collagenase inhibition, including direct inhibition of a range of matrix metalloproteinase (MMP) enzymes, but also their gene expression. In addition, they suppressed transcription factors, downregulation of which leading to inhibition of pro-inflammatory cytokines and MMP activity. They inhibit bone resorption, and are able to promote the attachment of fibroblasts to root surfaces.

Tetracyclines carry bacteriostatic action and inhibit the growth and multiplication of bacteria. They enter the bacteria in two distinct mechanisms, passive diffusion and energy dependent active transport system. By binding to 30S subunit of the ribosome and blocking the attachment of transfer RNA, they inhibit protein synthesis. Like all macrolide antibiotics, azithromycin reversibly inhibits bacterial protein synthesis by targeting the 23S ribosomal RNA of the 50S ribosomal subunit in susceptible organisms.

The present-day antibiotic treatments of periodontal diseases are unsatisfactory in several respects. It has been found that when the exposure to tetracycline is removed, the bacteria continue to grow. On the other hand, extensive use of bactericidal agents is undesired due to the triggering of antibacterial resistance formation and side effects related to gut microbiome changes.

Systemically administered antibiotics have side effects such as vomiting, diarrhea, rash, loss of appetite and potentially kidney problems, which also hamper their use for treatment of localized microbial infections. Local administration of antibiotics will achieve higher concentrations directly at infected sites and reduce possible systemic side effects.

However, local administration requires proper detection of the infected site or sites and correct topical application, which may need to be renewed several times depending on the condition and accessibility of the infected tissue.

Summary ~~of the Invention~~

It is an aim of the present ~~invention~~disclosure to eliminate at least a part of the problems relating to the art.

In one aspect, the present disclosure provides a use of a photosensitive antibiotic in the manufacture of a medicament for use in combinatorial therapy for treating microbial infection, wherein said medicament is to be administered in combination with photodynamic therapy, comprising that

– said photosensitive antibiotic is to be systemically administered to a subject having a microbial infection in a target tissue to provide a blood plasma concentration of said antibiotic in said subject; and

- the target tissue is to be subjected to photodynamic therapy in order to enhance the antimicrobial action of the antibiotic in the target tissue.

In another aspect, the present disclosure provides a kit for treating local microbial infections, comprising an optoelectronic device capable of simultaneously emitting a first light consisting of high energy and a second light consisting of low energy photons, said first and said second light amounting to at least 50 % of all light emitted from the optoelectronic component or device, and at least one systemically administered antibiotic.

In yet another aspect, the present disclosure provides a use of a systemically administered antibiotic in the manufacture of a medicament for use in combinatorial therapy for treating local microbial infections, wherein said medicament is to be administered in combination with antimicrobial photodynamic therapy.

In a first object, the present ~~invention~~disclosure provides a method of enhancing the antimicrobial action of a systemically administered antibiotic.

In a second object, the present ~~invention~~disclosure provides a systemically administered antibiotic for use in antimicrobial therapy of local microbial infections.

In a third object, the present ~~invention~~disclosure provides a method of enhancing matrix enzyme inhibition action of a pharmaceutical substance having antimicrobial activity.

In a fourth object, the present ~~invention~~disclosure provides a kit for enhancing the antimicrobial action of a systemically administered antibiotic.

In a fifth object, the present ~~invention~~disclosure provides a method of enhancing the enzyme inhibition action of a cyclic antibiotic for inhibition of collagenase enzyme activity.

In the present ~~invention~~disclosure it has been found that systemic administration of antibiotics can be combined with local application of photodynamic therapy to achieve an enhanced local antimicrobial action, in particular antibacterial action, of the systemically administered antibiotic.

Thus, provided are systemically administered antibiotics for use in antimicrobial photodynamic therapy of local, in particular topical, microbial infections.

A method of enhancing the antimicrobial action of an antibiotic, comprises the steps of:

- systemically administering a photosensitive antibiotic to a subject having a microbial infection in a target tissue to provide a blood plasma concentration of said antibiotic in said subject; and
- subjecting the target tissue to photodynamic therapy in order to enhance (i.e. to increase) the action, in particular antimicrobial action, of the antibiotic in the target area or tissue.

The method can also be used for enhancing the enzyme inhibition action of a pharmaceutical substance having an antimicrobial activity as well as for enhancing the

enzyme inhibition action of a cyclic photoactive antibiotic for inhibition of collagenase enzyme activity,

More specifically, the present ~~invention~~disclosure is mainly characterized by what is stated in the characterizing parts of the independent claims.

Considerable advantages are obtained by the present ~~invention~~disclosure. Thus, it has been observed that with light activation the efficacy of the photosensitizer antibiotic can be enhanced by up to 50 % or even more**.** It would appear, although this is merely one possible explanation, that the production of reactive oxygen by the antibiotic molecule changes partly the mechanism of action. As a result, locally (i.e. topically) administered light enhances the bactericidity of the molecule.

Due to the antimicrobial photodynamic effect, the spectrum of the microbial effect can also be broadened. Also, an antiviral effect can be obtained. Thus, generally, the present ~~invention~~disclosure can be exploited when there is a need for enhancement of the local antimicrobial effect.

Potentiating antibiotic activity with light or with combination of tissue healing and bacteria killing light has immense potential in promoting periodontal healing and in general oral bacteria management. It has been shown in studies of children with hearth problems that antibiotic treatment can reduce the formation of caries. In the present context it has been shown that the antibiotic effect of certain antibiotics can be increased with light activation.

Periodontal diseases are often difficult to treat, and presently constant low dose and ultra-low dose use of doxycycline has been proposed for treatment of periodontitis and treat and prevent peri-implant mucositis. Use of light activation to promote gum tissue healing and to increase the antibacterial effect of antibiotic treatment is new novel approach to treat gum health.

Further details and advantages of various ~~embodiment~~examples will appear from the following detailed description of ~~embodiment~~examples.

Claims:

1. Use of a photosensitive antibiotic in the manufacture of a medicament for use in combinatorial therapy for treating microbial infection, wherein said medicament is to be administered in combination with photodynamic therapy ~~Method of enhancing the antimicrobial action of an antibiotic~~, comprising that

- ~~systemically administering a~~ said photosensitive antibiotic is to be systemically administered to a subject having a microbial infection in a target tissue to provide a blood plasma concentration of said antibiotic in said subject; and
- ~~subjecting~~ the target tissue is to be subjected to photodynamic therapy in order to enhance the antimicrobial action of the antibiotic in the target tissue.

2. The ~~method~~ use according to claim 1, wherein the microbial infection is caused by virus, bacteria or fungus.

3. The ~~method~~ use according to claim 1 or 2, wherein the microbial infection to be treated is caused by gram-positive bacteria, such as bacteria of the streptococci or staphylococci species, such as *Streptococcus mutans* or *Staphylococcus aureaus*, or *Corynebacterium*, *Clostridium*, *Mycobacterium*, *Nocardia*, *Listeria*, *Bacillus*, or gram-negative bacteria, in particular selected from the group of *Proteobacteria, Aquificae, Chlamydiae, Bacteroidetes, Chlorobi, Cyanobacteria, Fibrobacteres, Verrucomicrobia, Planctomycetes, Spirochetes, Acidobacteria, Actinobacteria, Firmicutes, Thermotogae, Porphyromonas* and *Chloroflexi*.

4. The ~~method~~ use according to claim 1 or 2, wherein the antibiotic action is enhanced to provide for antiviral action and the microbial infection to be treated is caused by virus selected from the group of Adenoviruses, Herpesviruses, Poxviruses, Parvoviruses, Reoviruses, Picornaviruses, Togaviruses, Orthomyxoviruses, Rhabdoviruses, Retroviruses, Papillomavirus and Hepadnaviruses

5. The ~~method~~ use according to any of the preceding claims, comprising ~~administering~~ that an antibiotic selected from the group of macrolides, including levofloxacin, ofloxacin,

ciprofloxacin, clarithromycin, erythromycin, roxithromycin, or azithromycin; tetracyclines including doxycycline, ionocycline, tetracycline, chlortetracycline, demeclocycline, lymecycline, meclocycline, methacycline, rolitetracycline, tigecycline, eravacycline, sarecycline, omacycline, sarecycline, eravacycline, omadacycline, oxytetracycline; other antibiotics such as colchicine, trimethoprim or metronidatzole; and in particular azithromycin, doxycycline, minocycline or colchicine or metronidatzole, or any of their combinations is to be administered.

6. The ~~method~~ use according to any of the preceding claims, comprising ~~administering~~ that the antibiotic is to be administered orally or parenterally.

7. The ~~method~~ use according to any of the preceding claims, comprising raising the tissue concentration of the antibiotic by oral mucosal delivery.

8. The ~~method~~ use according to any of the preceding claims, comprising raising the antibiotic concentration in the Gingival Precrevicular Fluid.

9. The ~~method~~ use according to any of the preceding claims, comprising allowing the plasma concentration of the antibiotic increase to a predetermined level, in particular to at least 10 %, in particular 20 to 100 %, of the administered antibiotics' maximum plasma concentration before ~~subjecting~~ the target tissue is to be subjected to photodynamic therapy.

10. The ~~method~~ use according to any of the preceding claims, wherein the target tissue comprises soft tissues, biofilms, saliva, skin, plaque and teeth surfaces and mucous membranes.

11. The ~~method~~ use according to any of the preceding claims, wherein the target tissue comprises oral tissue, such as tissue in the oral cavity, including gum and oral mucosa as well as underlying tissue.

12. The ~~method~~ use according to any of the preceding claims, wherein the microbial infection of the target tissue comprises a gumline bacterial biofilm.

13. The ~~method~~ use according to any of claims 1 to 9, wherein the target tissue comprises tissue in the throat, in the nose or in the ears.

14. The ~~method~~ use according to claim 13, wherein the microbial infection of the target tissue comprises pharyngitis or otitis.

15. The ~~method~~ use according to any of the preceding claims, wherein the target tissue is to be topically subjected to photodynamic therapy.

16. The ~~method~~ use according to any of the preceding claims, wherein the antibiotic is photoactivated in order to eliminate pathogens inside tissue and host cells.

17. The ~~method~~ use according to any of the preceding claims, wherein the photodynamic therapy comprises ~~subjecting~~ that the target tissue is to be subjected to electromagnetic radiation in the form of light of either or two of the following energy levels: a first light with photons having a majority energy in the range from 3.5 eV to 2.8 eV, and a second light with photons having a majority energy in the range from 1.24 eV to 2.48 eV, wherein photons of the first light and the second light are simultaneously directed against the target tissue.

18. The ~~method~~ use according to any of the preceding claims, wherein

- non-coherent radiant light energy is generated at one first energy level, or preferably at least two different energy levels, a first and a second energy level;
- from the non-coherent radiant light energy there is provided first light having a wavelength corresponding to the majority energy of the first energy level, and optionally a second light having a wavelength corresponding to the majority energy of the second energy level; and
- the first and optionally the second light are then simultaneously directed against the target tissue, in particular against the surface of the target tissue.

19. The ~~method~~ use according to any of the preceding claims, wherein the photodynamic therapy comprises ~~subjecting~~that the target tissue is to be subjected to a light having a wavelength in the range of about 350 to 450 nm, for example about 370 to 410 nm, to light having a wavelength in the range of about 500 to 1000 nm, for example about 780 to 830 nm, or to a combination thereof, said light preferably comprising non-coherent light, for example produced by optoelectronic devices, such as light emitting diodes (LEDs).

20. The ~~method~~ use according to any of the preceding claims, wherein the photodynamic therapy comprises ~~subjecting~~ that the target tissue is to be subjected to a first light having a wavelength of 405 nm ±10 nm and second light having a wavelength of 810 nm ±15 nm is used, both the first and the second lights comprising non-coherent light, for example produced by optoelectronic devices, such as light emitting diodes (LEDs).

21. The ~~method~~ use according to any of the preceding claims, wherein the target tissue is to be subjected to endogenous and exogenous excitement, in particular so as to generate reactive oxygen singlets or reactive oxygen species or both.

22. The ~~method~~ use according to any of the preceding claims, wherein the light is combined with at least one photosensitive substance for treating the target tissue using photodynamic therapy.

23. The ~~method~~ use according to claim 22, wherein the photosensitive substance is selected from the group of Hypericin, curcumin, phenalenone derivatives, Cercosporin, psoralen, xanthotoxin, Angelicin, alpha-Terthienyl, Phenylthepatriyne, THC, Cannabidiol (CBD). Synthetic photosensitizers include the following: RB (Rose Bengal), MB, Porphyrin derivatives, Curcumin derivatives, Methylene Blue, Indocyanine Green, Erythosine, Phenalenone derivatives, Fullerene derivatives, Xanthene derivates and combinations thereof.

24. The ~~method~~ use according to any of claims 17 to 23, wherein the high energy photons and low energy photons are applied in conjugation with at least one exogeneous photosensitizer, which can be activated with the low energy photons.

25. The ~~method~~ use according to any of claims 17 to 24, wherein a photosensitizer is provided for ~~use in~~ topical treatment of mammalian tissues, wherein said sensitizer is to be applied to a superficial part of the tissue, such as on mammalian skin or on a mucous membrane and the part thus treated is to be subsequently or simultaneously subjected to light at two different wavelengths.

26. The ~~method~~ use according to any of the preceding claims, wherein a photosensitizer is to be contacted with micro-organisms, such as bacteria, virus and fungus, in the target tissue, such as in biofilm, saliva, skin, plaque and on teeth surfaces or mucous membranes, by applying it on the target in the form of an aqueous solution, an alcohol containing solution, a hydrophilic gel, a hydrophobic gel, a hydrophilic polymer, a hydrophobic polymer or a paste, lotion, tape, tablet, plaster or band-aid.

27. The ~~method~~ use according to any of the preceding claims, wherein the area of the target tissue subjected to photodynamic therapy is less than 100 cm^2, such as less than 50 cm^2, in particular less than 40 cm^2, for example 1 to 30 cm^2.

28. The ~~method~~ use according to any of the preceding claims, comprising that an antibiotic is to be topically ~~administering~~ administered to the target tissue ~~an antibiotic~~.

29. A kit for treating local microbial infections, comprising an optoelectronic device capable of simultaneously emitting a first light consisting of high energy and a second light consisting of low energy photons, said first and said second light amounting to at least 50 % of all light emitted from the optoelectronic component or device, and at least one systemically administered antibiotic.

~~30. The kit according to claim 29, comprising an optoelectronic device capable of emitting high energy photons with majority energy between 2.8 eV and 3.5 eV and low energy photons with majority energy between 1.24 eV and 1.65 eV.~~

~~31. The kit according to claim 29 or 30 comprising an optoelectronic device having a light emitting component that has two or more light emitting surfaces (EPIs), together with a photosensitizer or a plurality of photosensitizers.~~

~~32. The kit according to any of claims 29 to 31, wherein the systemically administered antibiotic is capable of achieving antimicrobial action in a target tissue of a subject.~~

~~33. The kit according to any of claims 29 to 32, wherein the antibiotic is selected from the group of macrolides, including levofloxacin, ofloxacin, ciprofloxacin, clarithromycin, erythromycin, roxithromycin, or azithromycin; tetracyclines including doxycycline, ionocycline, tetracycline, chlortetracycline, demeclocycline, lymecycline, meclocycline, methacycline, rolitetracycline, tigecycline, eravacycline, sarecycline, omacycline, sarecycline, eravacycline, omadacycline, oxytetracycline; other antibiotics such as colchicine, trimethoprim or metronidatzole; and in particular azithromycin, doxycycline, minocycline or colchicine or metronidatzole, or any of their combinations.~~

~~34. The kit according to any of claims 29 to 33, comprising a pharmaceutically acceptable composition of the antibiotic suitable for administration orally, parenterally or transdermally.~~

~~35. The kit according to any of claims 29 to 34, comprising a photosensitizer.~~

~~36. The kit according to any of claims 29 to 35, comprising a photosensitizer that can be activated by at least either of the high energy and low energy photons, preferably both.~~

~~37. The kit according to any of claims 29 to 36, comprising a photosensitizer selected from the group of Hypericin, curcumin, phenalenone derivatives, Cercosporin, psoralen, xanthotoxin, Angelicin, alpha-Terthienyl, Phenylthepatriyne, THC, Cannabidiol (CBD). Synthetic photosensitizers include the following: RB (Rose Bengal), MB, Porphyrin derivatives, Curcumin derivatives, Methylene Blue, Indocyanine Green, Erythosine, Phenalenone derivatives, Fullerene derivatives, and Xanthene derivates and combinations thereof.~~

~~38. The kit according to any of claims 29 to 37, comprising a photosensitizer capable of being topically applied to a target tissue of a subject.~~

~~39~~30. Use of a s~~S~~ystemically administered antibiotic in the manufacture of a medicament for use in combinatorial therapy for treating local microbial infections, wherein said medicament is to be administered in combination with antimicrobial photodynamic therapy ~~of local microbial infections~~.

~~40~~31. The ~~systemically administered antibiotic for~~ use ~~in antimicrobial photodynamic therapy~~ according to claim ~~39~~30, wherein the photodynamic therapy is carried out for treatment of oral diseases, such as periodontal diseases.

~~41~~32. The ~~systemically administered antibiotic for~~ use ~~in antimicrobial photodynamic therapy~~ according to claim ~~39~~ 30 or ~~40~~31, wherein the photodynamic therapy is carried out for treatment of bacterial biofilm, such as gumline bacterial biofilm.

~~42~~33. The ~~systemically administered antibiotic for~~ use ~~in antimicrobial photodynamic therapy~~ according to any of claims ~~39~~ 30 to ~~41~~32, wherein the systemic antibiotic is selected from the group of photosensitive antibiotics of the group of azithromycin, tetracycline, macrolide, and combinations thereof.

~~43~~34. The ~~systemically administered antibiotic for~~ use ~~in antimicrobial photodynamic therapy~~ according to any of claims ~~39~~ 30 to ~~42~~33, wherein a cyclic photoactive antibiotic is used to inhibit collagenase 2 enzyme.

~~44~~35. The ~~systemically administered antibiotic for~~ use ~~in antimicrobial photodynamic therapy~~ according to claim ~~43~~34, wherein the cyclic photoactive antibiotic is doxycycline or minocycline.

~~45. Method of enhancing the enzyme inhibition action of a pharmaceutical substance having a antimicrobial activity, comprising~~

- systemically administering a photosensitive pharmaceutical substance to a subject having a microbial infection in a target tissue to provide a plasma concentration of said substance in said subject;
- optionally allowing the plasma concentration of the antibiotic increase to a predetermined level; and
- subjecting the target tissue to photodynamic therapy in order to increase the enzyme inhibition action of the substance in the target tissue.

46. The method according to claim 45, comprising the use of cyclic photoactive antibiotics for inhibition of collagenase enzyme activity.

47. The method according to claim 45 or 46, wherein the cyclic photoactive antibiotic is used to inhibit MMP-8, MMP-9, MMP-13 or MMP-1 action or their gene expression or any of their combinations.

48. The method according to claim 46 or 47, wherein the cyclic photoactive antibiotic is doxycycline or minocycline.

49. Method of enhancing the enzyme inhibition action of a cyclic photoactive antibiotic for inhibition of collagenase enzyme activity, comprising

- systemically administering a photosensitive pharmaceutical substance to a subject having a microbial infection in a target tissue to provide a plasma concentration of said antibiotic in said subject;
- optionally allowing the plasma concentration of the substance increase to a predetermined level; and

subjecting the target tissue to photodynamic therapy in order to increase the enzyme inhibition action of the substance in the target tissue.