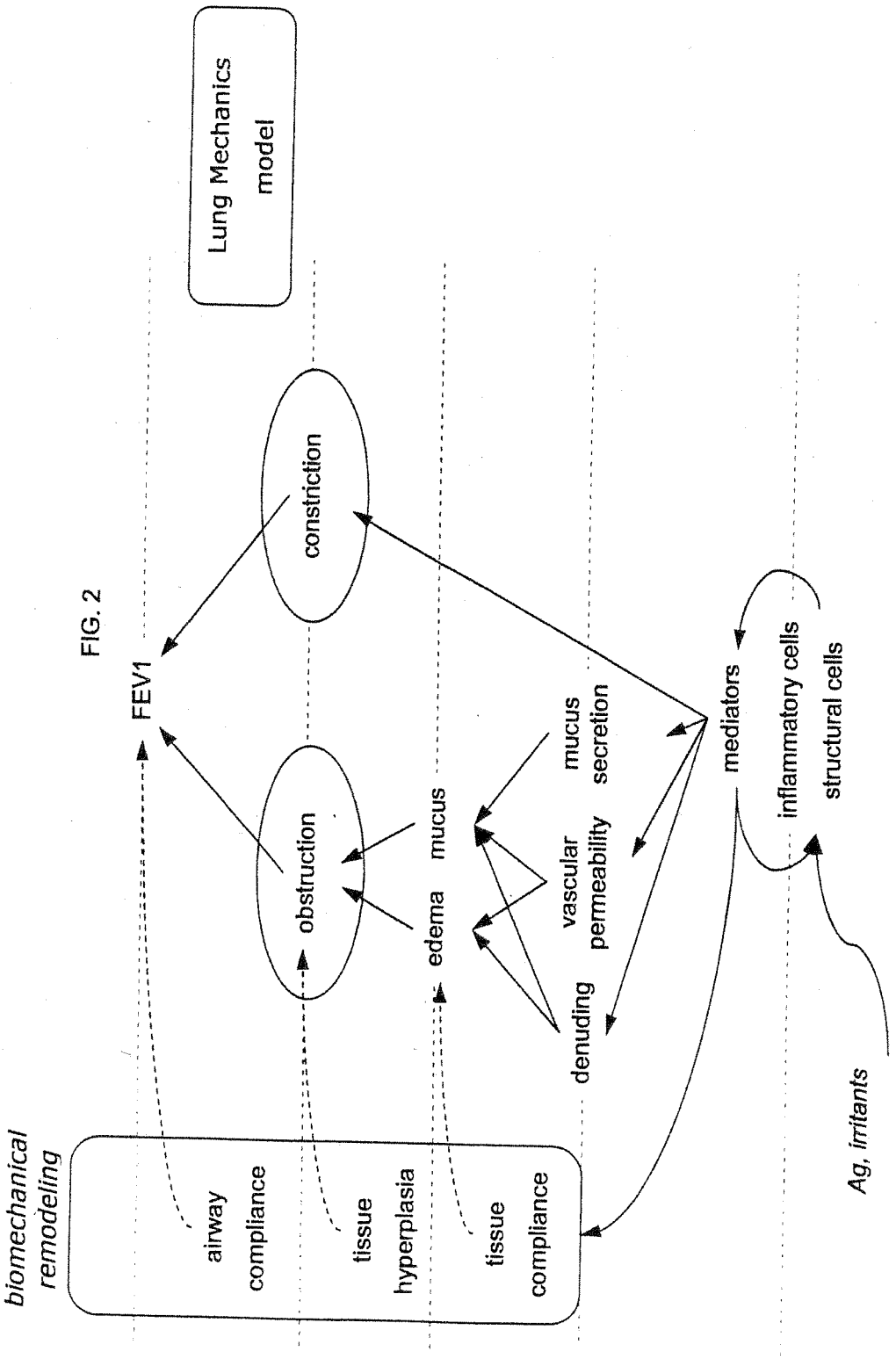

identifying one or more biological processes associated with airway obstruction
identifying one or more biological processes associated with airway constriction
mathematically representing each biological process to generate one or more dynamic representations of a biological process associated with airway obstruction one or more representations of a biological process associated with airway constriction
combining the representations of biological processes to form a computer model of the respiratory system

FIG. 2


Lung Mechanics model
constriction
FEV1
obstruction
mucus
edema
mucus secretion
vascular permeability
denuding
mediators
inflammatory cells
structural cells
Ag, irritants
biomechanical remodeling
airway compliance
tissue hyperplasia
tissue compliance

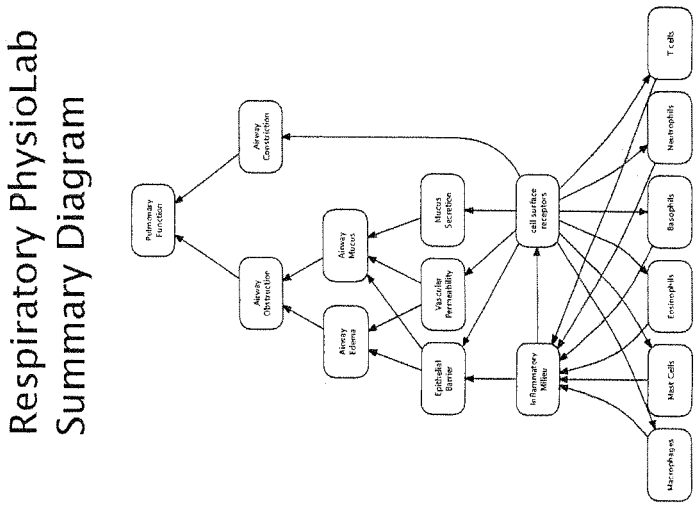

Respiratory PhysioLab
Summary Diagram
Pulmonary Function
Airway Constriction
Airway Obstruction
Airway Mucus
Airway Edema
Mucus Secretion
Vascular Permeability
Epithelial Barrier
cell surface receptors
Inflammatory Milieu
T cells
Neutrophils
Basophils
Eosinophils
Mast Cells
Macrophages

FIG. 3

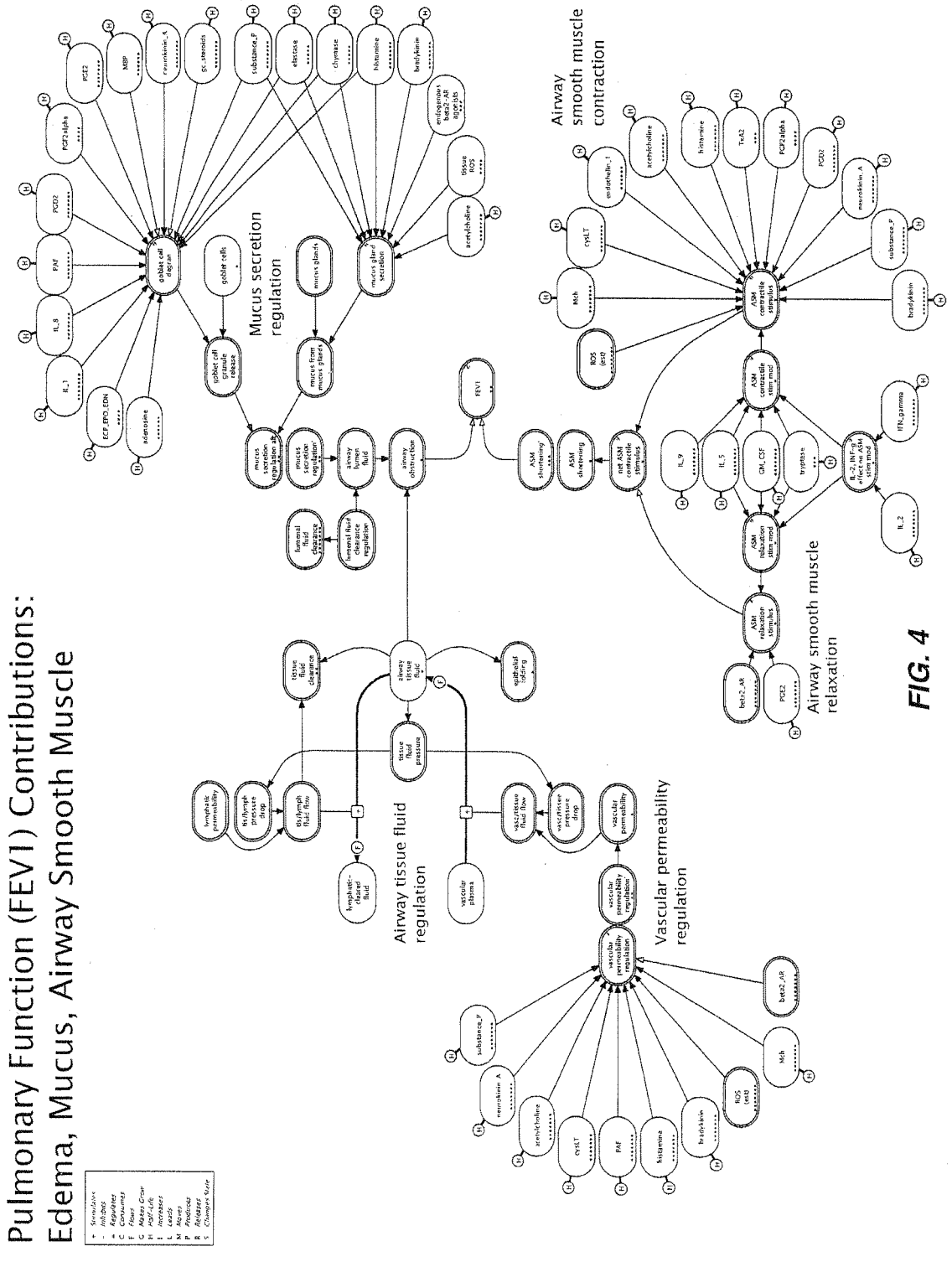

Pulmonary Function (FEV1) Contributions:
Edema, Mucus, Airway Smooth Muscle
Mucus secretion regulation
Airway smooth muscle contraction
Airway tissue fluid regulation
Vascular permeability regulation
Airway smooth muscle relaxation

FIG. 4

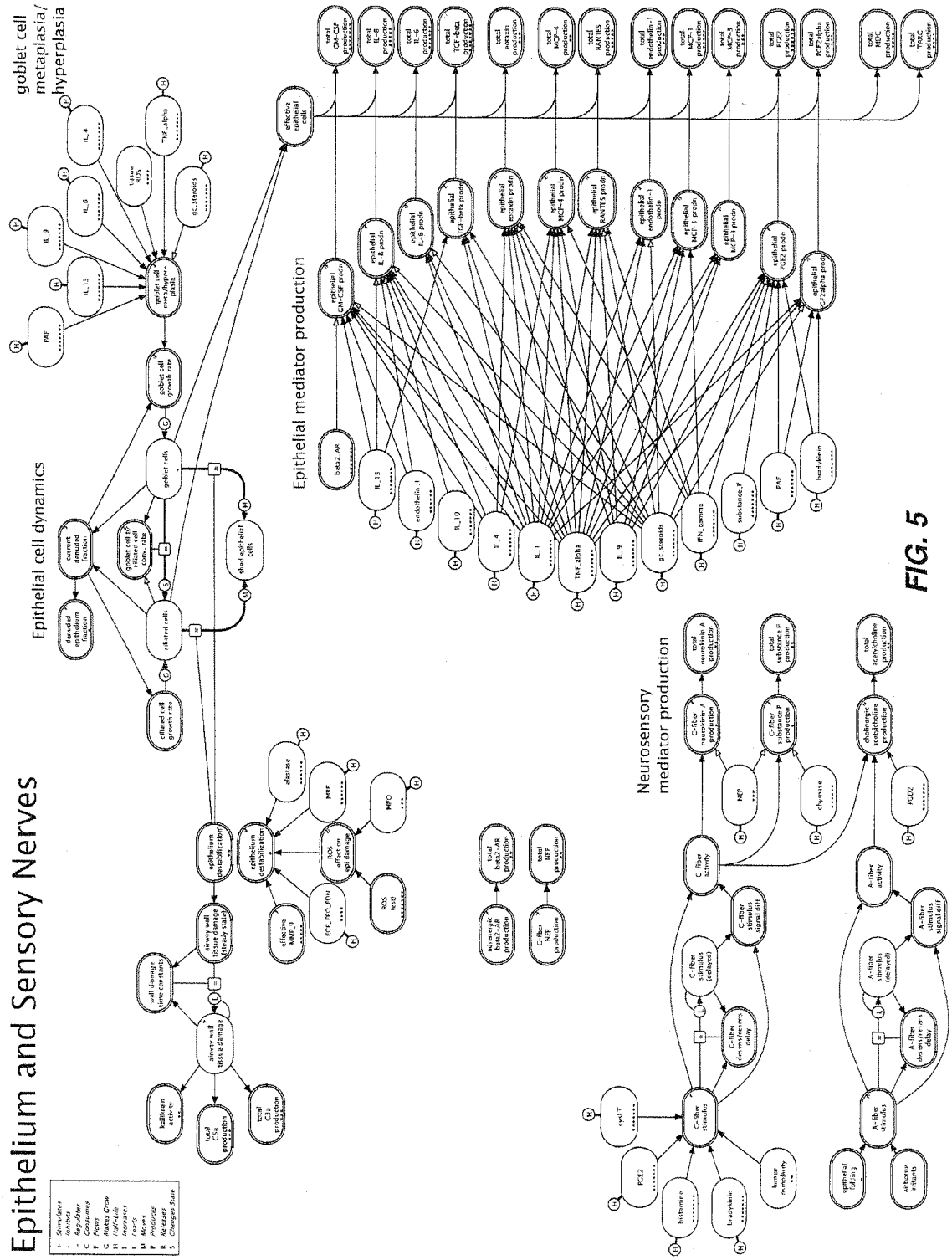

Epithelium and Sensory Nerves
Epithelial cell dynamics
goblet cell metaplasia/ hyperplasia
Epithelial mediator production
Neurosensory mediator production

FIG. 5

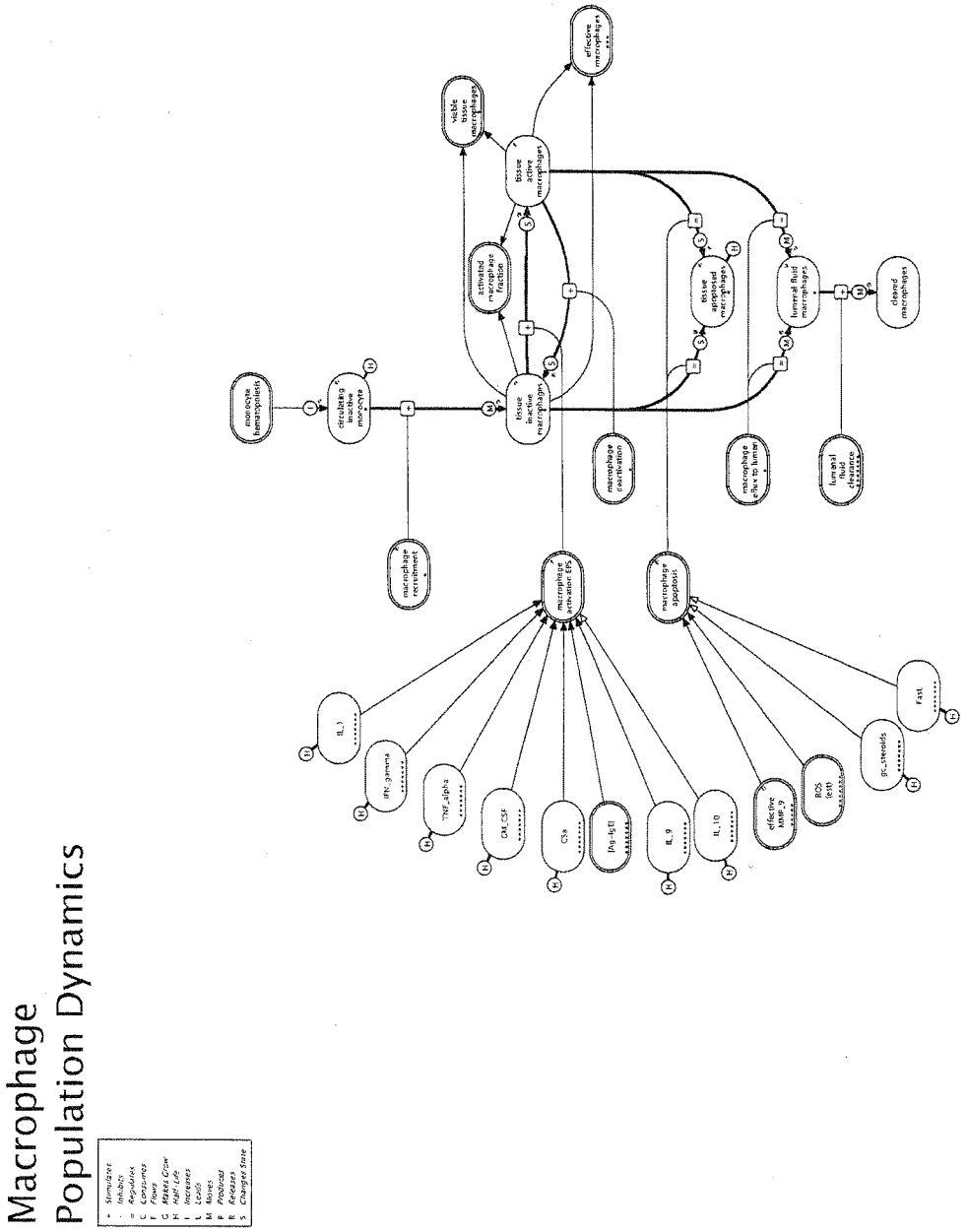

Macrophage
Population Dynamics
+ Stimulates
- Inhibits
= Requires
C Consumes
F Flows
E Enters / Grow
D Exits / Die
H Half-Life
I Increases
L Leads
M Moves
P Processes
R Releases
S Changes State
monocyte hemangioblasts
circulating inactive monocyte
tissue inactive macrophages
tissue active macrophages
activated macrophage fraction
viable tissue macrophages
effective macrophages
tissue apoptosed macrophages
luminal fluid macrophages
cleared macrophages
macrophage recruitment
macrophage activation EC50
macrophage apoptosis
macrophage proliferation
macrophage efflux to lumen
lumenal fluid clearance
IL_1
IFN_gamma
TNF_alpha
GM_CSF
C5a
Ig-IgE
IL_9
IL_10
effective MMP_9
ROS term
gc_steroids
Fast

FIG. 6

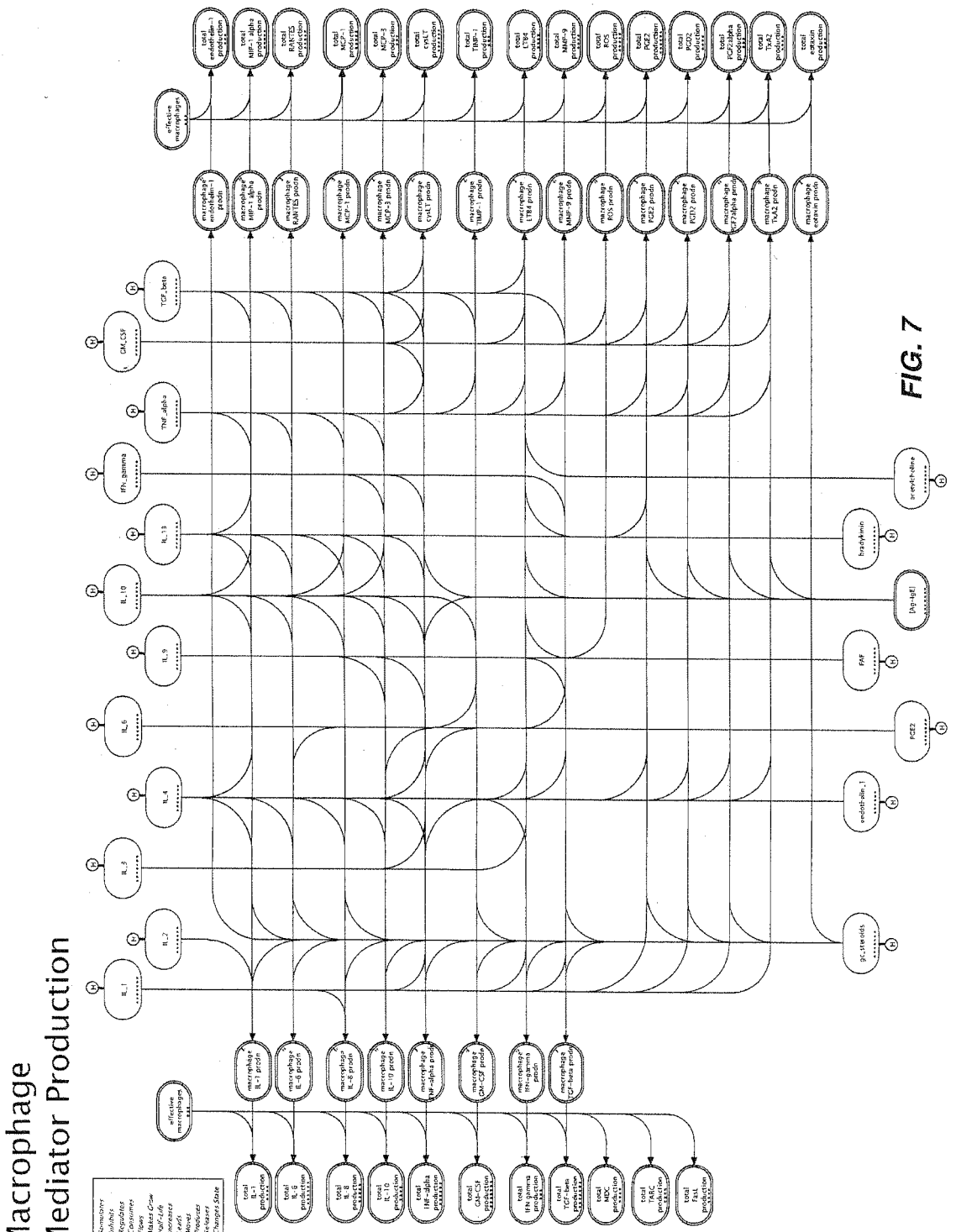

Macrophage
Mediator Production
effective macrophages
IL_1
IL_7
IL_3
IL_4
IL_6
IL_9
IL_10
IL_13
IFN_gamma
TNF_alpha
GM_CSF
TGF_beta
gc_steroids
endost-alin_1
PGE2
FAF
[Ag-IgE]
bradykinin
arachidonic
total endothelin-1 production
total MIP-1 alpha production
total RANTES production
total MCP-1 production
total MCP-3 production
total cysLT production
total TBXA2 production
total LTB4 production
total MMP-9 production
total ROS production
total PGE2 production
total PGD2 production
total PGF2alpha production
total TxA2 production
total eotaxin production
macrophage endothelin-1 prodn
macrophage MIP-1 alpha prodn
macrophage RANTES prodn
macrophage MCP-1 prodn
macrophage MCP-3 prodn
macrophage cysLT prodn
macrophage TBXA2 prodn
macrophage LTB4 prodn
macrophage MMP-9 prodn
macrophage ROS prodn
macrophage PGE2 prodn
macrophage PGD2 prodn
macrophage PGF2alpha prodn
macrophage TxA2 prodn
macrophage eotaxin prodn
effective macrophages
macrophage IL-1 prodn
macrophage IL-6 prodn
macrophage IL-8 prodn
macrophage IL-10 prodn
macrophage IFN-alpha prodn
macrophage GM-CSF prodn
macrophage IFN-gamma prodn
macrophage TGF-beta prodn
total IL-1 production
total IL-6 production
total IL-8 production
total IL-10 production
total IFN-alpha production
total GM-CSF production
total IFN-gamma production
total TGF-beta production
total MMP production
total TBXA2 production
total FAF production
Synonym
Inhibits
Regulates
Consumes
Flows
Makes Grow
Half-Life
Increases Levels
Moves
Produces
Reduces
Changes State

FIG. 7

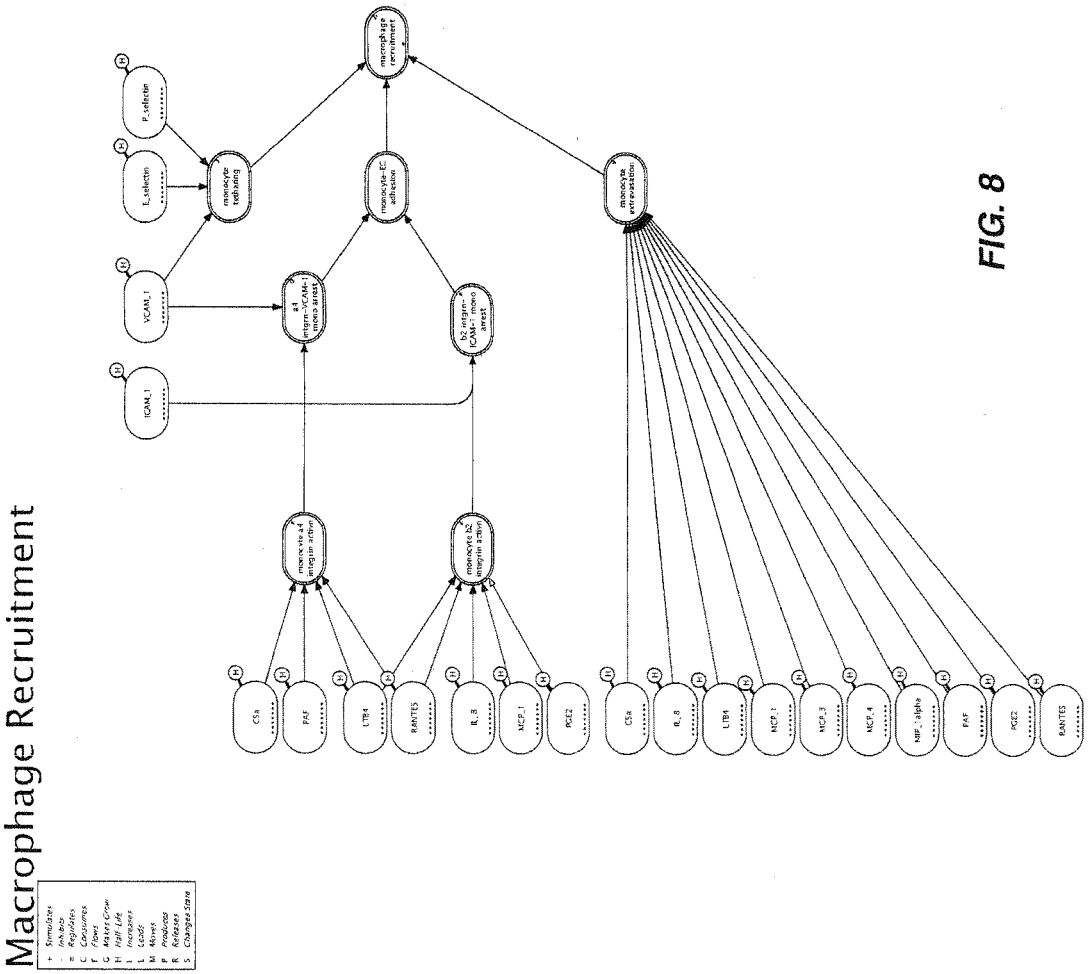

Macrophage Recruitment
+ Stimulates
- Inhibits
= Regulates
C Consumes
F Flows
G Makes Flow
H Half Life
I Increases
L Leads
M Moves
P Produces
R Releases
S Changes State
P_selection
E_selection
VCAM_1
ICAM_1
monocyte tethering
monocyte-EC adhesion
macrophage recruitment
a1 integrin-VCAM-1 mono arrest
b2 integrin-ICAM-1 mono arrest
monocyte transmigration
monocyte a1 migrat. state
monocyte b2 migrat. state
C5a
PAF
LTB4
RANTES
IL_8
MCP_1
PGE2
C5a
IL_8
LTB4
MCP_1
MCP_3
MCP_4
MIP_1alpha
PAF
PGE2
RANTES

FIG. 8

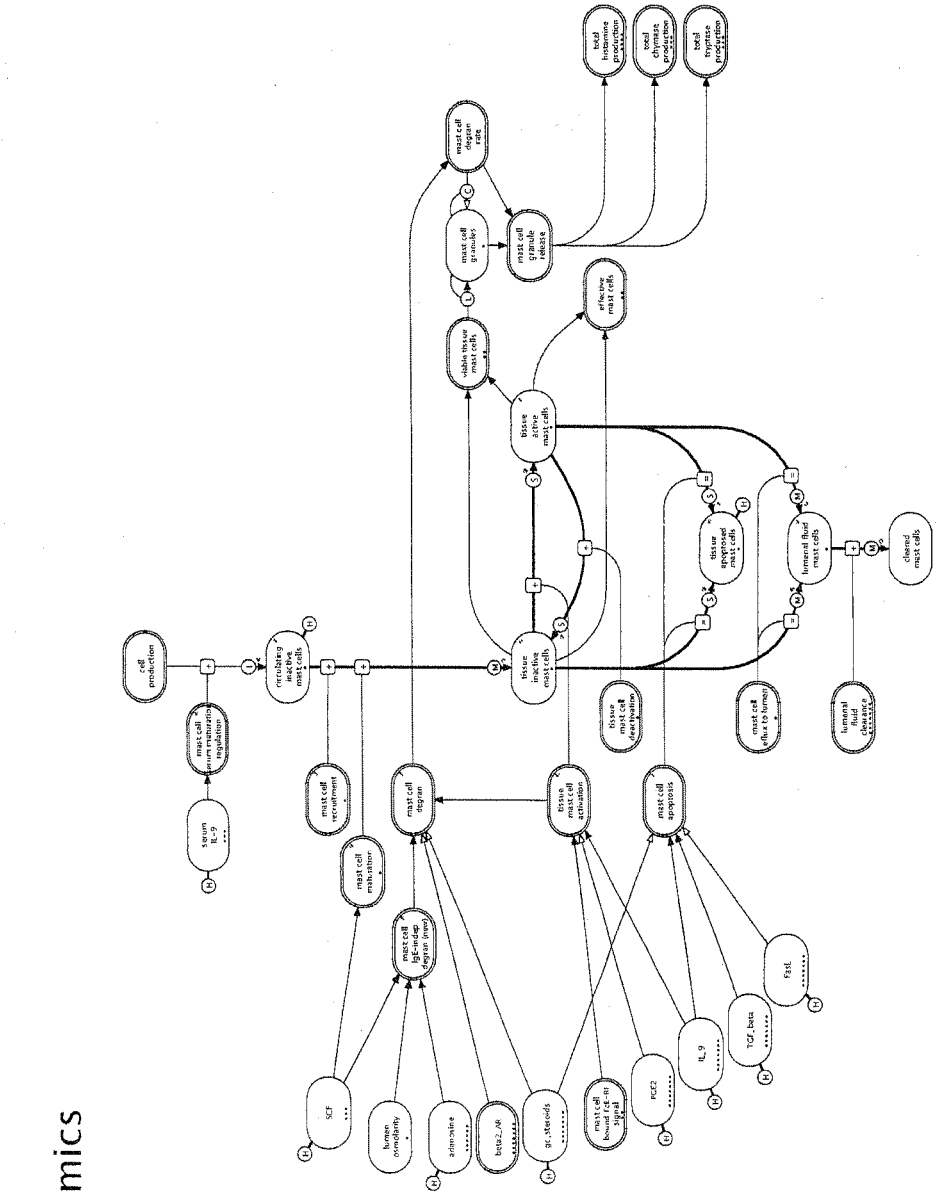

Mast Cell
Population Dynamics
S Stimulator
I Inhibits
E Equivalent
C Constants
F Flows
G Makes Grow
H Half-Life
I Increases
L Level
M Mixes
P Produces
R Releases
S Changes State
cell production
circulating inactive mast cells
tissue inactive mast cells
tissue active mast cells
tissue apoptosed mast cells
luminal fluid mast cells
cleared mast cells
mast cell recruitment
mast cell maturation
mast cell degran
mast cell activation
mast cell apoptosis
mast cell IgE-indep degran signal
mast cell degran rate
mast cell granules
mast cell granule release
total histamine production
total chymase production
total tryptase production
viable tissue mast cells
effective mast cells
tissue mast cell density
mast cell efflux to lymph
luminal fluid clearance
SCF
human cromolyn
adenosine
beta2_AR
gc_steroids
mast cell bound IgE-FcRI signal
PGE2
IL_9
TGF_beta
Fst

FIG. 9

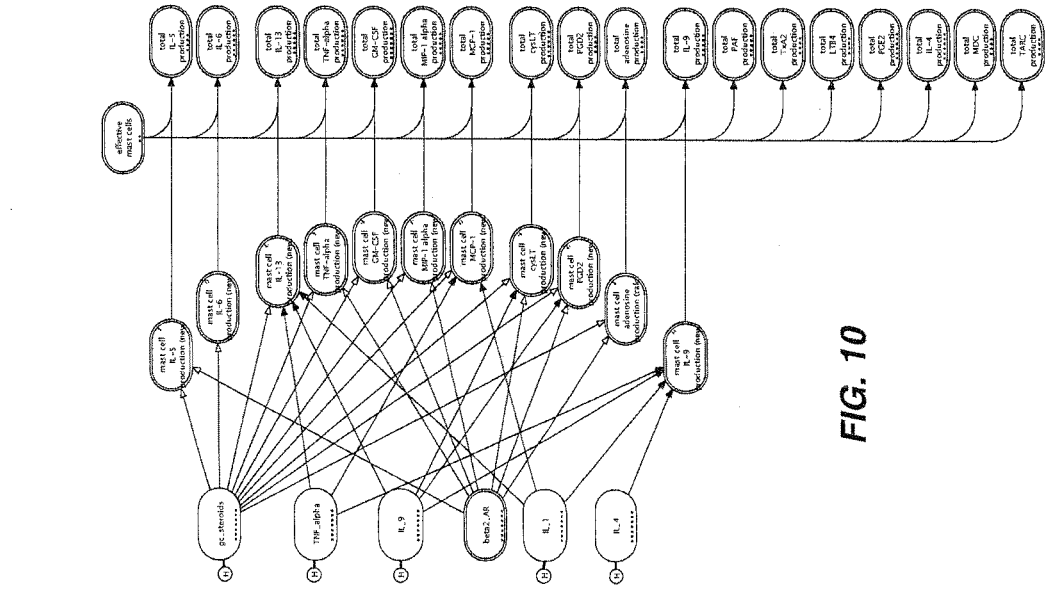

Mast Cell
Mediator Production
effective mast cells
pc.steroids
TNF_alpha
IL_9
beta2_AR
IL_1
IL_4

FIG. 10

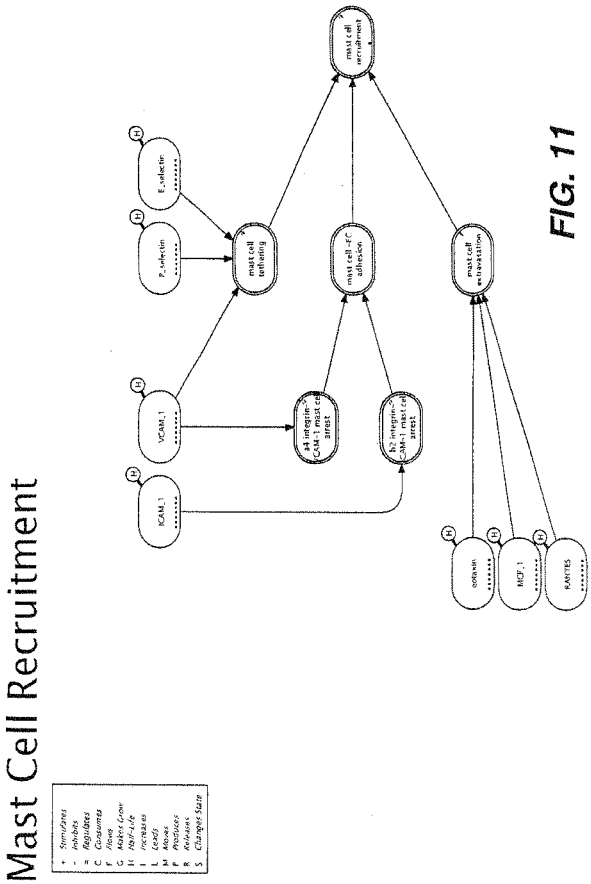

Mast Cell Recruitment
mast cell recruitment
E-selection
P-selection
VCAM-1
ICAM-1
mast cell tethering
α4 integrin-VCAM-1 mast cell arrest
mast cell-EC adhesion
β2 integrin-ICAM-1 mast cell arrest
mast cell extravasation
osteopontin
MCP-1
RANTES

FIG. 11

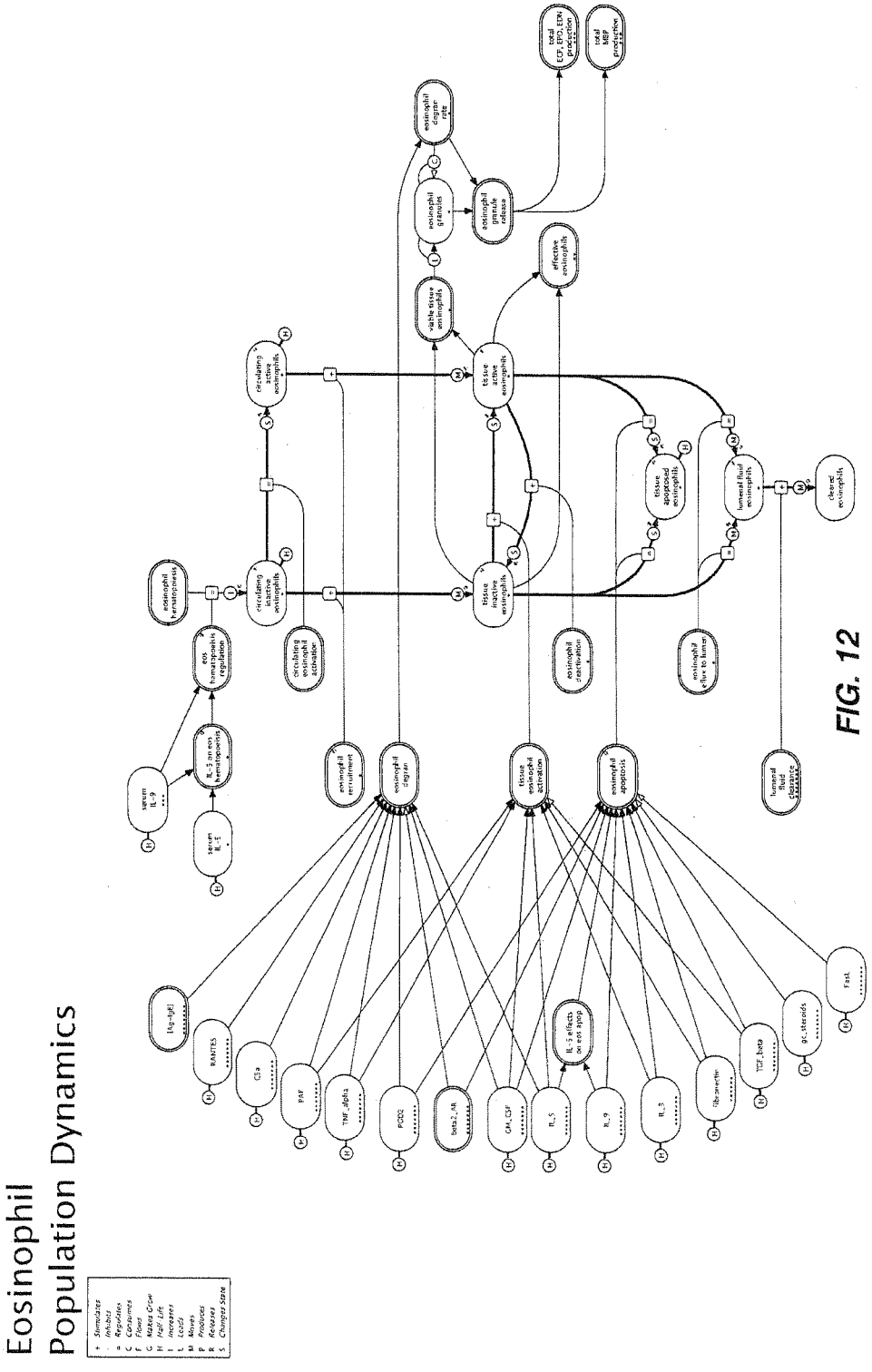

Eosinophil
Population Dynamics
+ Stimulates
- Inhibits
a Activates
C Concentrations
F Flows
G Makes Grow
H Half-Life
I Increases
L Levels
M Moves
P Produces
R Releases
S Changes State
serum IL-5
serum IL-3
IL-5 on eos hematopoiesis
eos hematopoiesis regulation
eosinophil hematopoiesis
circulating eosinophils
circulating activated eosinophils
circulating eosinophil activation
eosinophil recruitment
eosinophil degran
tissue inactive eosinophils
tissue active eosinophils
tissue eosinophil activation
eosinophil apoptosis
eosinophil granule release
eosinophil granules
eosinophil degran rate
viable tissue eosinophils
effective eosinophils
tissue apoptosed eosinophils
eosinophil clearance
eosinophil efflux to lumen
lumenal fluid eosinophils
lumenal fluid clearance
cleared eosinophils
total ECP, EDN, EPX production
total MBP production
[Ag-IgE]
RANTES
C5a
PAF
TNF_alpha
PDGF
beta2_AR
GM_CSF
IL_5
IL_5 effects on eos apop
IL_9
IL_3
fibronectin
TGF_beta
gc_steroids
Fast

FIG. 12

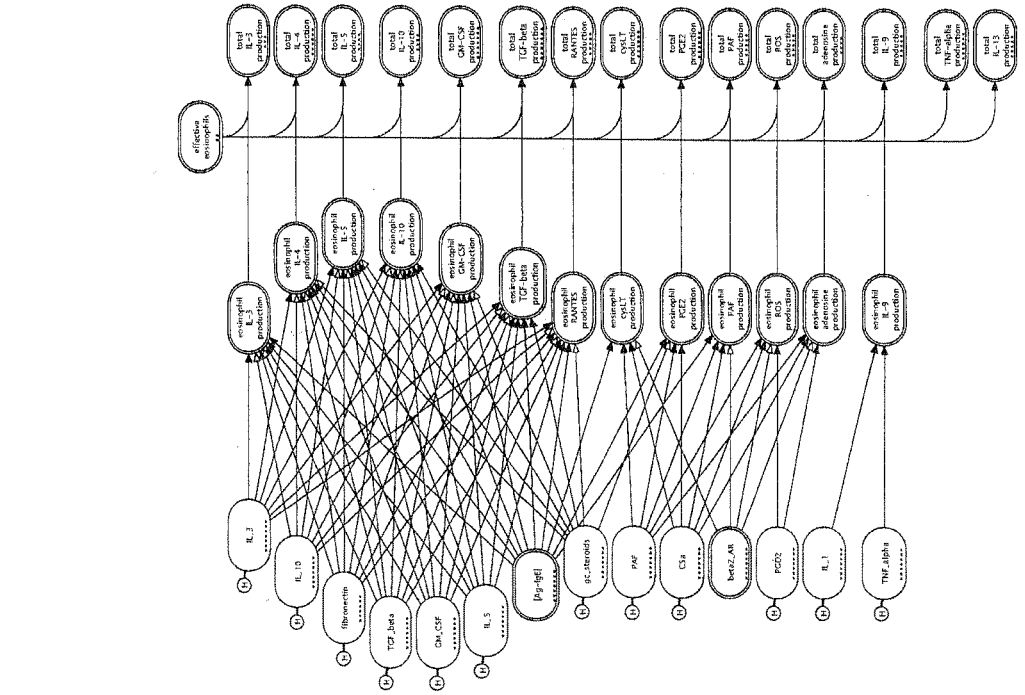

Eosinophil
Mediator Production
+ Stimulates
- Inhibits
= Regulates
C Consumes
F Forms
G Makes Grow
H Half-Life
I Increases
L Leads
M Moves
P Produces
R Released
S Changes Size
effective eosinophils
total IL-3 production
total IL-4 production
total IL-5 production
total IL-10 production
total GM-CSF production
total TGF-beta production
total histamine production
total cysLT production
total PGE2 production
total PAF production
total ROS production
total steroids production
total IL-1 production
total TNF-alpha production
total IL-13 production
eosinophil IL-3 production
eosinophil IL-4 production
eosinophil IL-5 production
eosinophil IL-10 production
eosinophil GM-CSF production
eosinophil TGF-beta production
eosinophil histamine production
eosinophil cysLT production
eosinophil PGE2 production
eosinophil PAF production
eosinophil ROS production
eosinophil steroids production
eosinophil IL-13 production
IL_3
IL_10
fibronectin
TGF_beta
GM_CSF
IL_5
[pg-tgtl
gc_steroids
PAF
C5a
beta2_AR
PGD2
IL_1
TNF_alpha

FIG. 13

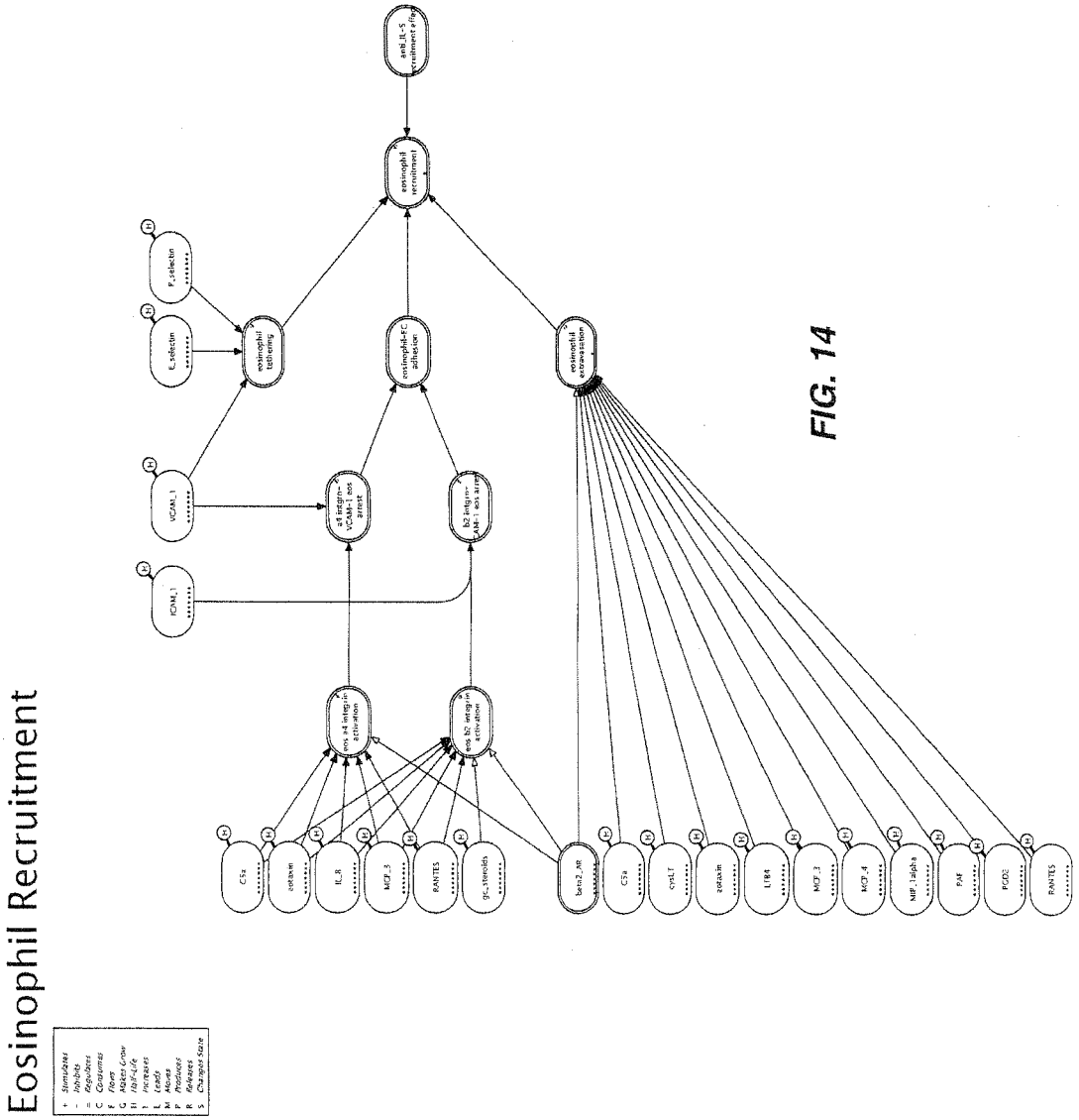

Eosinophil Recruitment
+ Stimulates
- Inhibits
= Activates
C Consumes
F Flows
G Makes Grow
H Half-Life
I Increases
L Leads
M Moves
P Produces
R Releases
S Changed State
anti_IL-5 recruitment effect
eosinophil recruitment
P_selectin
E_selectin
VCAM_1
ICAM_1
eosinophil adhesion
eosinophil-EC adhesion
eosinophil extravasation
α4 integrin VCAM-1 bas arrest
β2 integrin ICAM-1 bas arrest
eos α4 integrin activation
eos β2 integrin activation
C5a
cotaxin
IL-8
MCP_3
RANTES
gc_steroids
beta2_AR
C5a
cysLT
cotaxin
LTB4
MCP_3
MCP_4
MIP_1alpha
PAF
PGD2
RANTES

FIG. 14

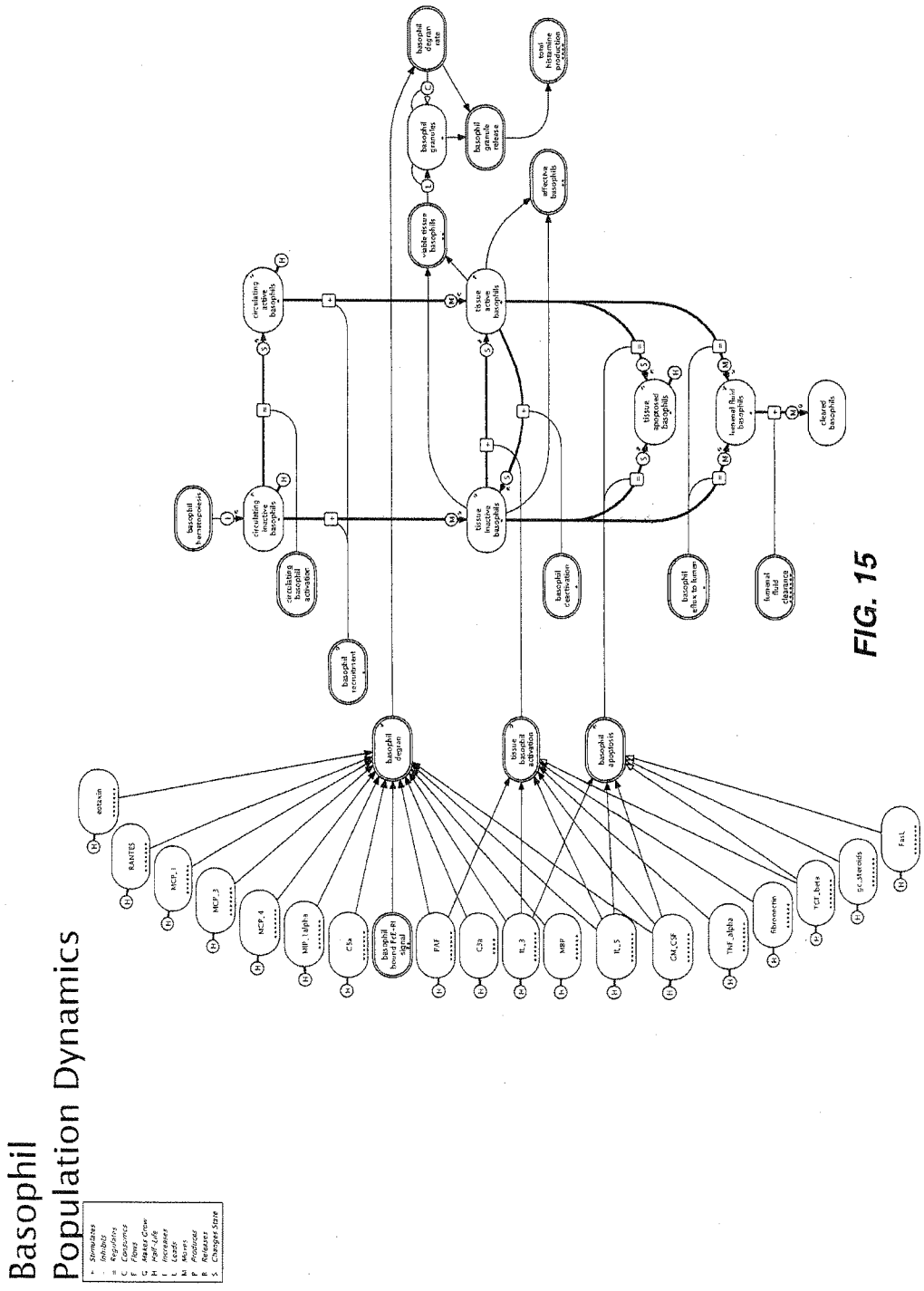

Basophil
Population Dynamics
Stimulates
Inhibits
Regulates
Consumes
Flows
MAKES Grow
Half_Life
Increases
Leads
Moves
Produced
Releases
Changes State
basophil hematopoiesis
circulating basophils
circulating basophil activator
basophil recruitment
basophil death rate
basophil granules
basophil granule release
total histamine production
viable tissue basophils
effective basophils
tissue active basophils
tissue inactive basophils
basophil activation
tissue apoptosed basophils
basophil exits to lumen
luminal fluid basophils
luminal fluid clearance
cleared basophils
basophil degran
tissue basophil activation
basophil apoptosis
eotaxin
RANTES
MCP_1
MCP_3
MCP_4
MIP_1alpha
C3a
basophil bound Fc-ε1 ligand
PAF
C5a
IL_3
MBP
IL_5
GM_CSF
TNF_alpha
fibronectin
TGF_beta
Gr_Steroids
Fas_L

FIG. 15

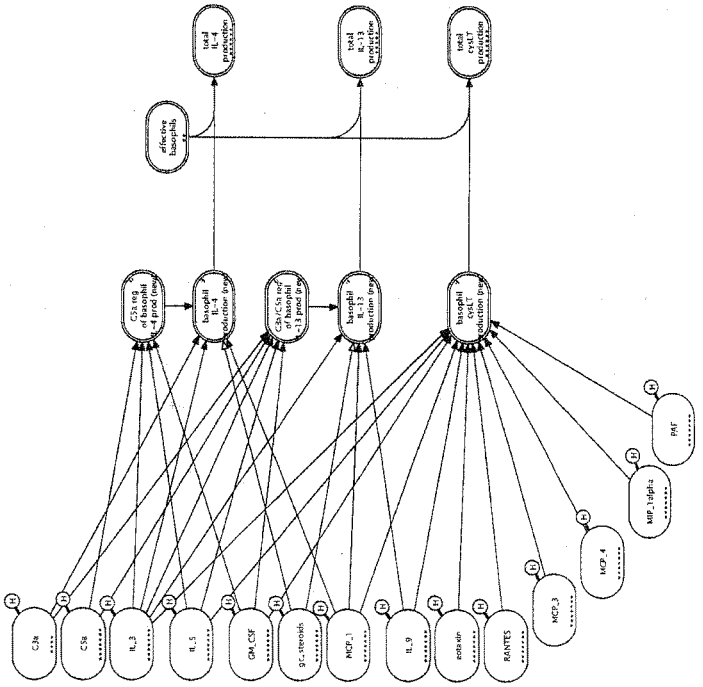

Basophil
Mediator Production
C3a
C5a
IL_3
IL_5
GM_CSF
gc_steroids
MCP_1
IL_9
eotaxin
RANTES
MCP_3
MCP_4
MIP_1alpha
PAF
C3a reg of basophil IL-4 prod fxn
C5a/C5a rec of basophil IL-13 prod fxn
basophil IL-4 production fxn
basophil IL-13 production fxn
basophil cysLT production fxn
effective basophils
total IL-4 production
total IL-13 production
total cysLT production

FIG. 16

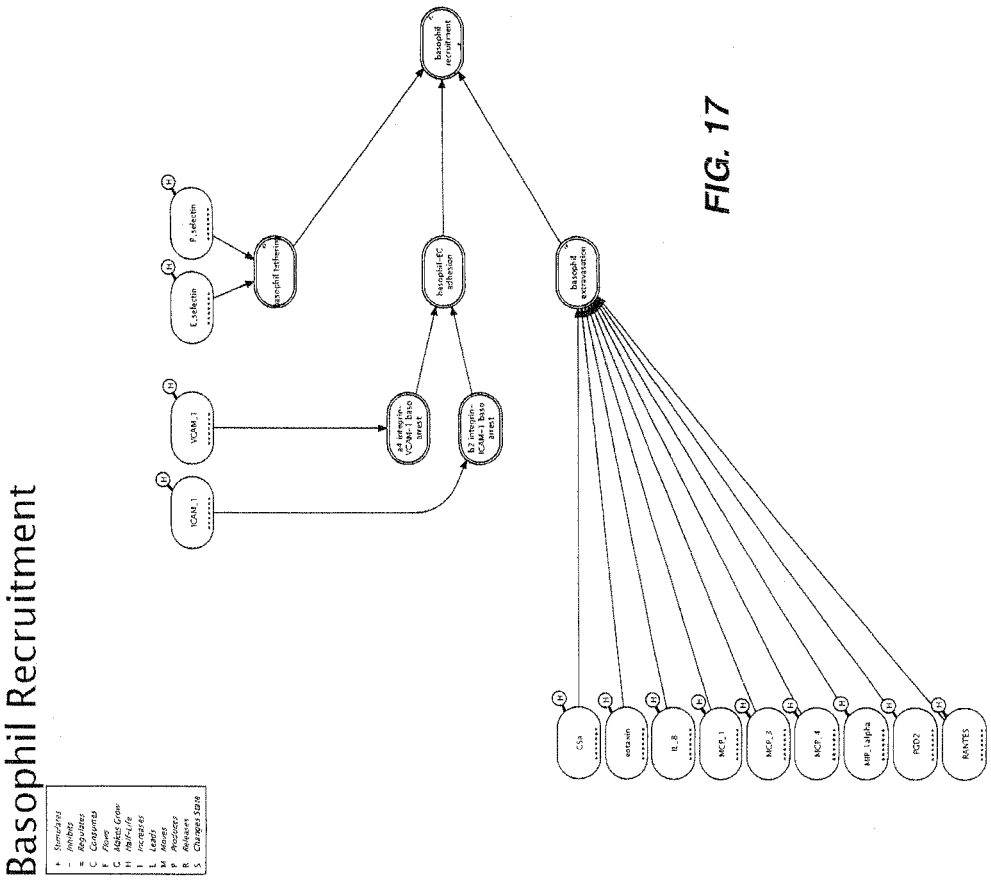

Basophil Recruitment
+ Stimulates
- Inhibits
= Regulates
C Consumes
F Flows
G Halted Grow
H Halt Flow
I Increases
L Leads
M Moves
P Produces
R Raises
S Changes State
basophil recruitment
basophil tethering
basophil-EC adhesion
basophil extravasation
P_selectin
E_selectin
VCAM_1
ICAM_1
a4 integrin-VCAM-1 bind
b2 integrin-ICAM-1 bind
C5a
eotaxin
IL_8
MCP_1
MCP_3
MCP_4
MIP_1alpha
PGD2
RANTES

FIG. 17

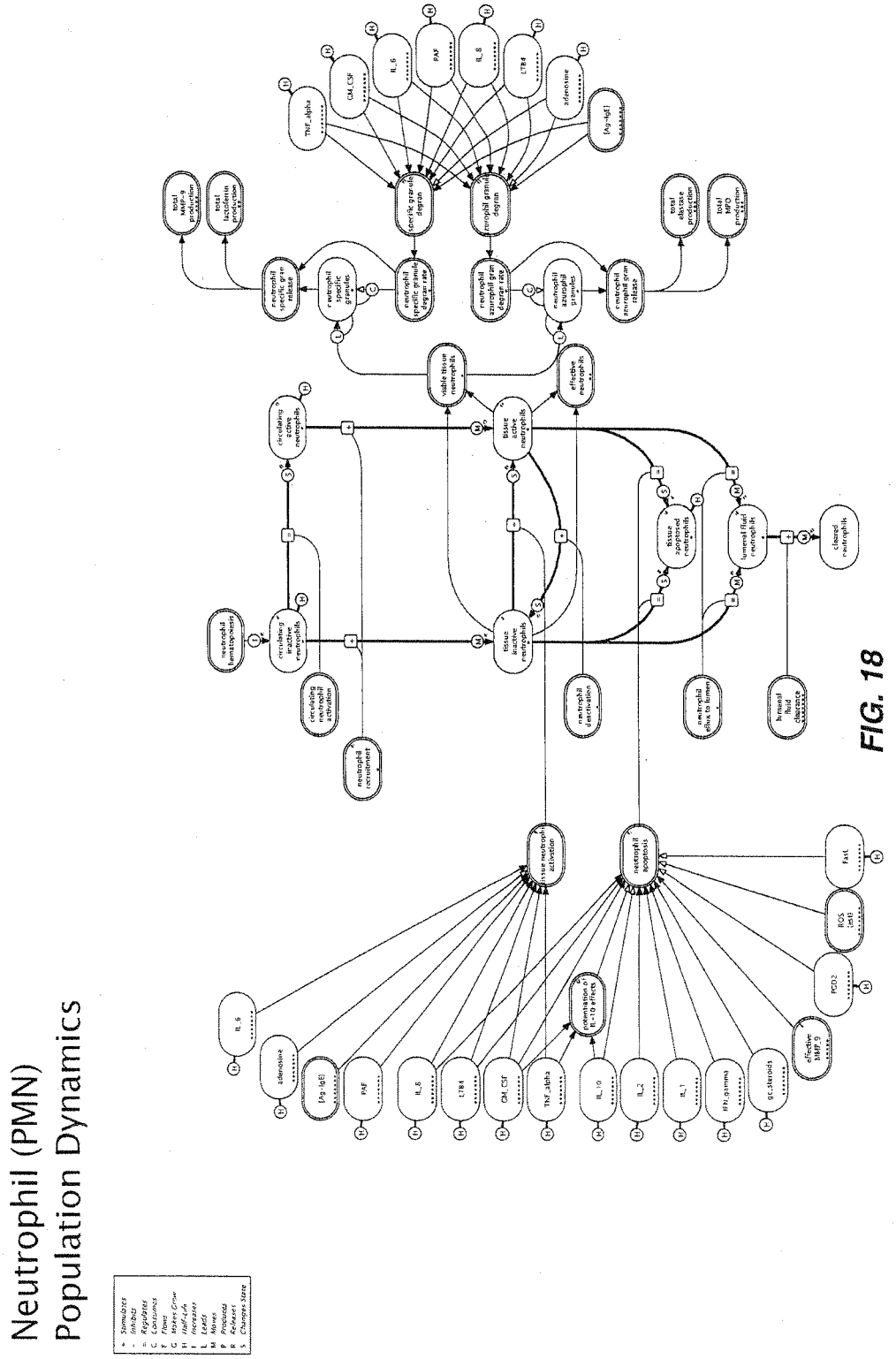

Neutrophil (PMN)
Population Dynamics
* Stimulates
- Inhibits
= Regulates
C Constants
F Flows
G Stores Grow
H Half-Life
I Increases
L Leads
M Moves
P Produced
R Reduces
S Changes State
TNF_alpha
GM_CSF
IL_6
PAF
IL_8
LTB4
adenosine
[Ag-IgE]
total lysozyme production
total lactoferrin production
specific granule degran
neutrophil granule degran
total elastase production
total MPO production
neutrophil specific gran release
neutrophil specific granules
neutrophil specific gran degran rate
neutrophil azurophil gran degran rate
neutrophil azurophil granules
neutrophil azurophil gran release
visible tissue neutrophils
effective neutrophils
circulating active neutrophils
tissue active neutrophils
tissue apoptosed neutrophils
luminal fluid neutrophils
cleared neutrophils
neutrophil hemitransits
circulating neutrophil activation
neutrophil recruitment
neutrophil deactivation
neutrophils ejtos to lumen
luminal fluid clearance
tissue neutrophil activation
neutrophil apoptosis
potentiation of IL-10 effects
IL_10
IL_2
IL_1
IFN_gamma
GC_steroids
effective MMP_9
PGD2
PGG2 and 4
Fas L

FIG. 18

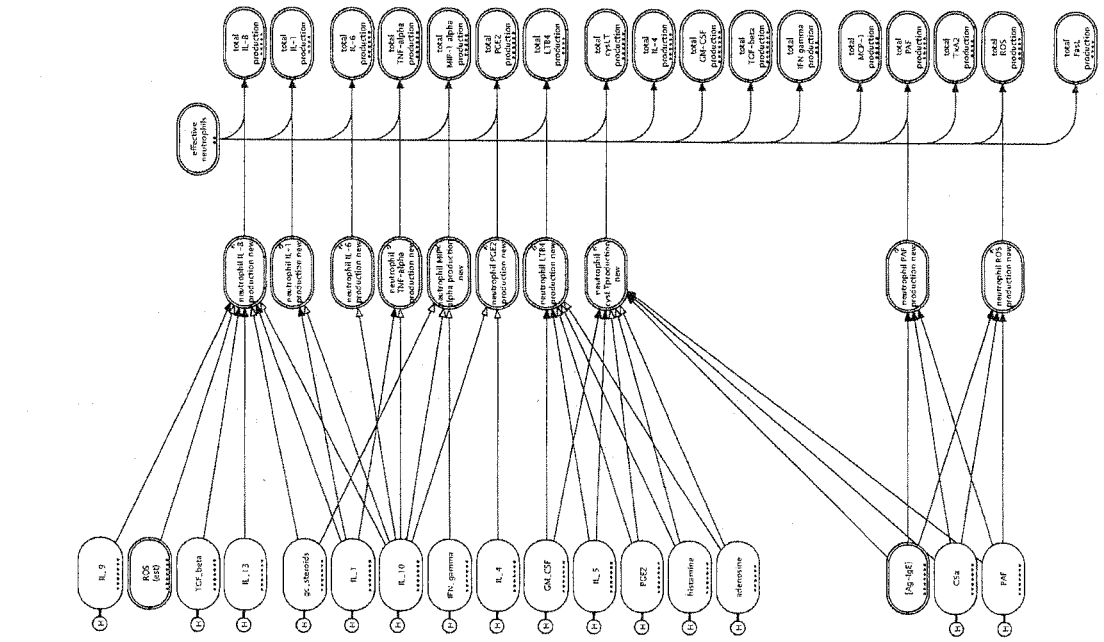

Neutrophil (PMN)
Mediator Production
S Stimulates
I Inhibits
R Regulates
C Consumes
F Forms
G Makes Grow
H Half-Life
I Increases
D Decays
M Makes
P Produces
R Releases
S Changes State
effective neutrophils
IL_9
ROS
TGF_beta
IL_13
glucocorticoids
IL_1
IL_10
IFN_gamma
IL_4
GM_CSF
IL_5
PGE2
histamine
adenosine
[Ag-IgE]
C5a
PAF

FIG. 19

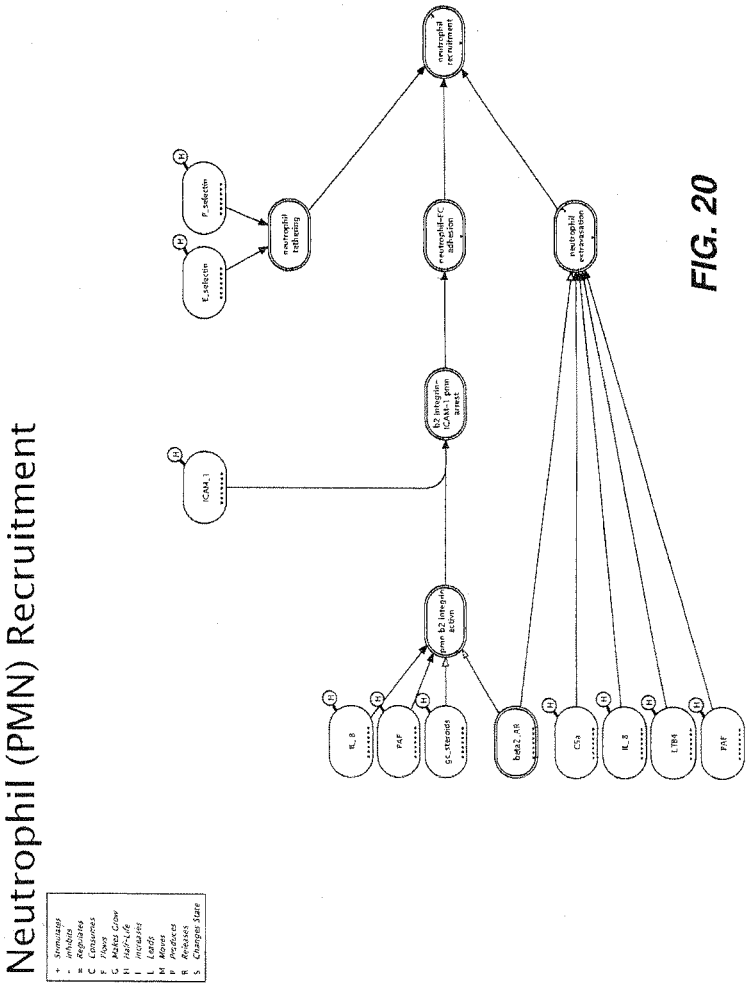

Neutrophil (PMN) Recruitment
+ Stimulates
- Inhibits
= Regulates
C Consumes
E Enters
G Makes Grow
H Half-Life
I Increases
L Leads
M Moves
P Produces
R Releases
S Changes State
IL_8
PAF
GC_steroids
Beta2_AR
C5a
IL_8
LTB4
PAF
ICAM_1
E_selection
P_selection
neutrophil rolling
β2 integrin-ICAM-1 prmn arrest
neutrophil-EC adhesion
neutrophil extravasation
neutrophil recruitment

FIG. 20

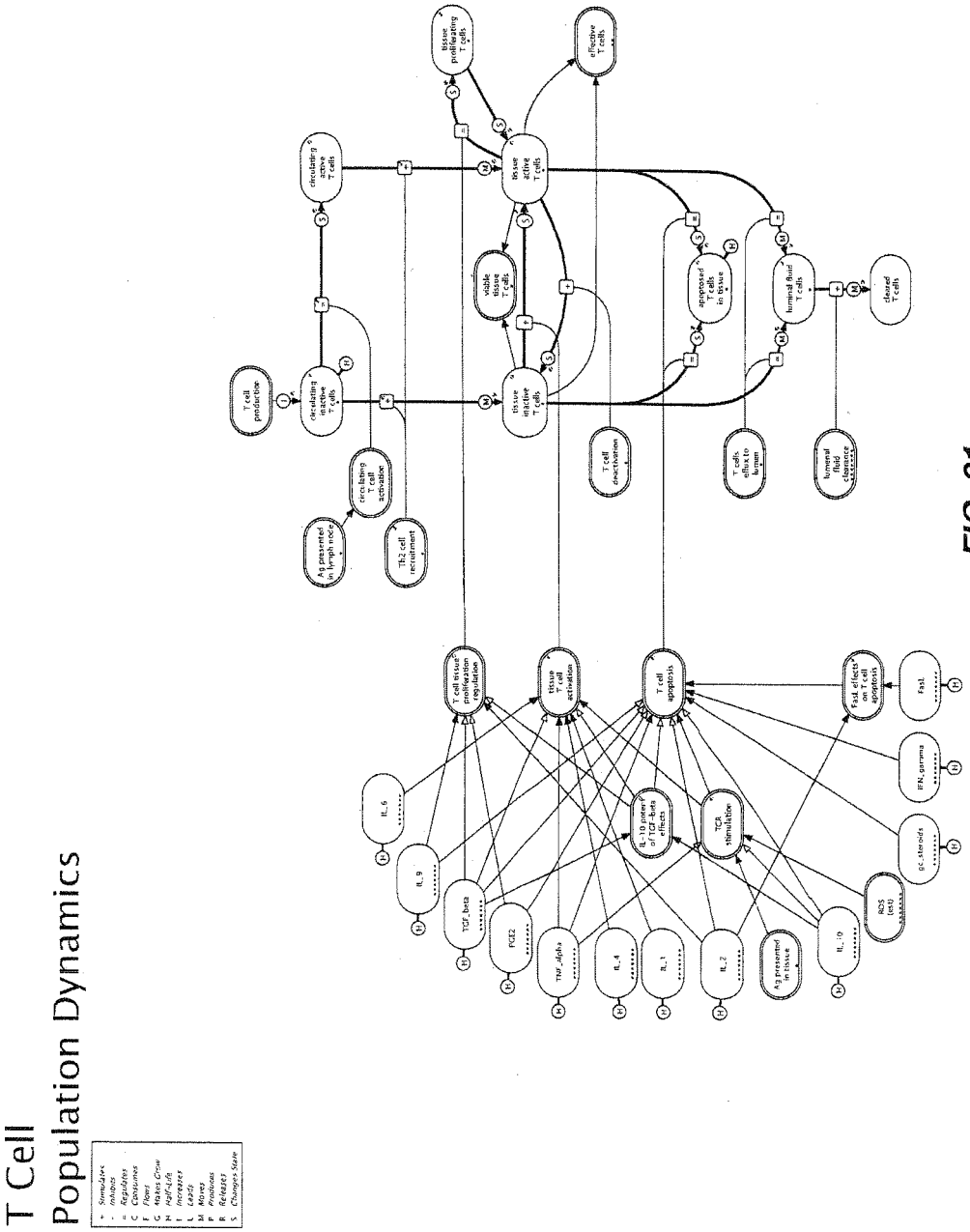

T Cell
Population Dynamics
* Stimulates
- Inhibits
= Regulates
C Consumes
F Flows
G Makes Grow
H Half-Life
I Increases
L Leads
M Moves
P Produces
R Releases
S Changes State
Tissue proliferating T cells
effective T cells
circulating naive T cells
tissue naive T cells
viable tissue T cells
apoptosed T cells in tissue
luminal fluid T cells
cleared T cells
T cell production
circulating activated T cells
tissue activated T cells
circulating T cell activation
Ag presented in lymph node
Th2 cell recruitment
T cell deactivation
T cells efflux to lumen
luminal fluid clearance
T cell tissue proliferation regulation
tissue T cell activation
T cell apoptosis
Fas effects on T cell apoptosis
Fasl
IFN_gamma
GC_steroids
IL_6
IL_9
TGF_beta
PGE2
Tnf_alpha
IL_4
IL_1
IL_2
Ag presented in tissue
IL_10
ROS local
IL-10 inter? of TGF-beta effects
TCR stimulation

FIG. 21

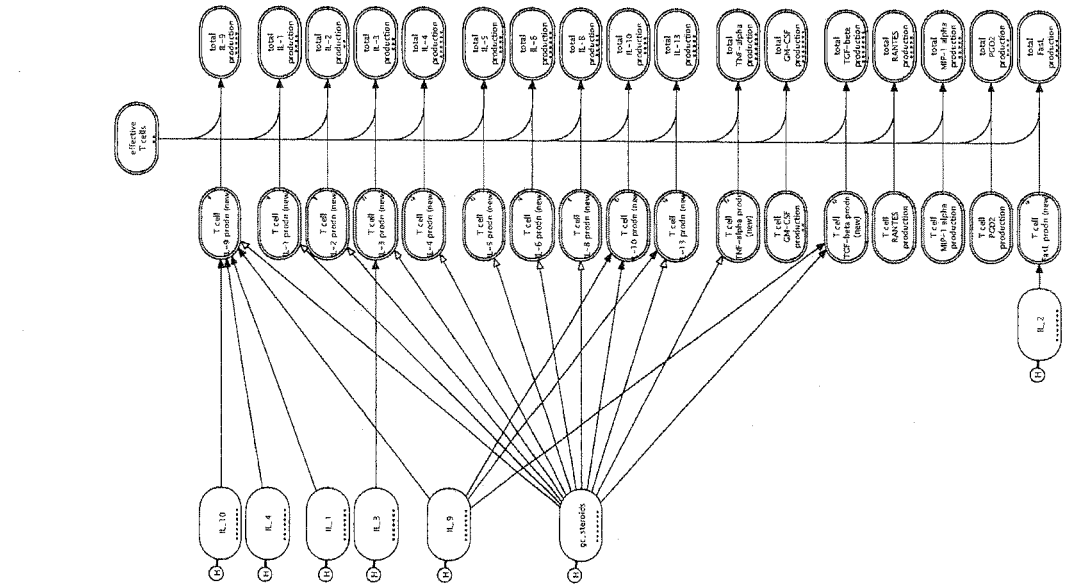

T Cell
Mediator Production
+ Stimulates
- Inhibits
= Regulates
C Consumes
F Flows
G Makes Grow
H Half-Life
I Increases
L Lasts
M Moves
P Produces
R Reduces
S Changes State
eTactive T Cells
IL_10
IL_4
IL_1
IL_3
IL_9
gc_steroids
IL_2

FIG. 22

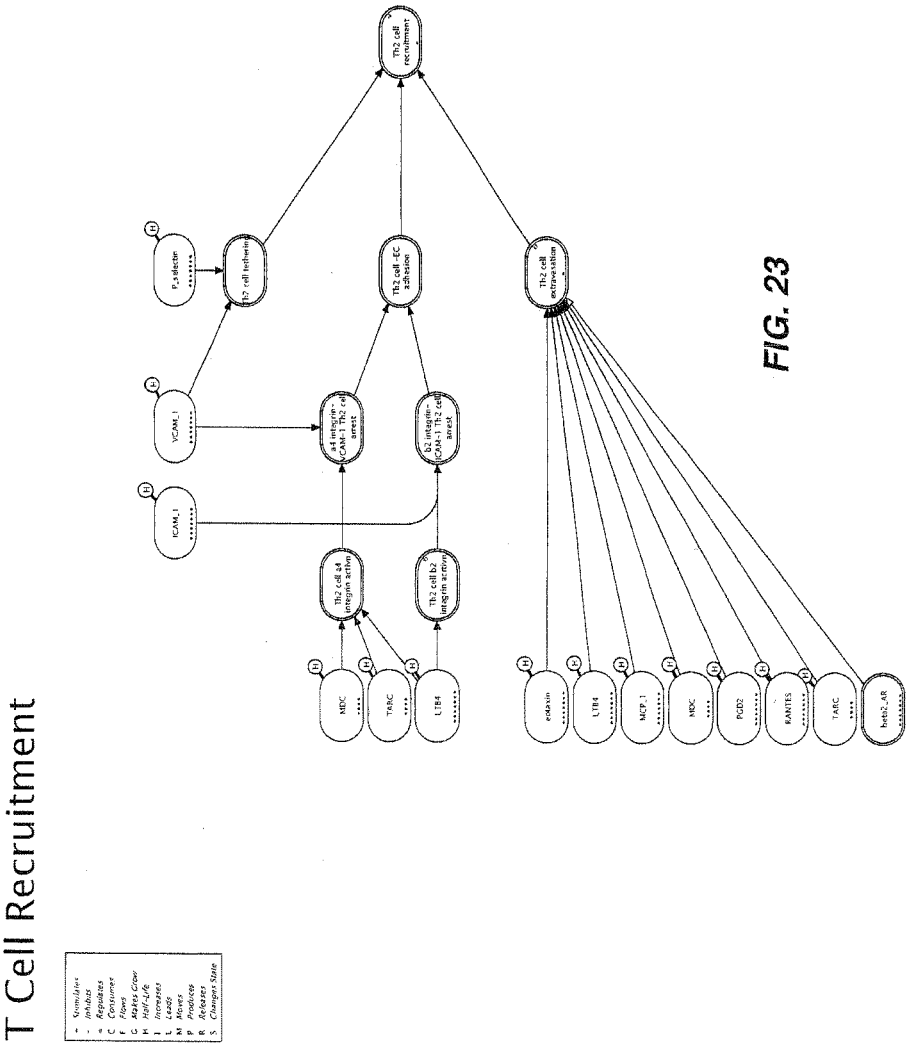

T Cell Recruitment
Th2 cell recruitment
Th2 cell -EC adhesion
Th2 cell extravasation
Th2 cell a4 integrin activation
Th2 cell b2 integrin activation
a4 integrin - VCAM-1 Th2 cell arrest
b2 integrin - ICAM-1 Th2 cell arrest
P-selectin
VCAM_1
ICAM_1
MDC
TARC
LTB4
eotaxin
MCP_1
PGD2
RANTES
beta2_AR

FIG. 23

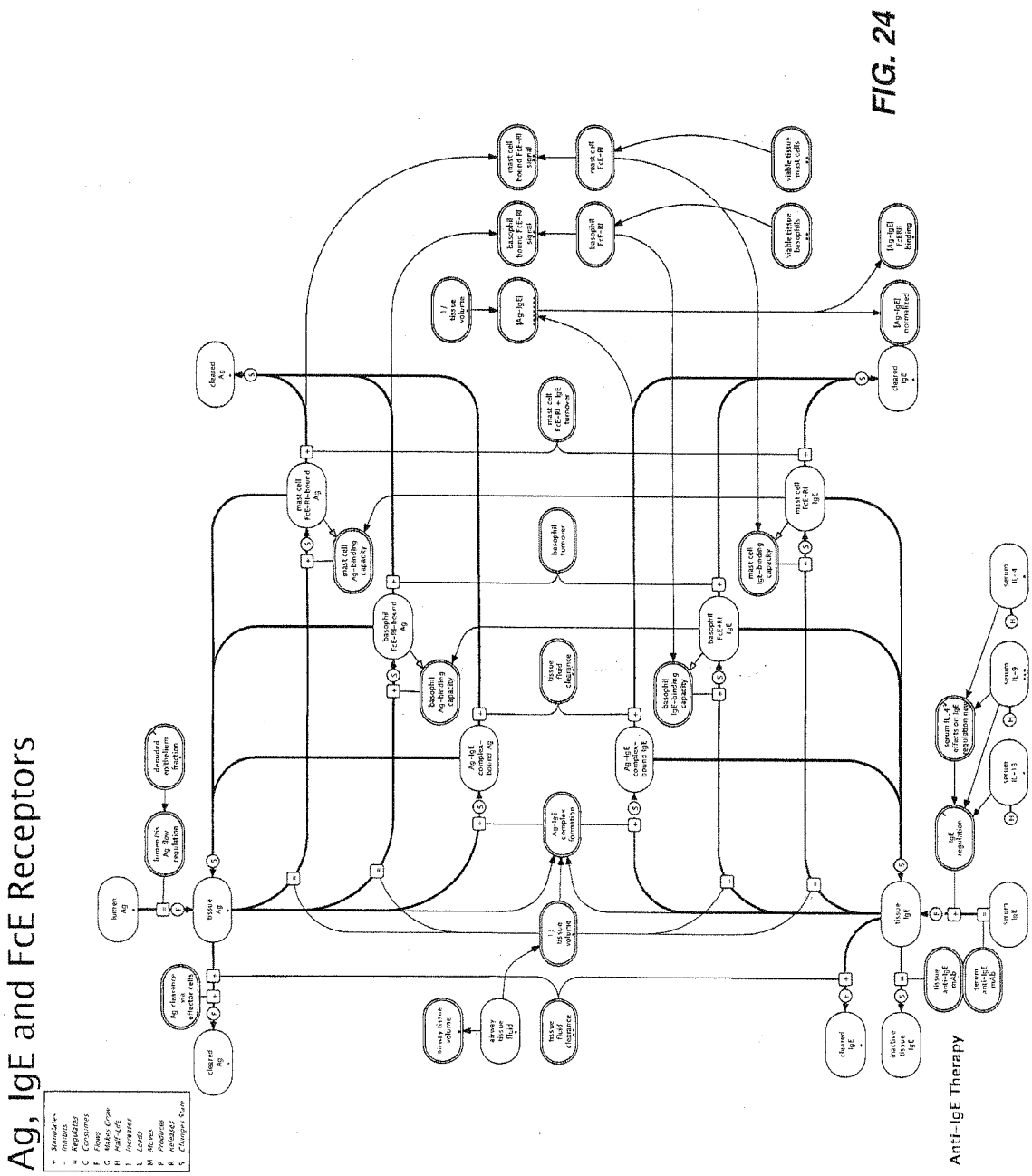


FIG. 24

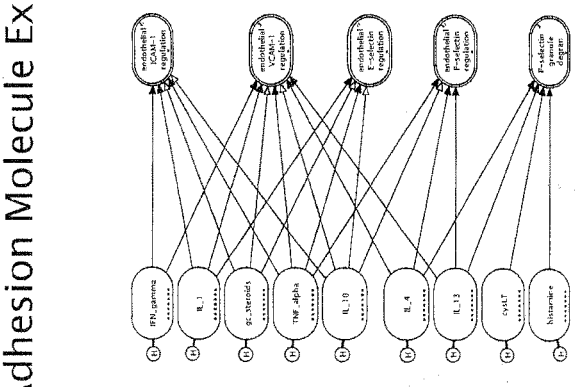
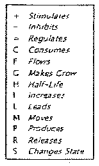

Endothelial Adhesion Molecule Expression
- Stimulates
- Inhibits
= Regulates
C Converts
F Flows
G Makes Grow
H Half-Life
I Increases
L Lyses
M Moves
P Produces
R Releases
S Changes State
IFN_gamma
IL_1
Gc_steroids
TNF_Alpha
IL_10
IL_4
IL_13
cyclT
histamine
endothelial ICAM-1 regulation
endothelial VCAM-1 regulation
endothelial E-selectin regulation
endothelial P-selectin regulation
P-selectin granule deficiency

FIG. 25

Therapeutics: CysLT Receptor Antagonist Pharmacokinetics



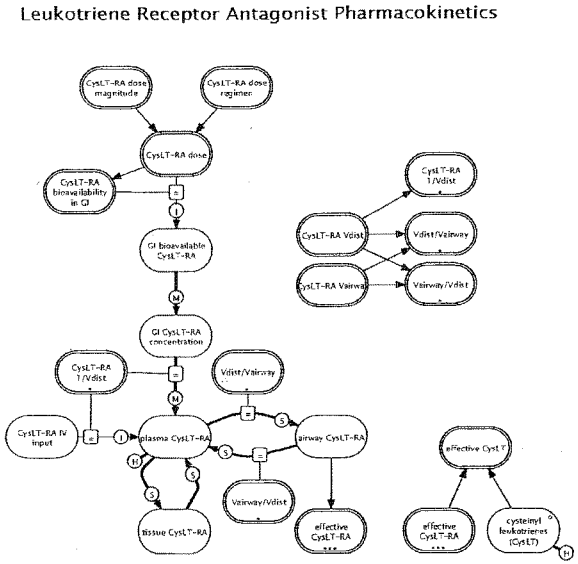
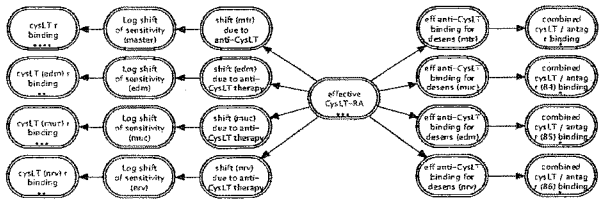


FIG. 26



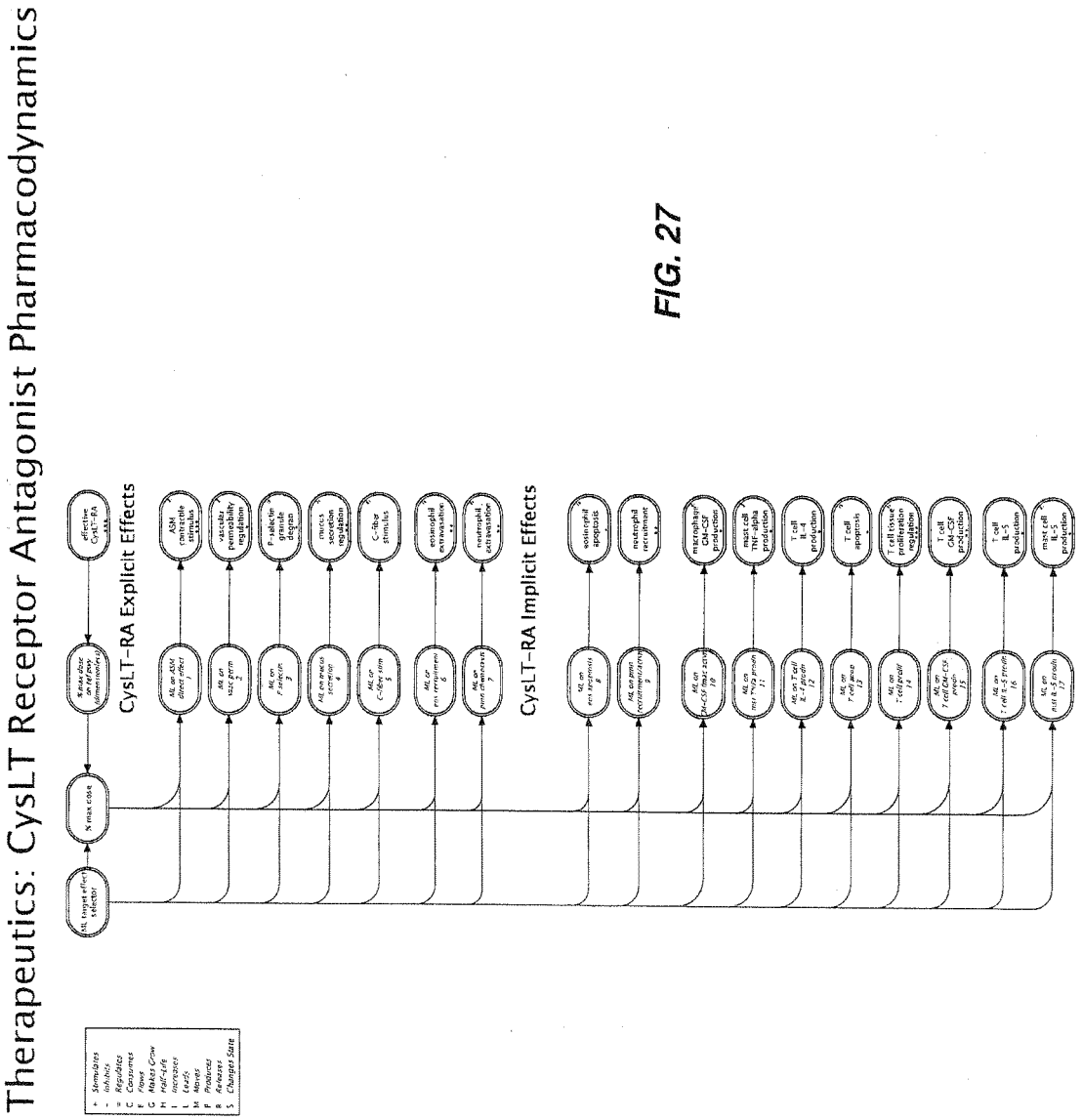

Therapeutics: CysLT Receptor Antagonist Pharmacodynamics
CysLT-RA Explicit Effects
CysLT-RA Implicit Effects

FIG. 27

Therapeutics: Beta-2 Adrenergic Receptor Agonist Pharmacokinetics

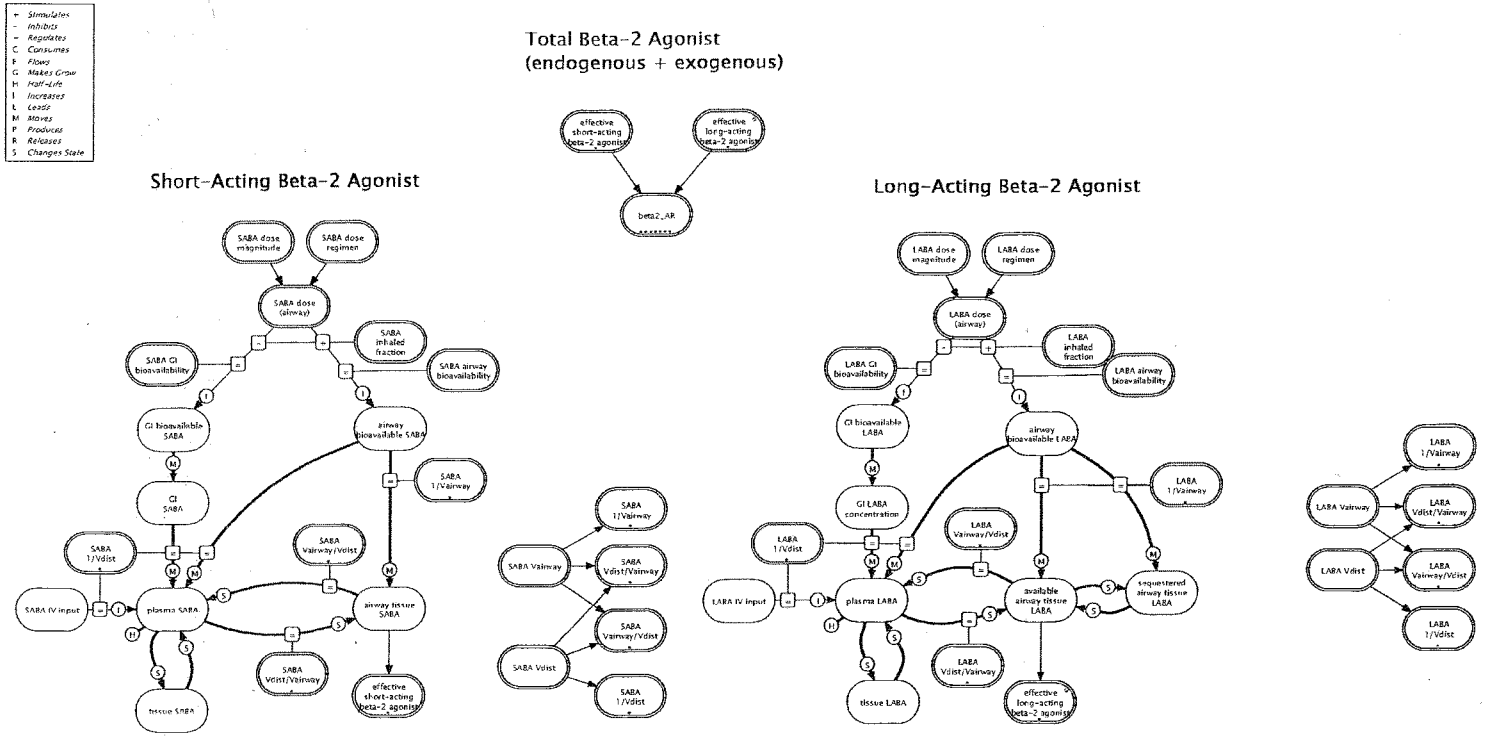
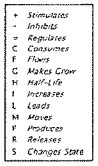
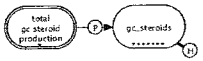


FIG. 28

Therapeutics:
Glucocorticosteroid Therapy
Anti-Histamine Therapy



Glucocorticosteroids



Histamine Receptor Antagonist Therapy

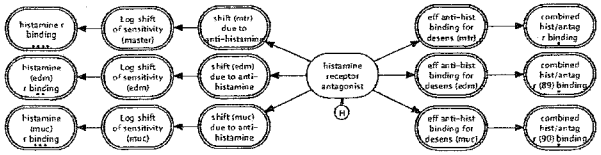
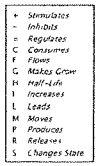
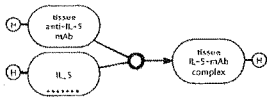


FIG. 29

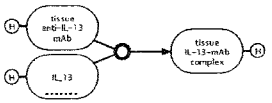
Therapeutics: mAb, sReceptor



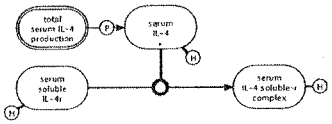
sIL-4 receptor therapy



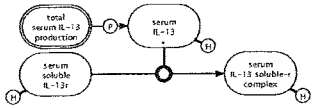
anti-IL-13 mAb therapy



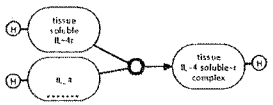
Serum IL-4



Serum IL-13



anti-IL-5 mAb therapy



Serum IL-5

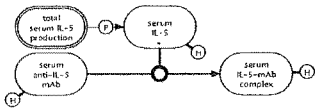


FIG. 30

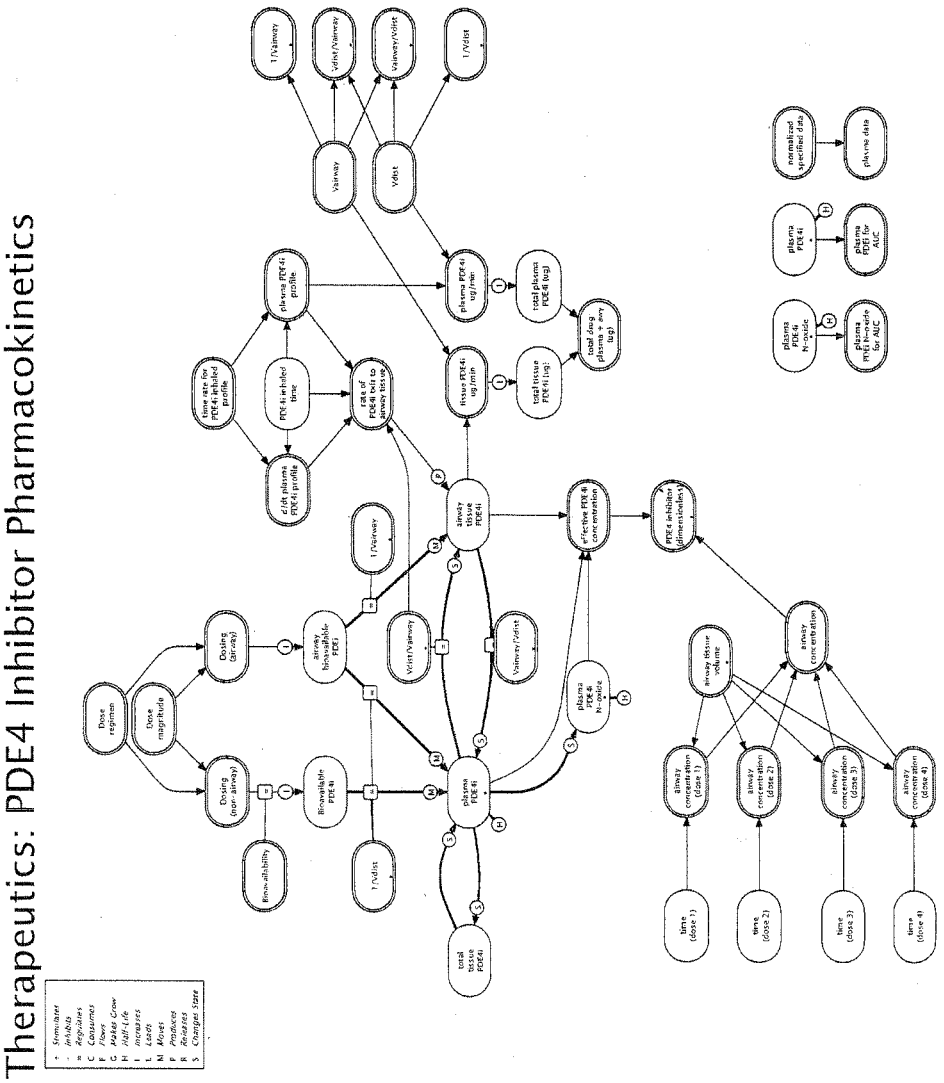

Therapeutics: PDE4 Inhibitor Pharmacokinetics
Dose region
Dose magnitude
Dosing (oral)
Dosing (pulm/nasal)
Bioavailability
Bioavailable PDE4i
1/Vplasma
1/Vtissue
Vplasma/Vtissue
Vtissue/Vplasma
plasma PDE4i
tissue PDE4i
total tissue PDE4i
plasma PDE4 inhibited profile
time for PDE4i inhibited profile
PDE4i inhibited time
rate of PDE4i inhibited to airway tissue
plasma PDE4i region
tissue PDE4i region
total plasma PDE4i (ug)
total tissue PDE4i (ug)
total drug plasma + airway (ug)
airway tissue PDE4i
effective PDE4i concentration
PDE4 inhibition (dimensionless)
plasma PDE4i N-oxide
airway tissue volume
airway concentration
airway concentration (dose 1)
airway concentration (dose 2)
airway concentration (dose 3)
airway concentration (dose 4)
time (dose 1)
time (dose 2)
time (dose 3)
time (dose 4)
normalized specified data
plasma data
plasma PDE4i
plasma PDE4i for AUC
plasma PDE4i N-oxide
plasma PDE4i N-oxide for AUC

FIG. 31

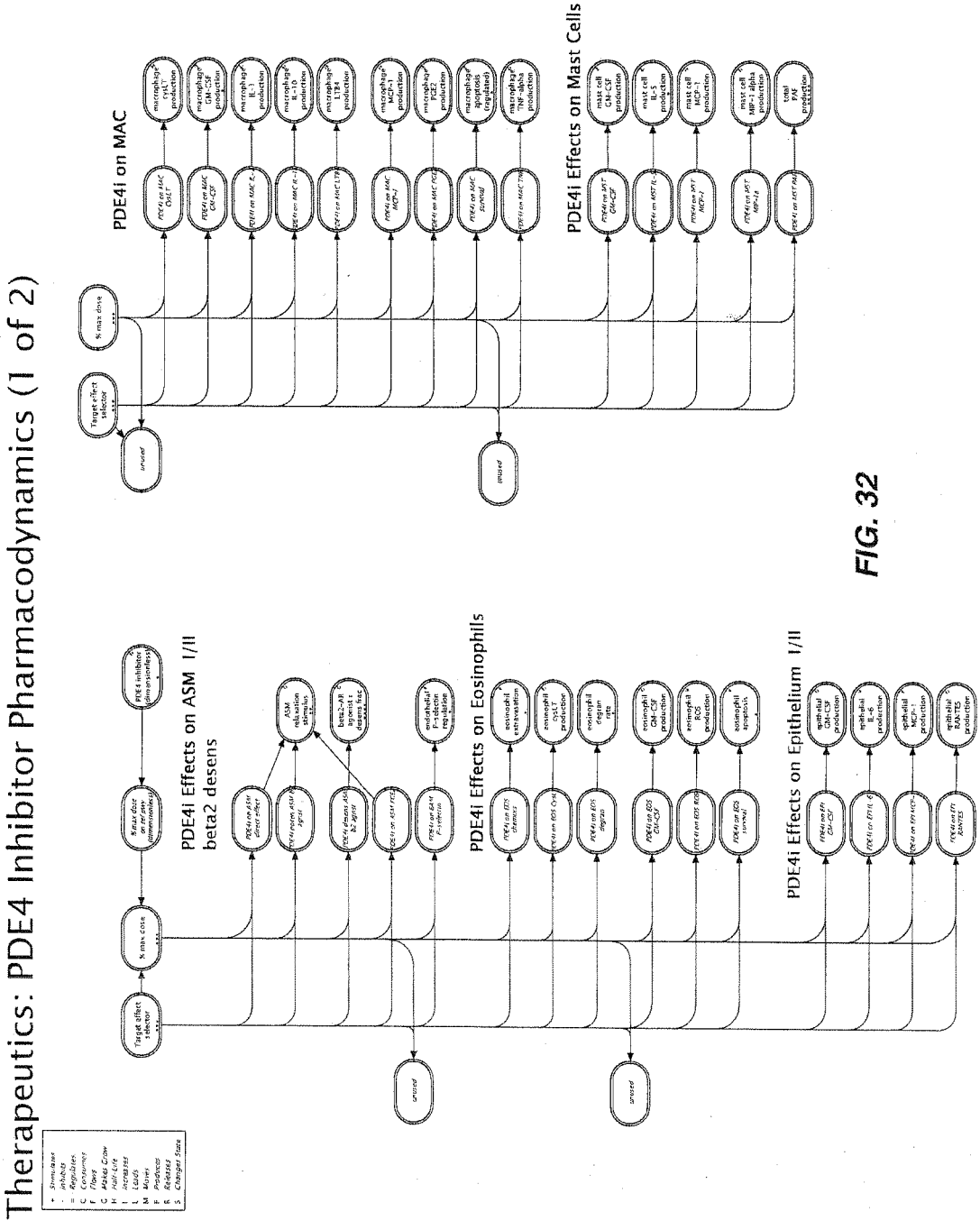

Therapeutics: PDE4 Inhibitor Pharmacodynamics (1 of 2)
PDE4i on MAC
PDE4i Effects on Mast Cells
PDE4i Effects on ASM I/II beta2 desens
PDE4i Effects on Eosinophils
PDE4i Effects on Epithelium I/II

FIG. 32

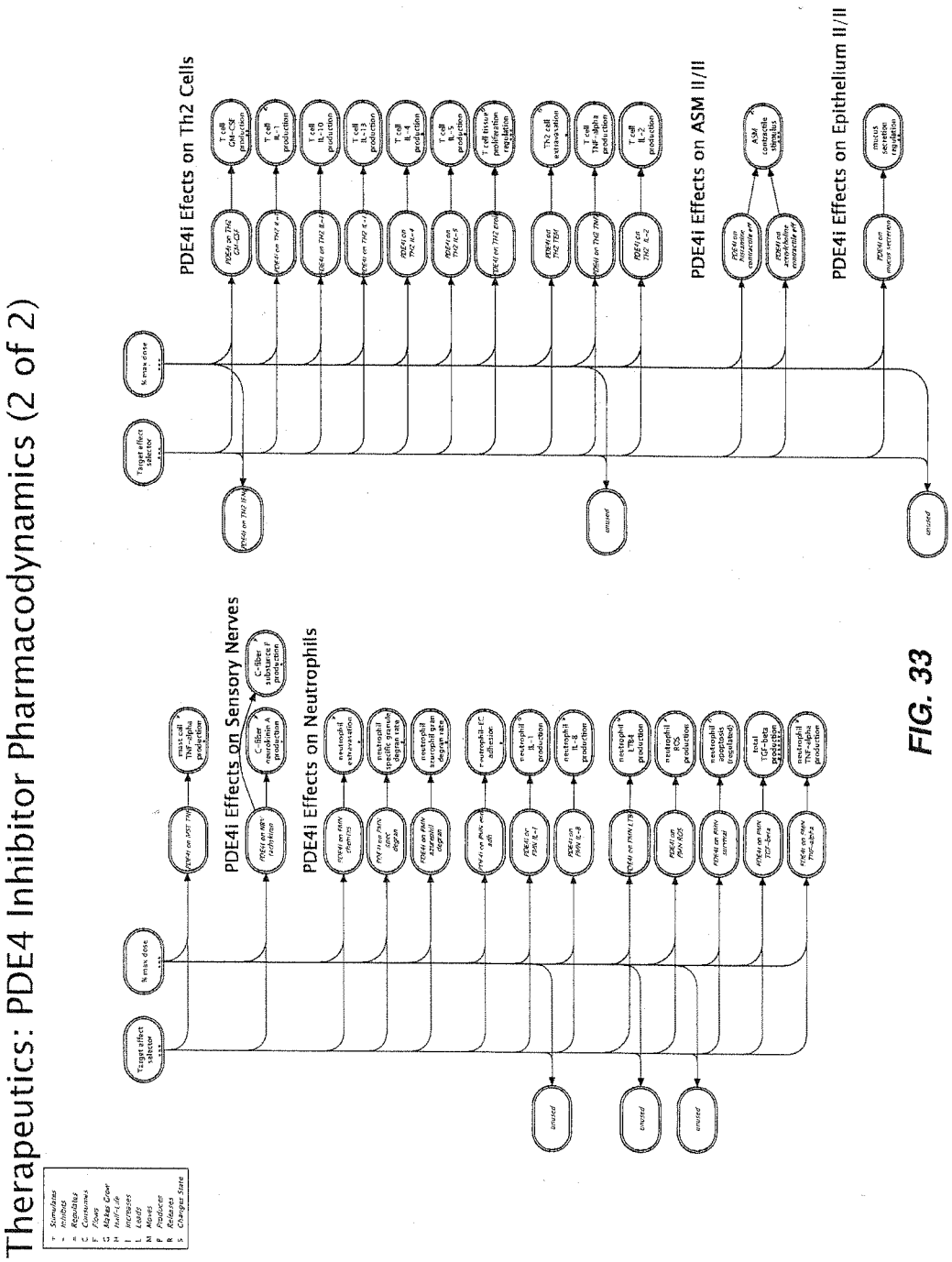

Therapeutics: PDE4 Inhibitor Pharmacodynamics (2 of 2)
PDE4i Effects on Th2 Cells
PDE4i Effects on Sensory Nerves
PDE4i Effects on Neutrophils
PDE4i Effects on ASM II/II
PDE4i Effects on Epithelium II/II

FIG. 33