Staphylococcus aureus. Because most phage and phage peptides studied to date exhibit activity often restricted to the related species, or subspecies, of bacteria from which they are isolated, the novel phage-based therapies may find particular use in the hospital setting, selectively targeting nosocomial pathogens without affecting the normal surrounding flora.

4. SUMMARY ~~OF THE INVENTION~~

[0007] The present ~~invention~~disclosure is directed to isolated bacteriophages and to isolated antibacterial polypeptides of bacteriophage origin for the treatment, prevention, or management of conditions associated with infection by Gram-positive or Gram-negative bacteria. In particular, the isolated bacteriophage or polypeptides of the ~~invention~~disclosure may be used in pharmaceutical compositions for the treatment, prophylaxis, or management of infection by nosocomial pathogens, *e.g.*, Gram-positive bacteria including but not limited to *Enterococcus faecalis, E. faecium, E. hirae, E. avium, Staphylococcus aureus, S. epidermidis, S. auricularis, S. capitis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans,* and *S. xylosis*; and/or Gram-negative bacteria including but not limited to *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. In certain embodiments, the pharmaceutical compositions of the ~~invention~~disclosure are of use in the treatment of conditions associated with infection by antibiotic resistant strains of bacteria, *e.g.*, methicillin resistant strains of *Staphylococcus aureus* (MRSA). In particular embodiments, the isolated bacteriophages or polypeptides of the ~~invention~~disclosure are used for the topical treatment of infection by nosocomial pathogens in a subject in need thereof. In other embodiments, the isolated bacteriophages or polypeptides of the ~~invention~~disclosure are used for the diagnosis of the infective agent in a sample (*e.g.*, tissue, blood, urine, sputum sample) derived from a patient. In other embodiments, the isolated bacteriophages or polypeptides of the ~~invention~~disclosure are used as a prophylactic disinfectant or anti-infective for the preparation of solid surfaces, including skin or other epidermal surfaces.

[0007a] In a first aspect, there is provided an isolated bacteriophage having a genome which comprises the nucleic acid sequence of SEQ ID NO:1.

[0007b] In a second aspect, there is provided a pharmaceutical composition comprising the bacteriophage as defined above and a pharmaceutically acceptable carrier.

[0007c] In a third aspect, there is provided an isolated lysin protein from bacteriophage F168/08, or a fragment thereof having antibacterial or antimicrobial activity against *Enterococcus faecalis* or *Enterococcus faecium*.

[0007d] In a fourth aspect, there is provided an isolated first protein having at least 85% sequence identity to a second protein of the same size, wherein said first protein has antibacterial or antimicrobial activity against *Enterococcus faecalis* or *Enterococcus faecium* and said second protein has the amino acid sequence of SEQ ID NO:68.

[0007e] In a fifth aspect, there is provided an isolated tail tape measure protein or tail protein from bacteriophage F168/08 or a fragment thereof having antibacterial or antimicrobial activity against *Enterococcus faecalis* or *Enterococcus faecium*.

[0007f] In a sixth aspect, there is provided an isolated first protein having at least 85% sequence identity to a second protein of the same size, wherein said first protein has a biological activity associated with bacteriophage F168/08 and said second protein has the amino acid sequence of SEQ ID NO:61 or SEQ ID NO:63.

[0007g] In a seventh aspect, there is provided a pharmaceutical composition comprising the isolated protein as defined above and a pharmaceutically acceptable carrier.

[0007h] In an eighth aspect, there is provided an isolated nucleic acid comprising a nucleotide sequence encoding the protein as defined above.

[0007i] In a ninth aspect, there is provided the use of the pharmaceutical composition as defined above in the manufacture of a medicament for treating or preventing a bacterial infection in a subject in need thereof.

[0007j] In a tenth aspect, there is provided a method for diagnosing the causative agent of a bacterial infection comprising

(i) culturing a tissue sample from a patient;

(ii) contacting the culture of step (i) with the bacteriophage as defined above, or protein as defined above; and

(iii) monitoring for evidence of growth or lysis of the culture;

wherein evidence of lysis of the culture indicates that the culture comprises a species or strain of bacteria that is known to be susceptible to the bacteriophage or protein used in step (ii).

[0007k] In an eleventh aspect, there is provided a method for reducing or inhibiting the colonization or growth of bacteria on a solid surface comprising contacting said solid surface with the bacteriophage as defined above, or protein as defined above.

[0007l] In a twelfth aspect, there is provided the use of a bacteriophage as defined above, or protein as defined above in the manufacture of a medicament for reducing or inhibiting the colonization or growth of bacteria on a surface.

[0008] In certain embodiments, the ~~invention~~disclosure provides an isolated bacteriophage, F168/08 or F170/08, having a genome comprising the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2, respectively, and exhibiting antibacterial activity against one or more strains of *Enterococcus faecalis* and/or *E. faecium*. In other embodiments, the ~~invention~~disclosure provides an isolated bacteriophage, F770/05, having a genome comprising the nucleic acid sequence of SEQ ID NO:3 and exhibiting antibacterial activity against one or more strains of *Pseudomonas aeruginosa*. In yet other embodiments, the ~~invention~~disclosure provides the isolated bacteriophage

F197/08, F86/06, F87s/06 or F91a/06 having a genome comprising the nucleic acid sequence of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7, respectively, and exhibiting antibacterial activity against one or more strains of *Staphylococcus aureus*. In still yet other embodiments, the ~~invention~~disclosure provides an isolated bacteriophage, F1245/05, having a genome comprising the nucleic acid sequence of SEQ ID NO:760 and exhibiting antibacterial activity against one or more strains of *Acinetobacter baumannii.*

[0009] The ~~invention~~disclosure also encompasses isolated bacteria infected with one or more bacteriophage of the ~~invention~~disclosure. In specific embodiments, the ~~invention~~disclosure provides an isolated *E. faecalis* infected with a bacteriophage having a genome comprising or consisting of the nucleic acid sequence of SEQ ID NO:1 and/or SEQ ID NO:2. In other embodiments, the ~~invention~~disclosure provides an isolated *E. faecium* infected with a bacteriophage having a genome comprising or consisting of the nucleic acid sequence of SEQ ID NO:1 and/or SEQ ID NO:2. In still other embodiments, the ~~invention~~disclosure provides an isolated *P. aeruginosa* infected with a bacteriophage having a genome comprising or consisting of the nucleic acid sequence of SEQ ID NO:3. In yet other embodiments, the ~~invention~~disclosure provides an isolated *S. aureus* infected with one or more bacteriophages having a genome comprising or consisting of the nucleic acid sequence of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 and/or SEQ ID NO:7. In still yet other embodiments, the ~~invention~~disclosure provides an isolated *A. baumannii* infected with a bacteriophage having a genome comprising or consisting of the nucleic acid sequence of SEQ ID NO:760.

[0010] The present ~~invention~~disclosure encompasses polypeptides isolated from bacteriophage F1245/05, F168/08, F170/08, F770/05, F197/08, F86/06, F87s/06 and/or F91a/06, which polypeptides exhibit antibacterial activity against one or more species or strains of Gram-positive or Gram-negative bacterium, *e.g.*, *A. baumannii*, *E. faecalis*, *E. faecium*, *P. aeruginosa* and/or *S. aureus*. In specific embodiments, the polypeptides of the ~~invention~~disclosure isolated or derived from F168/08 or F/170/08 exhibit antibacterial or antimicrobial activity, *e.g.*, lytic killing activity, against at least *E. faecalis* and/or *E. faecium*; those isolated or derived from F770/05 against at least *P. aeruginosa*; those isolated or derived from F197/08, F86/06, F87s/06 or F91a/06 against at least *S. aureus*; and those isolated or derived from F1245/05 against at least *A. baumannii*.

[0011] In certain embodiments, a polypeptide of the ~~invention~~disclosure comprises or consists of an isolated endolysin or fragment thereof (*e.g.*, a CHAP domain) that exhibits antibacterial activity against one or more species or strains of bacteria, *e.g.*, Gram-positive bacteria and/or Gram-

negative bacteria such as *A. baumannii*, *E. faecalis*, *E. faecium, P. aeruginosa* and/or *S. aureus*. In specific embodiments, the polypeptide of the ~~invention~~disclosure is an isolated lysin protein, *e.g.*, an endolysin or tail lysin, comprising or consisting of the amino acid sequence SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:575, SEQ ID NO:641 or SEQ ID NO:712. In yet still other embodiments, the ~~invention~~disclosure provides a polypeptide comprising or consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 761 to SEQ ID NO: 816.

[0012] In other embodiments, a polypeptide of the ~~invention~~disclosure comprises a fragment, variant or derivative of SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:575, SEQ ID NO:641 or SEQ ID NO:712, wherein said fragment, variant or derivative has antibacterial activity or antimicrobial activity, *e.g.*, lytic killing activity, against one or more strains of *E. faecalis*, *E. faecium, P. aeruginosa* and/or *S. aureus*. In specific examples in accordance with this embodiment, the variant, fragment or derivative of the amino acid sequence of SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202 and/or SEQ ID NO:203 exhibits antibacterial or antimicrobial activity (*e.g.*, lytic killing activity) against one or more strains of *E. faecalis* and/or *E. faecium*. In other examples in accordance with this embodiment, the variant, fragment or derivative of the amino acid sequence of SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:575, SEQ ID NO:641 and/or SEQ ID NO:712 exhibits antibacterial or antimicrobial activity (*e.g.*, lytic killing activity) against one or more strains of *S. aureus*.

[0013] In specific embodiments, the isolated polypeptide of the ~~invention~~disclosure comprises or consists of the CHAP domain of SEQ ID NO:68, SEQ ID NO:446, SEQ ID NO:575, SEQ ID NO:641 or SEQ ID NO:712. In certain embodiments, the isolated polypeptide comprises or consists of the CHAP domain of SEQ ID NO:68, SEQ ID NO:446, SEQ ID NO:575, SEQ ID NO:641 or SEQ ID NO:712, e.g., having the amino acid sequence of SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758 or SEQ ID NO:759, respectively. In other embodiments, a polypeptide of the ~~invention~~disclosure comprises a fragment, variant or derivative of SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758 or SEQ ID NO:759, wherein said fragment, variant or derivative has antibacterial activity or antimicrobial activity, *e.g.*, lytic killing activity, against at least one or more strains of *E. faecalis*, *E. faecium, P. aeruginosa* and/or *S. aureus*. In yet still other embodiments, a polypeptide of the ~~invention~~disclosure comprises a fragment, variant or

derivative of SEQ ID NO: 761 to SEQ ID NO: 816, wherein said fragment, variant or derivative has antibacterial activity or antimicrobial activity, *e.g.*, lytic killing activity, against at least one or more strains of *A. baumannii*.

[0014] In other embodiments, a polypeptide of the ~~invention~~disclosure comprises or consists of an isolated tail length tape measure protein or tail protein (*e.g.*, tail component, tail fiber protein, adsorption associated tail protein), or fragment thereof, having a biologic function associated with the bacteriophage from which it is derived, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against at least one or more species or strains of *E. faecalis*, *E. faecium, P. aeruginosa*, *S. aureus*, and/or *A. baumannii*. In specific embodiments, the polypeptide of the ~~invention~~disclosure is an isolated tail length tape measure protein or tail proteins comprising or consisting of the amino acid sequence SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704 or SEQ ID NO:795. In other embodiments, a polypeptide of the ~~invention~~disclosure comprises a fragment, variant or derivative of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704 or SEQ ID NO:795, wherein said fragment, variant or derivative exhibits a biologic function associated with the bacteriophage from which it is derived, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *E. faecalis*, *E. faecium, P. aeruginosa*, *S. aureus*, and/or *A. baumannii*.

[0015] In certain embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NO:61 or SEQ ID NO:63 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid

sequence SEQ ID NO:1, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *E. faecalis* and/or *E. faecium*. In other embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NO:204 or SEQ ID NO:214 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:2, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *E. faecalis* and/or *E. faecium*.

[0016] In certain embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NO:435 or SEQ ID NO:438 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:3, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *P. aeruginosa*.

[0017] In certain embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NO:440, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538 or SEQ ID NO:539 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:4, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *S. aureus*. In other embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NO:567 or SEQ ID NO:568 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:5, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *S. aureus*. In yet other embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NO:632 or SEQ ID NO:633 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:6, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *S. aureus*. In yet other embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703 or

SEQ ID NO:704 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:7, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *S. aureus*.

[0018] In certain embodiments, the ~~invention~~disclosure encompasses a variant, fragment or derivative of the amino acid sequence of SEQ ID NOS: 761-816 that exhibits a biologic function associated with the bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:760, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), which function is directed against one or more strains of *A. baumannii.*

[0019] In certain embodiments, the ~~invention~~disclosure provides for isolated polypeptides that exhibit antimicrobial or antibacterial activity (*e.g.*, lytic killing activity) against one or more strains of bacteria (*e.g.*, Gram-positive bacteria (*e.g.*, *E. faecalis*, *E. faecium*, *S. aureus*), Gram-negative bacteria (*e.g.*, of *A. baumannii, P. aeruginosa*) or bacteria not classified as either Gram-positive or Gram-negative), wherein the isolated polypeptides have an amino acid sequence with at least 60%, 65%, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or greater sequence identity to a second amino acid sequence of the same length (*i.e.*, consisting of the same number of residues), which second amino acid sequence is SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:575, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:641, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704, SEQ ID NO:712, SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758, SEQ ID NO:759, SEQ ID NOS:761-816, and/or a fragment thereof.

[0020] The ~~invention~~disclosure further provides isolated polypeptides comprising or consisting of the amino acid sequence of any of SEQ ID NOS:8-130, SEQ ID NOS:131-343, SEQ ID NOS:344-438, SEQ ID NOS:439-553, SEQ ID NOS:554-616, SEQ ID NOS:617-681, SEQ ID NOS:682-759, and SEQ ID NOS:761-816. In other embodiments, isolated polypeptides of the ~~invention~~disclosure

recombinantly fused or chemically conjugated (*e.g.*, covalent or non-covalent conjugation) to therapeutic agents (*e.g.*, heterologous polypeptides or small molecules) are provided.

[0021] The ~~invention~~disclosure also encompasses polynucleotides that encode the polypeptides of the ~~invention~~disclosure. In a specific embodiment, the ~~invention~~disclosure provides an isolated nucleic acid comprising a nucleic acid sequence encoding the polypeptide of any of SEQ ID NOS:8-130, SEQ ID NOS:131-343, SEQ ID NOS:344-438, SEQ ID NOS:439-553, SEQ ID NOS:554-616, SEQ ID NOS:617-681, SEQ ID NOS:682-759, and SEQ ID NOS 761-816. In other embodiments, the ~~invention~~disclosure provides an isolated nucleic acid comprising a nucleic acid sequence encoding the polypeptide of any of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:575, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:641, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704, SEQ ID NO:712, SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758, SEQ ID NO:759, SEQ ID NOS 761-816, or active fragment, variant or derivative thereof, which polypeptide or active fragment, variant or derivative exhibits a biologic function associated with the bacteriophage from which it is isolated and/or derived, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity). The ~~invention~~disclosure also relates to a vector comprising said nucleic acid. In one specific embodiment, said vector is an expression vector. The ~~invention~~disclosure further provides host cells containing a vector comprising polynucleotides encoding the polypeptides of the ~~invention~~disclosure.

[0022] The present ~~invention~~disclosure encompasses methods for the production of polypeptides of the ~~invention~~disclosure or active fragments thereof, in particular for use in pharmaceutical compositions, *i.e.*, antimicrobial compositions. For example, the polypeptides of the ~~invention~~disclosure may be isolated directly from cell cultures (e.g., bacterial cell cultures) infected with bacteriophage F1245/05, F168/08, F170/08, F770/05, F197/08, F86/06, F87s/06 or F91a/06. Alternatively, the polypeptides of the present ~~invention~~disclosure may be derived by recombinant means using expression vectors comprising nucleic acid sequence encoding polypeptides of the ~~invention~~disclosure, *e.g.*, SEQ ID

NO:61, SEQ ID NO:63, SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:575, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:641, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704, SEQ ID NO:712, SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758, SEQ ID NO:759, SEQ ID NOS:761-816, or active fragments, derivatives or variants thereof. The polypeptides of the ~~invention~~disclosure or fragments thereof can be produced by any method known in the art for the production of a polypeptide, in particular, by chemical synthesis or by recombinant expression techniques. In specific embodiments, the ~~invention~~disclosure relates to a method for recombinantly producing a phage protein, *e.g.*, a lysin protein, tail protein or active fragment, variant or derivative thereof, said method comprising: (i) culturing under conditions suitable for the expression of said protein in a medium, a host cell containing a vector comprising a nucleic acid sequence encoding the amino acid sequence SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:575, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:641, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704, SEQ ID NO:712, SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758, SEQ ID NO:759, SEQ ID NOS:761-816, or fragment thereof; and (ii) recovery of said protein from said medium. In certain embodiments, the nucleic acid sequence encoding the polypeptide of the ~~invention~~disclosure is operably linked to a heterologous promoter.

[0023] The ~~invention~~disclosure also encompasses methods for the diagnosis of the causative agent in a clinical presentation of bacterial infection. The isolated bacteriophages or polypeptides of the ~~invention~~disclosure may be used to aid in the determination of species of bacteria in a patient sample by

establishing susceptibility of the bacteria in the sample to the bacteriophages and/or polypeptides of the ~~invention~~disclosure. Such methods further encompass methods of evaluation of antibacterial activity of the isolated bacteriophages and/or polypeptides of the ~~invention~~disclosure. Antibacterial activity of the bacteriophages or the polypeptides of the ~~invention~~disclosure, or susceptibility of an unknown sample to such activity, may be assessed by any method known in the art and/or described herein. In certain embodiments, antibacterial activity and/or susceptibility is assessed by culturing known bacteria and/or patient tissue, blood, fluid or swab samples according to standard techniques (*e.g.*, in liquid culture or on agar plates), contacting the culture with bacteriophages and/or polypeptides of the ~~invention~~disclosure and monitoring cell growth after said contacting. For example, in a liquid culture, the bacteria (*e.g.*, *A. baumannii*, *E. faecalis*, *E. faecium*, *P. aeruginosa*, *S. aureus*) may be grown to a optical density ("OD") representative of a mid-point in exponential growth of the culture; the culture is exposed to one or more concentrations of one or more bacteriophages and/or polypeptides of the ~~invention~~disclosure and the OD is monitored relative to a control culture. Decreased OD relative to a control culture is representative of a bacteriophage and/or polypeptide exhibiting antibacterial activity (*e.g.*, exhibits lytic killing activity) against the tested sample or bacterial species and/or strain in the culture. Similarly, bacterial colonies can be allowed to form on an agar plate, the plate exposed to a bacteriophage or polypeptide of the ~~invention~~disclosure, and subsequent growth of the colonies evaluated relative to control plates. Decreased size of colonies, or decreased total numbers of colonies, indicates a bacteriophage and/or polypeptide with antibacterial activity against the tested sample and/or cultured species or strain.

[0024] The present ~~invention~~disclosure is also directed to pharmaceutical compositions comprising or consisting of a bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7, or SEQ ID NO:760. In certain embodiments, the pharmaceutical composition of the ~~invention~~disclosure comprises a bacteriophage having the genome comprising or consisting of the nucleic acid sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7, or SEQ ID NO:760 in addition to one or more other bacteriophages. The one or more other bacteriophages may be one or more bacteriophages of the ~~invention~~disclosure (*e.g.*, having a genome comprising or consisting of a nucleic acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7, or SEQ ID NO:760), one or more strains thereof, or may be one or

more bacteriophages known in the art. Further, the one or more bacteriophages in the pharmaceutical composition of the ~~invention~~disclosure may target the same or different species or strains of bacteria. In certain embodiments, the pharmaceutical compositions comprising one or more bacteriophages of the ~~invention~~disclosure further comprise one or more polypeptides of the ~~invention~~disclosure and/or other phage products as described herein or known in the art.

[0025] In certain embodiments, the ~~invention~~disclosure provides pharmaceutical compositions comprising polypeptides, or active fragments thereof, in particular those having anti-microbial and/or antibacterial activity, isolated from bacteriophage having a genome comprising or consisting of the nucleic acid sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 SEQ ID NO:7, and/or SEQ ID NO:760. In specific embodiments, the pharmaceutical compositions of the ~~invention~~disclosure comprise one or more polypeptides having an amino acid sequence of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:575, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:641, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704, SEQ ID NO:712, SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758, SEQ ID NO:759 or SEQ ID NOS:761-816. In other embodiments, the pharmaceutical compositions of the ~~invention~~disclosure comprise a polypeptide that is a variant, derivative or fragment of SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:68, SEQ ID NO:184, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:214, SEQ ID NO:435, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:575, SEQ ID NO:632, SEQ ID NO:633, SEQ ID NO:641, SEQ ID NO:700, SEQ ID NO:701, SEQ ID NO:702, SEQ ID NO:703, SEQ ID NO:704, SEQ ID NO:712, SEQ ID NO:755, SEQ ID NO:756, SEQ ID NO:757, SEQ ID NO:758, SEQ ID

NO:759, or SEQ ID NOS:761-816 wherein the variant, derivative or fragment retains a biologic function of the polypeptide from which it is derived, *e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic killing activity), preferably against one or more strains of *A. baumannii*, *E. faecalis*, *E. faecium*, *P. aeruginosa* and/or *S. aureus*.

[0026] The pharmaceutical compositions of the ~~invention~~disclosure may additionally comprise a pharmaceutically acceptable carrier, excipient, or stabilizer. In certain embodiments, the pharmaceutical compositions of the ~~invention~~disclosure are antibiotic compositions (in that they exhibit antibacterial activity) or therapeutic compositions for the treatment, prevention, and/or amelioration of symptoms of a disease or disorder associated with infection by bacteria in a subject in need thereof. In specific embodiments, the pharmaceutical compositions of the ~~invention~~disclosure are antibacterial compositions or therapeutic compositions for the treatment, prevention, and/or amelioration of symptoms of a disease or disorder associated with infection by *A. baumannii*, *E. faecalis*, *E. faecium*, *P. aeruginosa* and/or *S. aureus*. In certain embodiments, the subject receiving a pharmaceutical composition of the ~~invention~~disclosure is a mammal (*e.g.*, bovine, ovine, caprine, equid, primate (*e.g.*, human), rodent, lagomorph or avian (*e.g.*, chicken, duck, goose)).

[0027] The present ~~invention~~disclosure provides for methods for the treatment or prevention of bacterial infection comprising administering to a subject in need thereof a pharmaceutical composition comprising one or more bacteriophages or phage products (*e.g.*, an isolated bacteriophage polypeptide or active fragment, variant or derivative thereof), optionally in addition to one or more other bacteriophages or other phage products, as described herein. In the context of the present ~~invention~~disclosure, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to eliminate, lessen, decrease the severity of, slow the progression of or delay or prevent the symptoms or underlying cause (*e.g.*, bacterial infection) associated with the pathological condition or disorder. The pharmaceutical compositions of the present ~~invention~~disclosure may be used in the treatment or management of infections associated with any bacterial infection, including, but not limited to *A. baumanni, S. aureus, S. epidermidis, S. auricularis, S. capitis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans, S. xylosis, M. luteus, B. subtilis, B. pumilus, E. faecalis, E. hirae, E. faecium, E. avium, P. aeruginosa* and combinations thereof. In certain embodiments, the pharmaceutical compositions may be used to treat conditions or disorders associated with bacterial infections including, but

not limited to, post-operative endophtalmitis, endocarditis, infections of the central nervous system, pneumonia, osteomylelitis, wound infections (*e.g.*, diabetic foot ulcers), mastitis, septicemia, food poisoning and meningitis and/or other conditions associated with nosocomial bacterial infections.

[0028] In certain embodiments, the ~~invention~~disclosure provides for the use of a bacteriophage or an isolated phage product (*e.g.*, an isolated phage polypeptide or active fragment, variant or derivative thereof) as a single agent therapy. In other embodiments, the ~~invention~~disclosure provides for the use of a bacteriophage, or phage product (*e.g.*, an isolated phage polypeptide or active fragment, variant or derivative thereof), in combination with a standard or experimental treatment for bacterial infection. Such combination therapy may enhance the efficacy of the standard or experimental treatment. Examples of therapeutic agents that are particularly useful in combination with a polypeptide of the ~~invention~~disclosure are anti-inflammatory agents, standard chemotherapeutic antibiotic agents (*e.g.*, penicillin, synthetic penicillins, bacitracin, methicillin, cephalosporin, polymyxin, cefaclor, Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefmetazole, cefonioid, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftizoxime, ceftriaxone, cefriaxone moxalactam, cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef mafate and chelating agents), local anesthetic agents, and/or corticosteroids. In yet another embodiment, the compositions of the present ~~invention~~disclosure may be combined with one or more bacteriophages or phage products known in the art. The combination therapies encompassed by the ~~invention~~disclosure may be formulated into a single pharmaceutical composition or may be administered in separate compositions, but as part of an overall treatment regimen.

[0029] The pharmaceutical compositions of the ~~invention~~disclosure may be administered by any method known in the art suitable for administration of an antibacterial compound (*e.g.*, via oral or parenteral (*e.g.*, inhalation, intramuscular, intravenous, or epidermal)) delivery. In preferred embodiments, the pharmaceutical compositions of the ~~invention~~disclosure are administered topically, e.g., in a topical formulation. The compositions of the ~~invention~~disclosure may be used topically to treat and/or prevent common nosocomial infections, such as infections at surgical incision sites or associated with catheters or drains. In other embodiments, the compositions of the ~~invention~~disclosure are use to treat

bacterial infections of the skin or upper dermal layers (*e.g.*, infections of diabetic ulcers of the foot).

[0030] The pharmaceutical compositions of the present ~~invention~~disclosure may also be used for traditionally non-therapeutic uses such as antibacterial agents in cosmetics, or in sprays or solutions for use on solid surfaces to prevent the colonization of bacteria (*i.e.*, as disinfectants).

[0031] The present ~~invention~~disclosure is also directed to methods for screening peptides for antibacterial activity. In one embodiment the method comprises screening contiguous amino acid sequences of at least 6, 10, 15, 20 or 25 residues in length that are encoded by the open reading frames of the nucleic acid sequence SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, or SEQ ID NO:760 for antibacterial activity, said antibacterial activity measured by the peptides ability to inhibit bacterial growth in agar or liquid culture.

4.1 DEFINITIONS

[0032] As used herein, the term "fragment" refers to a peptide or polypeptide comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least contiguous 80 amino acid residues, at least contiguous 90 amino acid residues, at least contiguous 100 amino acid residues, at least contiguous 125 amino acid residues, at least 150 contiguous amino acid residues, at least contiguous 175 amino acid residues, at least contiguous 200 amino acid residues, or at least contiguous 250 amino acid residues of the amino acid sequence of a protein. In a specific embodiment, the fragment is a functional fragment in that it retains at least one function of the protein from which it is isolated (*e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic cell killing)).

[0033] As used herein the terms "active bacteriophage products" and "bacteriophage products" refer to polypeptides, or fragments, variants or derivatives thereof, isolated from a bacteriophage of the invention, which polypeptide, or fragment, variant or derivative thereof, exhibits a biological function or activity associated with the bacteriophage from which it was isolated or derived (*e.g.*, antimicrobial or antibacterial activity (*e.g.*, lytic cell killing)).

5. An isolated lysin protein from bacteriophage F168/08, or a fragment_thereof having antibacterial or antimicrobial activity against *Enterococcus faecalis* or *Enterococcus faecium*.

6. The isolated lysin protein of claim 5, said protein having the amino acid sequence of SEQ ID NO:68 or a fragment_thereof, which fragment has antibacterial or antimicrobial activity against *Enterococcus faecalis* or *Enterococcus faecium*.

7. An isolated first protein having at least 85% sequence identity to a second protein of the same size, wherein said first protein has antibacterial or antimicrobial activity against *Enterococcus faecalis* or *Enterococcus faecium* and said second protein has the amino acid sequence of SEQ ID NO:68.

8. The isolated first protein of claim 7 having at least 95% sequence identity to said second protein.