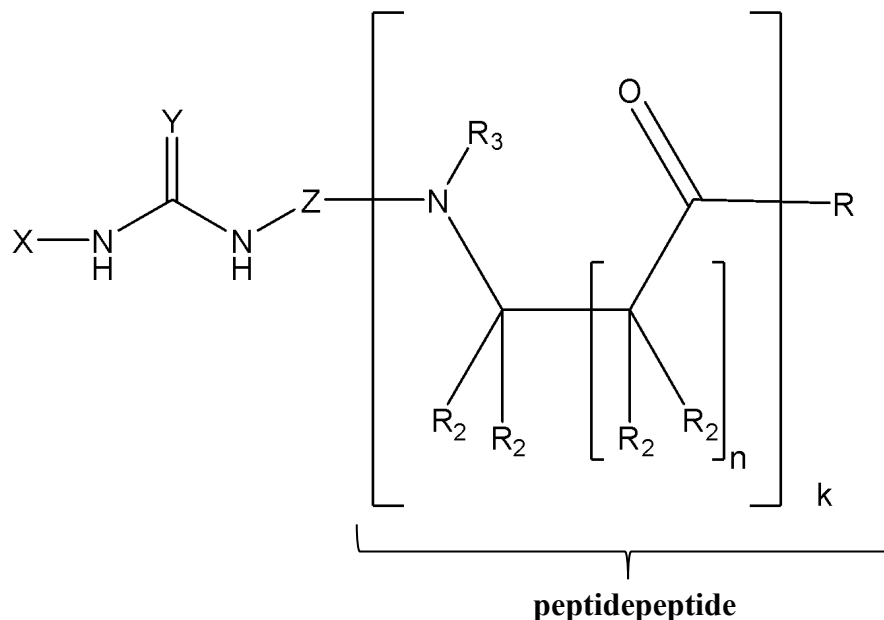


Claims ~~What is claimed is:~~

1. A compound of Formula (X):



5 or pharmaceutically acceptable stereoisomers, enantiomers, diastereomers, racemic mixtures, polymorphs, tautomers, solvates, salts, esters, prodrugs or combinations thereof, wherein,

$n = 0-10$

$k = 1-200$

10 $X = H$, C1-10 alkyl or cycloalkyl, aryl, protecting group, C1-10 acyl, biotin, fluorescent and radioactive tracer, alkyl, cycloalkyl and acyl groups substituted with N, O, S, P, Se, Si, As, halides

$Y = O, S, NH, CH_2, N-OR,$

15 $Z = C1-10$ alkyl or cycloalkyl, aryl, protecting group, C1-10 acyl, biotin, fluorescent and radioactive tracer, alkyl, cycloalkyl and acyl groups substituted with N, O, S, P, Se, Si, As, halides

$R = H, OH, O\text{-alkyl}, NH, N\text{-alkyl}, SH, S\text{-alkyl},$ alkyl, alkenyl, alkynyl, $NH-NH_2,$

R2 = H, C1-10 alkyl or cycloalkyl, aryl, these substituted with N, O, S, P, Se, Si, As, halides, and form a ring system, and glycosylated, and

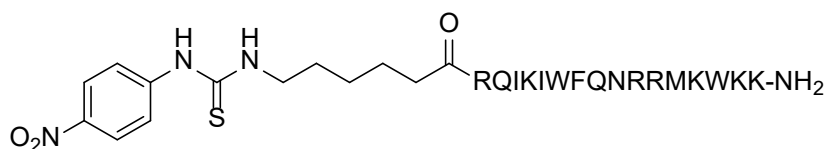
R3 = H, C1-10 alkyl or cycloalkyl, aryl, these ideally substituted with N, O, S, P, Se, Si, As, halides, and may form ideally a ring system, and may be glycosylated, and stereoisomers including enantiomers, diastereomers, racemic mixtures, mixtures of enantiomers or combinations thereof, as well as polymorphs, tautomers, solvates, salts, esters and prodrugs thereof.

2. The compound as recited in Claim 1, wherein said peptide domain comprises one or more positively charged residues.

3. The compound as recited in Claims 1 or 2, wherein said peptide domain comprises arginine or lysine side-chains.

4. The compound as recited in any of Claims 1 to 3, wherein said peptide domain comprises one or more cell membrane penetrating domains (CPPs), such as cationic, amphipathic, hydrophobic or amphiphilic CPPs, selected from the group consisting of SP, pVEC, poly-arginine (arginine stretch), transportan, TAT, and penetratin, or variants thereof having at least having at least 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, or 95% identity to any of SEQ ID NOs: 16, 17, 18, 19, 24 or 25, and having cell penetrating activity, preferably selected from: residue 48-60 of TAT or penetratin, or variants thereof.

5. A compound as recited in any of Claims 1 to 4, wherein said compound has Formula (I):



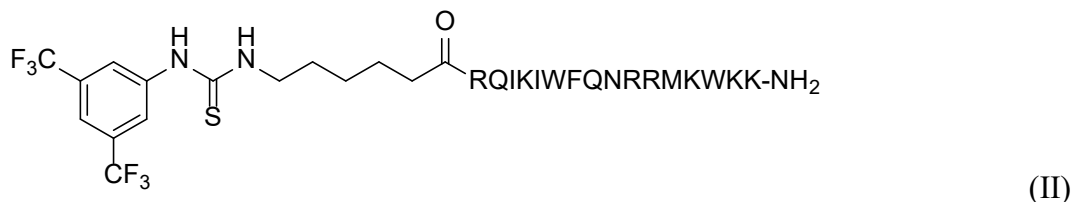
(I)

optionally wherein the molecular weight (MW) of the compound is 2537.4 Daltons.

6. A compound as recited in Claim 5, wherein said compound is selected from pharmaceutically acceptable stereoisomers, enantiomers, diastereomers, racemic

mixtures, polymorphs, tautomers, solvates, salts, esters, prodrugs or combinations thereof.

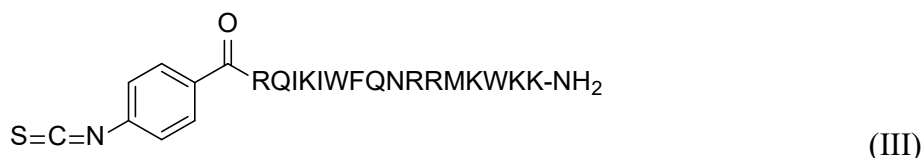
7. A compound as recited in any of Claims 1 to 4, wherein said compound has Formula (II):



optionally wherein the molecular weight (MW) of the compound is 2628.4 Daltons.

8. A compound as recited in Claim 7, wherein said compound is selected from pharmaceutically acceptable stereoisomers, enantiomers, diastereomers, racemic mixtures, polymorphs, tautomers, solvates, salts, esters, prodrugs or combinations thereof.
- 10

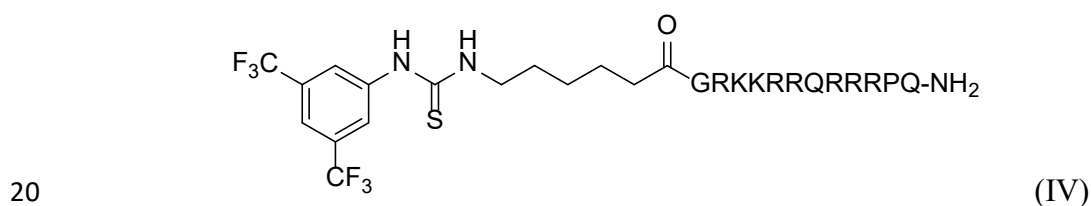
9. A compound as recited in any of Claims 1 to 4, wherein said compound has Formula (III):



optionally wherein the molecular weight (MW) of the compound is 2405.3 Daltons.

10. A compound as recited in Claim 9, wherein said compound is selected from pharmaceutically acceptable stereoisomers, enantiomers, diastereomers, racemic mixtures, polymorphs, tautomers, solvates, salts, esters, prodrugs or combinations thereof.
- 15

11. A compound as recited in Claim 1, wherein said compound has Formula (IV):



optionally wherein the molecular weight (MW) of the compound is 2004.4 Daltons.

12. A compound as recited in Claim 11, wherein said compound is selected from pharmaceutically acceptable stereoisomers, enantiomers, diastereomers, racemic mixtures, polymorphs, tautomers, solvates, salts, esters, prodrugs or combinations thereof.

5 13. A compound as recited in any of Claims 1 to 12, wherein said compound does not induce apoptosis or necrosis in a concentration range from 100 nM to 100 μ M.

14. A compound as recited in any of Claims 1 to 12, wherein said compound decreases the intracellular chloride ion concentration, when applied to HEK-293 cells at a concentration between 100 nM and 10 μ M, optionally in a dose-dependent manner.

15. A compound as recited in any of ~~Claims~~Points 1 to 12, wherein said compound decreases the intracellular chloride ion concentration when applied to 3D pancreatic organoids or to pancreatic ductal fragments in the absence of CFTR at a concentration of 100 nM to 10 μ M, optionally in a dose-dependent manner.

16. ~~A compound as recited in any of Claims 1 to 12, wherein said compound decreases the intracellular chloride ion concentration when applied to pancreatic ductal fragments in the absence of CFTR, at a concentration of 100 nM to 10 μ M, optionally in a dose-dependent manner~~

17. 16. A pharmaceutical composition comprising a compound as recited in any of Claims 1 to 12, and a pharmaceutically acceptable excipient or carrier, wherein said pharmaceutical composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, buccal, nasal, and topical administration; and/or formulated as a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules; and/or presented as a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; and/or presented as an enema formulation, iontophoretic application, coating an implantable medical device; or combinations thereof.

18. ~~A pharmaceutical composition comprising a compound as recited in any of Claims 1 to 12, wherein said pharmaceutical composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, buccal, nasal, and topical administration; and/or formulated as a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules; and/or presented as a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; and/or presented as an enema formulation, iontophoretic application, coating an implantable medical device; or combinations thereof.~~

19. ~~A pharmaceutical composition according to any of Claims 17 or 18, for use in the manufacture of a medicament.~~

20. ~~17.~~ A pharmaceutical composition according to ~~any of Claims 16~~ 7 to 19, for use in the treatment, reduction, inhibition or control of viscous sputum or mucus associated with cystic fibrosis in a human subject, wherein said pharmaceutical composition increases the electrolyte content of said viscous mucus or sputum, such as chloride, optionally wherein said pharmaceutical composition is administered to the lungs of said human subject by pulmonary or aerosol delivery as a solution or suspension in a liquid vehicle, or as a dry powder.

21. ~~A compound as recited in any of Claims 1 to 12 or a composition as recited in any of Claims 17 to 20 for use in therapy.~~

22. ~~A compound as recited in any of Claims 1 to 12, or a composition as recited in any of Points 17 to 20 for use in the treatment of CFTR-mediated diseases selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, mucopolysaccharidoses, chloride channelopathies such as myotonia congenita~~

(Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy.

23.18. _____ A method of treating, reducing, inhibiting or controlling viscous sputum or mucus associated with cystic fibrosis in a human subject, wherein said method comprises administration of a compound as recited in any of Claims 1 to 12, or a composition as recited in ~~any of Claims 16 or 17 to 20~~ wherein said administration method increases the electrolyte content of said viscous mucus or sputum, such as chloride, optionally wherein said pharmaceutical composition is administered to the lungs of said human subject by pulmonary or aerosol delivery as a solution or suspension in a liquid vehicle, or as a dry powder, and wherein said compound is optionally selected from Formula (I), (II), (III) and (IV).

24.19. _____ A method of treating, reducing, inhibiting or controlling at least one sign or symptom of cystic fibrosis in a subject, wherein said method comprises administration of a therapeutically effective amount of one or more compounds as recited in any of Claims 1 to 12 or a composition as recited in ~~any of Claims 16 or 17 to 20~~ to the human subject, optionally in combination with one or more therapeutic agents, wherein said sign or symptom is associated with the airways or respiratory system and includes one or more of the following: abnormally viscous mucus accumulation; increased total mucin content; elevated inflammatory factor concentration; decreased cellular secretion of chloride ions; impaired fluid secretion; increased apical sodium absorption by airway epithelial cells; acidification and decreased height of the apical airway surface liquid; chronic cough; chronic lung infection, and combinations thereof.

25.20. _____ A pharmaceutical composition according to ~~any of Claims 16 or 17 to 20~~, or method according to ~~any of Claims 1823 or to 1924~~ wherein said compound is preferably selected from Formula (I), (II), (III) and (IV).