surgical site.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure provides methods for preventing, inhibiting or treating a surgical site infection associated with a surgical operation comprising the step of applying to the surgical site a biocompatible, biodegradable substrate being impregnated and/or having its surface coated fully or partially with a matrix composition which provides local controlled and prolonged release of at least one pharmaceutically active agent at the surgical site. Specifically, the matrix composition comprises (a) a biocompatible polymer, (b) a first lipid component comprising a sterol, (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) a pharmaceutically active agent selected from the group consisting of an antibiotic agent, antiseptic agent, an anti-inflammatory agent, anti-fungal agent and any combination thereof. In one aspect, the present disclosure provides a use of a biodegradable mineral substrate in the manufacture of a medicament for the treatment or prophylaxis of a soft tissue incision site infection associated with a surgical operation, wherein the biodegradable mineral substrate shaped in the form of particles is to be administered directly to the soft-tissue incision site, wherein the mineral substrate is impregnated or has its surface coated fully or partially with a matrix composition, wherein the matrix composition comprises: (a) a biodegradable polyester, (b) a first lipid component comprising at least one sterol, wherein the at least one sterol is non-covalently associated with the biodegradable polyester; (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) an antibiotic agent selected from the group consisting of: doxycycline and doxycycline hyclate.

The substrate being impregnated and/or having its surface coated fully or partially with a matrix composition described herein is intended for local administration to soft tissues and solid organs during surgical procedures and provides localized infection prevention and treatment by reducing the overall infection rate post-surgery and by reducing or eradicating soft tissue infections that may exist prior to surgery. According to some ~~embodiments~~examples, the drug coated substrate described herein prevents or inhibits the formation of biofilm that may form at the surgical site and its vicinity, thereby preventing or inhibiting surgical site infections. Inhibition of biofilm formation at the surgical site refers

to inhibition of biofilm formation on surfaces such as biological tissues and/or materials or devices that may be used during surgery (e.g. wound tissue, necrotic cells, biomaterials and surgical implants (e.g. sutures and hard ware-stainless steel wires)). According to some ~~embodiments~~examples, the drug coated substrate disclosed herein is capable of eradicating an existing biofilm.

Following its application to the surgical site, the substrate being impregnated and/or having its surface coated fully or partially with a matrix composition described herein provides local controlled release of the drug at the surgical site and its surrounding over a predetermined, prolonged period of time, preferably between several days to

CLAIMS:

1. Use of a biodegradable mineral substrate in the manufacture of a medicament for ~~A method for~~ the treatment or prophylaxis of a soft tissue incision ~~surgical~~ site infection associated with a surgical operation, wherein ~~comprising the step of administering to the surgical site a~~ the biodegradable mineral substrate shaped in the form of particles is to be administered directly to the soft-tissue incision site, wherein the mineral substrate is impregnated or has ~~having~~ its surface coated fully or partially with a matrix composition, wherein the matrix composition comprises: ~~comprising~~ (a) a ~~biocompatible~~ biodegradable polyester~~mer~~, (b) a first lipid component comprising at least one sterol, wherein the at least one sterol ~~which~~ is non-covalently associated with the biodegradable polyester; ~~biocompatible polymer,~~ (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) ~~a pharmaceutically active agent~~an antibiotic agent selected from the group consisting of: doxycycline and doxycycline hyclate.

~~2. The method of claim 1, useful for at least one of reducing the overall infection rate post-surgery, eradicating soft tissue infections that may exist prior to surgery, Inhibition of biofilm formation at the surgical site and eradicating an existing biofilm at the surgical site.~~

~~3.~~2. The ~~method~~ use according to claim 1, wherein the soft tissue incision is associated with a surgical operation ~~surgical operation in~~ selected from the group consisting of orthopedic surgical operations, spine surgical operations, ~~surgical~~ operations on a digestive system organ, gastric ulcer procedures, gastric cancer procedures, open gastric bypass, appendectomy, colectomy, cholecystectomy, vagotomy, open biliary tract procedures, small intestine procedures, colorectal procedures, cardiac procedures, hernia repair, vascular procedures, caesarian, prostatectomy, obstetric and gynecologic surgical operations, head and neck cancer surgery, transplantation surgeries, neurosurgery and plastic surgeries.

3. The use according to claim 2, wherein the surgical operation is a surgical operation on a digestive system organ.

4. The use of claim 3, wherein the digestive organ is selected from the group consisting of: esophagus, stomach, small intestine, large intestine, rectum, colon, appendix, liver, pancreas, gallbladder, and any combination thereof.

5. The use of claim 2, wherein the surgical operation on a digestive system organ includes a procedure selected from the group consisting of open gastric bypass, appendectomy, colectomy, cholecystectomy, vagotomy, open biliary tract procedures, small intestine procedures, colorectal procedures, and any combination thereof.

6. The use according to claim 2, wherein the soft tissue incision is associated with cardiac surgery procedures.

~~4. The method according to any one of claims 1-3, implemented in addition to standard of care procedures for reduction in the inoculum of bacteria selected from the group consisting of appropriate surgical site preparation, systemic preventive antibiotics, cell based therapy, and enhancement of the host by perioperative supplemental oxygenation, maintenance of normothermia and glycemic control.~~

~~5. The method according to claim 1 to 4, wherein the biodegradable substrate is selected from the group consisting of a mineral substrate, a natural polymer material, a water soluble synthetic polymer and a bioabsorbable hydrophobic material.~~

~~6.~~7.The use~~method~~ according to claim 1~~5~~, wherein the ~~biodegradable substrate is a~~ mineral substrate is selected from the group consisting of hydroxyapatite, fluorapatite, oxyapatite, wollastonite, apatite/wollastonite glass ceramics, anorthite, calcium fluoride, calcium sulfate, calcium carbonate, tetracalcium phosphate, α-tricalcium phosphate (α-TCP), β-tricalcium phosphate (β-TCP), amorphous calcium phosphate, dicalcium phosphate, agrellite, devitrite, canasite, phlogopite, monetite, brushite, octocalcium phosphate, whitlockite, cordierite, berlinite, combeite, phosphoric acid crystals, disodium hydrogen phosphate, and ~~other phosphate salt based bioceramics~~any combination thereof.

8. The use according to claim 7, wherein the mineral substrate is β-TCP.

~~7. The method according to claim 5, wherein the biodegradable substrate is a natural polymer material selected from the group consisting of gelatin, hyaluronic acid, hyaluronic acid derivatives, such as, a polyionic complex of hyaluronic acid, triethanolamine alginate, casein, keratin, myosin and/or fibroin, collagen, collagen derivatives, such as, succinylated collagen or methylated collagen, chondrotin sulfate, chitosan, chitosan derivatives, such as, methylpyrrolidone chitosan, polyaminogalactosamine.~~

~~8. The method of claim 5, the substrate is a water soluble synthetic polymer.~~

~~9. The method of claim 8, wherein the substrate is poly vinyl alcohol (PVA).~~

~~10.~~9. The use~~method~~ according to ~~any one of~~ claim~~s~~ 1~~ to 9~~, wherein the mineral ~~biodegradable~~ substrate comprises ~~consists of~~ particles having an average particle size of less than about 200 microns (μm).

~~11. The method according to claim 10, wherein the biodegradable substrate consists of particles having an average particle size of less than about 150 microns (μm).~~

~~12.~~10. The use~~method~~ according to claim 9~~11~~, wherein the ~~biodegradable substrate consists of particles having an~~ average particle size is from ~~in the range of~~ 50 to ~~–~~150 ~~microns (~~μm~~)~~.

~~13. The method according to claim 12, wherein the biodegradable substrate consists of particles having an average particle size in the range of 50 – 100 microns (μm).~~

~~14.~~11. The use~~method~~ according to ~~anyone of claims 10-13~~claim 1, wherein a majority of the particles are spherical, ~~and/or~~ spheroidal, or any combination thereof.

~~15.~~12. The use~~method~~ according to claim 1~~any one of claims 1 to 14~~, wherein the matrix composition comprises a phospholipid selected from a phosphatidylcholine or a combination of phosphatidylcholines having fatty acid moieties having at least ~~12~~ 14 carbons.

~~16.~~13. The use~~method~~ according to ~~of~~ claim 12~~15~~, wherein ~~said~~ the phospholipid is a phosphatidylcholine or a combination of phosphatidylcholines having fatty acid moieties having 14 — 18 carbons.

~~17.~~14. The use~~method~~ according to claim 1, ~~any one of claims 1 to 16~~ wherein the ~~biocompatible polymer in the matrix composition, is a~~ biodegradable polyester is selected from the group consisting of PLA (polylactic acid), PGA (poly glycolic acid) and PLGA (Poly (lactic co glycolic acid).

~~18. The method according to any one of claims 1 to 16, wherein the biocompatible polymer in the matrix composition is poly ethylene glycol (PEG).~~

~~19.~~15. The use~~method~~ according to claim 1~~any one of claims 1 to 18~~, wherein the matrix composition further comprises a pharmaceutically active agent ~~is~~ selected from the group consisting of: an antibiotic agent, an antiseptic agent, an anti-inflammatory agent, anti-fungal agent and any combination thereof.

~~20. The method according to any one of claims 1 to 18, wherein the pharmaceutically active agent comprises a plurality of antibiotic agents.~~

~~21. The method according to any one of claims 1 to 18, wherein the pharmaceutically active agent comprises at least one antibiotic agent and at least one anti-inflammatory agent.~~

~~22. The method according to any one of claims 19-21, wherein the antibiotic agent is selected from the group consisting of penicillin antibiotics, cephem antibiotics, macrolide antibiotics, tetracycline antibiotics, fosfomycin antibiotics, aminoglycoside antibiotics, and new quinolone antibiotics~~

~~23.~~16. The use~~method~~ according to ~~any one of claims 1-22~~claim 1, wherein the at least one sterol in the matrix composition comprises ~~is~~ a cholesterol.

~~24. The method according to any one of claims 1 to 23, wherein the weight ratio of total lipids to said biocompatible polymer is between 1:1 and 9:1 inclusive.~~

~~25. The method according to any one of the preceding claims wherein the coated substrate comprises between about 60-90% (w/w) of substrate and 10-40% (w/w) of the matrix composition.~~

~~26. The method according to claim 25, wherein the coated substrate comprises between about 70-90% (w/w) of substrate and 10-30% (w/w) of the matrix composition.~~

~~27. The method according to any one of claims 1 to 26, wherein said matrix composition is substantially free of water.~~

~~28.~~17. The use~~method~~ according to ~~any one of claims 1 to 27~~claim 1, wherein when the coated or impregnated mineral substrate is maintained in an aqueous environment, the matrix composition provides sustained release of said antibiotic ~~pharmaceutically active~~ agent, wherein at least 30% of the antibiotic ~~said pharmaceutical active~~ agent is released from the composition at zero-order kinetics.

18. The use according to claim 1, wherein the matrix composition comprises:
(a) 10-30% w/w of a biodegradable polyester by weight of the matrix composition;
(b) 5-30% w/w of a first lipid component by weight of the matrix composition;
(c) 40-75% w/w of a second lipid component by weight of the matrix composition; and
(d) 1-20% w/w of doxycycline or doxycycline hyclate, by weight of the matrix composition.

19. The use according to claim 1, wherein the coated biodegradable mineral substrate comprises between about 60-90% (w/w) of biodegradable mineral substrate and 10-40% (w/w) of the matrix composition.

20. The use of claim 1, wherein the infection is caused by hospital acquired resistant bacteria.

21. The use of claim 20, wherein the hospital acquired resistant bacteria include Methicillin-resistant S. aureus (MRSA).

22. The use according to claim 1, wherein the coated mineral substrate is formulated as a paste prior to application of the coated mineral substrate to the soft-tissue incision site.

~~29. A method for the treatment or prophylaxis of a surgical site infection associated with surgical operation comprising the step of applying to the surgical site a biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition comprises: (a) 15-25% (w/w) poly (lactic-co-glycolic acid) (PLGA) (b) 5-15% (w/w) of cholesterol; (c) 50-70% (w/w) of a mixture of 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), wherein the ratio of DPPC to~~

DSPC is between 5:1 and 2:1 and (d) 7-12% (w/w) of doxycycline or doxycycline hyclate, wherein the substrate constitutes between about 80-90% (w/w) and the matrix composition constitutes about 10-20% (w/w) of the total weight of the coated substrate.

30. A biodegradable substrate impregnated or having its surface coated fully or partially with a matrix composition comprising (a) a biocompatible polymer, (b) a first lipid component comprising at least one sterol which is non-covalently associated with the biocompatible polymer, (c) a second lipid component comprising at least one phospholipid having fatty acid moieties of at least 12 carbons; and (d) a pharmaceutically active agent for use in the treatment or prophylaxis of a surgical site infection associated with surgical operation in a subject in need thereof.

31. The biodegradable substrate of claim 30 useful for at least one of reducing the overall infection rate post-surgery, eradicating soft tissue infections that may exist prior to surgery, Inhibition of biofilm formation at the surgical site and eradicating an existing biofilm at the surgical site.

32. The biodegradable substrate of claims 30 or 31, wherein the surgical operation in selected from orthopedic surgical operations, spine surgical operations, surgical operations on a digestive system organ, cardiac procedures, hernia repair, vascular procedures, caesarian, prostatectomy, obstetric and gynecologic surgical operations, head and neck cancer surgery, transplantation surgeries, neurosurgery and plastic surgeries.

33. The biodegradable substrate according to any one of claims 30-32, for use in the treatment or prophylaxis of a surgical site infection associated with surgical operation in a subject in need thereof in addition to standard of care procedures for reduction in the inoculum of bacteria selected from the group consisting of appropriate surgical site preparation, systemic preventive antibiotics, cell based therapy, and enhancement of the host by perioperative supplemental oxygenation, maintenance of normothermia and glycemic control.

34. The biodegradable substrate according to claims 30 to 33, wherein the biodegradable substrate is selected from the group consisting of a mineral substrate, a natural polymer material, a water soluble synthetic polymer and a bioabsorbable hydrophobic material.

35. The biodegradable substrate according to claim 34, wherein the biodegradable substrate is a mineral substrate selected from the group consisting of hydroxyapatite, fluorapatite, oxyapatite, wollastonite, apatite/wollastonite glass ceramics, anorthite, calcium fluoride, calcium sulfate, calcium carbonate, tetracalcium phosphate, α-tricalcium phosphate (α-TCP), β-tricalcium phosphate (β-TCP), amorphous calcium phosphate, dicalcium phosphate, agrellite, devitrite, canasite, phlogopite, monetite, brushite, octocalcium phosphate, whitlockite, cordierite, berlinite, combeite, phosphoric acid crystals, disodium hydrogen phosphate, and other phosphate salt-based bioceramics.

36. The biodegradable substrate according to claim 34, wherein the biodegradable substrate is a natural polymer material selected from the group consisting of gelatin, hyaluronic acid, hyaluronic acid derivatives, such as, a polyionic complex of hyaluronic acid, triethanolamine alginate, casein, keratin, myosin and/or fibroin, collagen, collagen derivatives, such as, succinylated collagen or methylated collagen, chondrotin sulfate, chitosan, chitosan derivatives, such as, methylpyrrolidone chitosan, polyaminogalactosamine.

37. The biodegradable substrate of claim 34, wherein the substrate is a water soluble synthetic polymer.

38. The biodegradable substrate of claim 37, wherein the substrate is poly vinyl alchohol (PVA).

39. The biodegradable substrate according to any one of claims 30 to 38, consisting of particles having an average particle size of less than about 200 microns (μm).

40. The biodegradable substrate according to any one of claims 30 to 39, wherein the matrix composition comprises a phospholipid selected from a phosphatidylcholine or a combination of phosphatidylcholines having fatty acid moieties having at least 12 carbons.

41. The biodegradable substrate according to of claim 40, wherein said phospholipid is a phosphatidylcholine or a combination of phosphatidylcholines having fatty acid moieties having 14 — 18 carbons.

42. The biodegradable substrate according to any one of claims 30 to 41 wherein the biocompatible polymer in the matrix composition, is a biodegradable polyester selected from the group consisting of PLA (polylactic acid), PGA (poly glycolic acid) and PLGA (Poly (lactic co glycolic acid).

43. The biodegradable substrate according to any one of claims 30 to 41, wherein the biocompatible polymer in the matrix composition is poly ethylene glycol (PEG).

44. The biodegradable substrate according to any one of claims 30 to 43, wherein the pharmaceutically active agent is selected from the group consisting of an antibiotic agent, an antiseptic agent, an anti inflammatory agent, anti fungal agent and any combination thereof.

45. The biodegradable substrate according to any one of claims 30 to 43, wherein the pharmaceutically active agent comprises a plurality of antibiotic agents.

46. The biodegradable substrate according to any one of claims 30 to 43, wherein the pharmaceutically active agent comprises at least one antibiotic agent and at least one anti inflammatory agent.

47. The biodegradable substrate according to any one of claims 44-46, wherein the antibiotic agent is selected from the group consisting of penicillin

antibiotics, cephem antibiotics, macrolide antibiotics, tetracycline antibiotics, fosfomycin antibiotics, aminoglycoside antibiotics, and new quinolone antibiotics

48. The biodegradable substrate according to any one of claims 30-47, wherein the sterol in the matrix composition is a cholesterol.

49. The biodegradable substrate according to any one of claims 30 to 48, wherein the weight ratio of total lipids to said biocompatible polymer is between 1:1 and 9:1 inclusive.

50. The biodegradable substrate according to any one of the preceding claims wherein the coated biodegradable substrate comprises between about 60-90% (w/w) of biodegradable substrate and 10-40% (w/w) of the matrix composition.

51. The biodegradable substrate according to claim 50, wherein the coated biodegradable substrate comprises between about 70-90% (w/w) of biodegradable substrate and 10-30% (w/w) of the matrix composition.

52. The biodegradable substrate according to any one of claims 30 to 51, wherein said matrix composition is substantially free of water.

53. The biodegradable substrate according to any one of claims 30 to 52, wherein when the coated biodegradable substrate is maintained in an aqueous environment, the matrix composition provides sustained release of said pharmaceutically active agent, wherein at least 30% of said pharmaceutical active agent is released from the composition at zero-order kinetics.