



(51) International Patent Classification:

A61K 35/74 (2015.01) A61P 31/04 (2006.01)

A61K 35/76 (2015.01) C12N 1/20 (2006.01)

A61P 25/16 (2006.01) C12Q 1/689 (2018.01)

SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(21) International Application Number:

PCT/US2024/049907

(22) International Filing Date:

04 October 2024 (04.10.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/588,409 06 October 2023 (06.10.2023) US

63/619,365 10 January 2024 (10.01.2024) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE,

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

- with international search report (Art. 21(3))

(54) Title: COMPOSITIONS AND METHODS FOR ANALYZING THE EFFECT OF MICROBIOTA ON HOST PROTEIN CONFORMATION AND TREATING NEURODEGENERATIVE DISEASES

(57) Abstract: Described are compositions and methods comprising *Prevotellacorporis* for treating or preventing protein conformational diseases.



WO 2025/076308 A1

**Compositions and Methods for Analyzing the Effect of Microbiota on Host Protein
Conformation and Treating Neurodegenerative Diseases**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/588,409, filed October 6, 2023, and U.S. Provisional Application No. 63/619,365, filed January 10, 2024, each of which is incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under Grant No. AG070580 awarded by the National Institutes of Health. The government has certain rights in the invention.

[0003] This invention was created in part from funding received from the IDSA Foundation.

[0004] This invention was created in part while Dr. Daniel Czyz was a Glenn Foundation for Medical Research and AFAR Grant for Junior Faculty awardee.

BACKGROUND

[0005] Neurodegenerative protein conformational diseases (PCDs), such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis, are a leading cause of death and disability worldwide and have no known cures or effective treatments. Emerging evidence suggests a role for the gut microbiota in the pathogenesis of neurodegenerative PCDs; however, the influence of specific bacteria on the culprit proteins associated with each of these diseases remains elusive, primarily due to the complexity of the microbiota.

[0006] Neurodegenerative PCDs are characterized by disturbances in proteostasis that result in the aggregation of disease-associated proteins, ultimately leading to tissue death. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are among the most prevalent neurodegenerative diseases, with AD recognized by the World Health Organization (WHO) as one of the leading causes of death worldwide. However, despite their increasing prevalence, the etiology and potential therapeutic targets remain obscure. The sporadic onset and variable severity of neurodegenerative diseases, along with their idiopathic nature, suggest the possibility of a triggering factor for their onset and progression. Multiple factors have been associated with the pathogenicity of PCDs, including an expanding body of evidence that suggests the involvement of microbes, but primarily those within the human gut microbiota (HGM). The HGM is considered an "organ" due to its production of essential proteins and metabolites, including

vitamins, hormones, and neurotransmitters. Hence, dysbiosis of the gut microbiota has been linked to various ailments, including neurodegenerative diseases (Intili G et al. “From Dysbiosis to Neurodegenerative Diseases through Different Communication Pathways: An Overview.” *Biology* 2023, 12(2):195).

[0007] The complexity of the microbiome has made it challenging to determine the precise role of bacteria in the pathogenesis of neurodegenerative diseases. In addition, most of the evidence that associates bacteria with the occurrence of neurodegenerative diseases is based on correlation (Fang, P et al. “The Microbiome as a Modifier of Neurodegenerative Disease Risk.” *Cell Host Microbe* 2020, 28(2):201–222). Interestingly, correlational evidence does not demonstrate any selectivity between different neurodegenerative diseases, despite each disease featuring a unique, specific culprit protein species. For example, a lower abundance of *Prevotella* species has been observed in patients with different PCDs, including PD and ALS. Due to this lack of specificity, we hypothesized that bacteria could be affecting these diseases through the host proteostasis network—upstream of protein aggregate formation. This hypothesis is further supported by our previous study in which we identified gram-negative enteropathogens that significantly disrupt proteostasis across tissues in *C. elegans* (Walker AC et al. 2021). The utility of *C. elegans* as a model to study host-microbe interaction is strengthened by its unique ability to be colonized by a single bacterial strain. Such a feature simplifies the complexity of the microbiome, allowing us to study the effect of individual species on host proteostasis.

[0008] Here, we characterized the effect bacterial isolates on the aggregation of disease-associated proteins in *C. elegans*, using transgenic nematodes expressing A β ₁₋₄₂, α -synuclein, and polyglutamine (PolyQ), proteins that adopt amyloid conformation and are associated with AD, PD, and HD, respectively, in which their toxic aggregation culminates in neurodegeneration.

SUMMARY

[0009] Described are compositions for use in treating or preventing a protein conformational disease (PCD) in a subject. The compositions comprise: *Prevotella corporis*; a composition containing *Prevotella corporis*; a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof; a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or combinations thereof. In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient and/or one or

more additional active ingredients. The PCD can be, but is not limited to, a neurodegenerative disease. The neurodegenerative disease can be, but is not limited to, Alzheimer's disease, Parkinson's disease, or Huntington's disease, amyotrophic lateral sclerosis, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

[0010] A composition comprising *Prevotella corporis* can be provided as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, or a granular powder. A composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof, or a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject, can be provided as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, or a nutraceutical, or a supplement.

[0011] In some embodiments, the composition further comprises one or more additional active ingredients that decrease the abundance or inhibit the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject. In some embodiments, the one or more additional active ingredients comprises at least one bacteriophage. In some embodiments, the phage is a lytic phage specific for a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species.

[0012] Also described are compositions for use in treating a PCD in a subject, wherein the composition specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject and/or specifically decreases the abundance or inhibits the growth of a one or more of *Shigella* species in the gut of the subject. In some embodiments, the composition comprises at least one bacteriophage. The composition can be provided as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, a nutraceutical, or a supplement. In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient and/or one or more additional active ingredients. The one or more additional active ingredients can be, but is not limited to, *Prevotella corporis*, a composition containing *Prevotella corporis*, a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof, or a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject. The PCD can be, but is not limited to, a neurodegenerative disease. The

neurodegenerative disease can be, but is not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

[0013] Also described are compositions for use in treating a PCD in a subject, wherein the composition specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject. In some embodiments, the composition comprises at least one bacteriophage. The composition can be provided as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, a nutraceutical, or a supplement. In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient and/or one or more additional active ingredients. The one or more additional active ingredients can be, but is not limited to, a *Prevotella* species, a composition containing *Prevotella* species, a composition comprising a *Prevotella* species lysate or an extract or a fraction thereof, or a composition that increases abundance or supports growth of *Prevotella* species in the gut of the subject. The PCD can be, but is not limited to, a neurodegenerative disease. The neurodegenerative disease can be, but is not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

[0014] Also described are methods of treating a subject suffering from a PCD or at risk of developing a PCD, the methods comprising: administering to the subject one or more of:

- (a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition containing killed *Prevotella* species, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;
- (b) a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject; and
- (c) a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject.
- (d) a composition that specifically decreases the abundance or inhibits the growth of an *Achromobacter* species in the gut of the subject.

(e) a composition that specifically decreases the abundance or inhibits the growth of a *Ralstonia* species in the gut of the subject.

(f) a composition that specifically decreases the abundance or inhibits the growth of a *Klebsiella* species in the gut of the subject.

(g) a composition that specifically decreases the abundance or inhibits the growth of an *Arcobacter* species in the gut of the subject.

(h) a composition that specifically decreases the abundance or inhibits the growth of a *Citrobacter* species in the gut of the subject.

(i) a composition that specifically decreases the abundance or inhibits the growth of an *Escherichia* species in the gut of the subject.

[0015] In some embodiments, the methods for treating a subject suffering from a PCD or at risk of developing a PCD, comprise administering to the subject:

(a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition containing killed *Prevotella* species, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; and

(b) a composition that specifically decreases the abundance or inhibits the growth of one or more of: a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species in the gut of the subject.

[0016] In some embodiments, the *Prevotella* species is *Prevotella corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogencia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

[0017] In some embodiments, the *Pseudomonas* species is *Pseudomonas aeruginosa* or *Pseudomonas stutzeri*.

[0018] In some embodiments, the *Shigella* species is *Shigella flexneri*, *Shigella sonnei*, *Shigella dysenteriae*, or *Shigella boydii*.

[0019] In some embodiments, the *Achromobacter* species is *Achromobacter xylosoxidans*, *Achromobacter rubefaciens*, *Achromobacter insuavis*, *Achromobacter dolens*, or *Achromobacter spanius*.

[0020] In some embodiments, the *Ralstonia* species is *Ralstonia pickettii* or *Ralstonia mannitolilytica*.

[0021] In some embodiments, the *Klebsiella* species is *Klebsiella pneumoniae*, *Klebsiella oxytoca*, or *Klebsiella ozaenae*.

[0022] In some embodiments, the *Arcobacter* species is *Arcobacter butzleri*, *Arcobacter cryaerophilus*, or *Arcobacter skirrowii*.

[0023] In some embodiments, the *Citrobacter* species is *Citrobacter portucalensis*, *Citrobacter freundii*, *Citrobacter koseri*, or *Citrobacter braakii*.

[0024] In some embodiments, the *Escherichia* species is *Escherichia coli*.

[0025] In some embodiments, the subject is human. In some embodiments, the PCD comprises a neurodegenerative disease. The neurodegenerative disease can be, but is not limited to: Alzheimer's disease, Parkinson's disease, or Huntington's disease, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

[0026] In some embodiments, the methods further comprise: monitoring the abundance of one or more of the *Prevotella* species, *Pseudomonas* species, and the *Shigella* species in the gut of the subject and, (a) if the abundance of *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; and/or (b) if the abundance of the *Pseudomonas* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject; and/or (c) if the abundance of the *Shigella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject.

[0027] In some embodiments, the methods further comprise:

(a) analyzing a sample of a microbiota from a gut or a stool sample from the subject to determine an amount of one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample;

(b) comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample to a predetermined control; and

(i) if the amount of the *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;

(ii) if the amount of the *Pseudomonas* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject; and/or

(iii) if the amount of the *Shigella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject.

[0028] In some embodiments, the methods further comprise: monitoring the abundance of one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the gut of the subject and, (a) if the abundance of *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; and/or (b) if the abundance of the *Pseudomonas* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject; (c) if the abundance of the *Shigella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject; (d) if the abundance of the *Achromobacter* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Achromobacter* species in the gut of the subject; (e) if the abundance of the *Ralstonia* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Ralstonia* species in the gut of the subject; (f) if the abundance of the *Klebsiella* species in the gut of the subject is above a

predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Klebsiella* species in the gut of the subject; (g) if the abundance of the *Arcobacter* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Arcobacter* species in the gut of the subject; (h) if the abundance of the *Citrobacter* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Citrobacter* species in the gut of the subject; and/or (i) if the abundance of the *Escherichia* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Escherichia* species in the gut of the subject.

[0029] In some embodiments, the methods further comprise:

(a) analyzing a sample of a microbiota from a gut or a stool sample from the subject to determine an amount of one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the sample;

(b) comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the sample to a predetermined control; and

(i) if the amount of the *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;

(ii) if the amount of the *Pseudomonas* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject;

(iii) if the amount of the *Shigella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject.

(iv) if the amount of the *Achromobacter* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Achromobacter* species in the gut of the subject;

(v) if the amount of the *Ralstonia* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Ralstonia* species in the gut of the subject;

(vi) if the amount of the *Klebsiella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Klebsiella* species in the gut of the subject;

(vii) if the amount of the *Arcobacter* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Arcobacter* species in the gut of the subject;

(viii) if the amount of the *Citrobacter* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Citrobacter* species in the gut of the subject; and/or

(ix) if the amount of the *Escherichia* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Escherichia* species in the gut of the subject.

[0030] In some embodiments, the sample is a microbial sample or a fecal sample. Monitoring the abundance or analyzing the sample can comprise analyzing nucleic acid in the sample.

[0031] Treating PCD include, but is not limited to, reducing or ameliorating the severity of the disease, reducing or ameliorating the severity of one or more symptoms associated with the disease, slowing progression of the disease, slowing progression of one or more symptoms associated with the disease, reducing severity of the disease, reducing severity of one or more symptoms of the disease, delaying onset of the disease, delaying onset of one or more symptoms associated with the disease, preventing the disease, preventing one or more symptoms associated with the disease, reduce the duration of a symptom associated with a disease, regressing the disease, regressing one or more symptoms associated with the disease,

reducing recurrence of one or more symptom associated with the disease, or increasing or prolonging survival of a subject with a disease.

[0032] Described are methods of determining a risk of developing a PCD or one or more symptoms of a PCD comprising: (a) analyzing a sample of a microbiota from a gut or a stool sample of a subject to determine an amount of one or more of a *Prevotella* species, a *Pseudomonas* species, and a *Shigella* species in the sample; and (b) comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample to a predetermined control; wherein an amount of the *Prevotella* species in the sample lower than the predetermined control, and/or an amount of *Pseudomonas* species and/or the *Shigella* species in the sample that is higher than the predetermined control, indicates the subject is at increased risk of developing the PCD. In some embodiments, the PCD comprises a neurodegenerative disease. The neurodegenerative disease can be, but is not limited to, Alzheimer's disease, Parkinson's disease, or Huntington's disease, amyotrophic lateral sclerosis, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

[0033] Described are methods of determining a risk of developing a PCD or one or more symptoms of a PCD comprising: (a) analyzing a sample of a microbiota from a gut or a stool sample of a subject to determine an amount of one or more of a *Prevotella* species, a *Pseudomonas* species, and a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and a *Escherichia* species in the sample; and (b) comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the sample to a predetermined control; wherein an amount of the *Prevotella* species in the sample lower than the predetermined control, and/or an amount of *Pseudomonas* species, the *Shigella* species the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species in the sample that is higher than the predetermined control, indicates the subject is at increased risk of developing the PCD. In some embodiments, the PCD comprises a neurodegenerative disease. The neurodegenerative disease can be, but is not limited to, Alzheimer's disease, Parkinson's disease, or Huntington's disease, amyotrophic lateral sclerosis, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

[0034] Described are methods of treating or preventing a PCD in a subject, the methods comprising: administering to the subject one or more therapeutic treatments that target one or more identified bacteria that disrupt proteostasis. In some embodiments, the one or more therapeutic treatments comprise bacteriophages that specifically target the one or more identified bacteria that disrupt proteostasis. In some embodiments, the bacteria are a *Pseudomonas* species, a *Shigella* species, or a combination thereof. In some embodiments, the bacteria are a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, an *Escherichia* species, or a combination two or more thereof. The therapeutic can be, but is not limited to, a bacteriophage. In some embodiments, the one or more therapeutics comprises a bacteriophage that specifically targets the *Pseudomonas* species. In some embodiments, the one or more therapeutics comprises a bacteriophage that specifically targets the *Shigella* species. In some embodiments, the one or more therapeutics comprises a bacteriophage that specifically targets the *Pseudomonas* species and a bacteriophage that specifically targets the *Shigella* species. In some embodiments, the PCD is a neurodegenerative disease. The PCD can be, but is not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, or a prion disease.

[0035] Described are methods of decreasing protein misfolding in a subject, the methods comprising administering to the subject one or more of:

(a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprising lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;

(b) a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject; and

(c) a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject.

In some embodiments, the method comprises (a) and (b). In some embodiments, the method comprises (a) and (c). In some embodiments, the methods comprise (a), (b) and (c). In some embodiments, the composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species comprises a bacteriophage. In some embodiments, the composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species comprises a bacteriophage.

[0036] Described are methods for increasing expression of HSP and/or activation of a heat shock response in a subject comprising: administering to the subject *Prevotella corporis*; a composition containing *Prevotella corporis*; a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof; a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or combinations thereof.

[0037] Described are methods for increasing expression of mucin-associated membrane proteins MUC3 and/or MUC4 in a subject comprising: administering to the subject *Prevotella corporis*; a composition containing *Prevotella corporis*; a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof; a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or combinations thereof.

[0038] Described are methods for inhibiting proteotoxicity caused by a bacterial species in a subject, comprising administering to the subject *Prevotella corporis*; a composition containing *Prevotella corporis*; a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof; a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] FIG. 1. Schematic illustrating the method used to assess the effect of bacterial isolates on *C. elegans* proteostasis.

[0040] FIG. 2. Heat map showing the extent of the screen that identified the effect of human bacterial isolates on *C. elegans* intestinal polyQ aggregation using a biophysical method (fluorescent aggregate count) and a biochemical method (Western blotting). Aggregation data are normalized to worms fed control *E. coli* OP50.

[0041] FIG. 3. The effect of *Prevotella* species on proteins associated with neurodegenerative diseases. A) The effect of *Prevotella* species on *C. elegans* intestinal polyQ aggregation (“Aggregates”) and the associated toxicity (“Motility”). Checkered bars represent bacteria-associated developmental delay. The three strongest suppressors of polyQ aggregation that did not affect development were tested using intestinal polyQ, B) neuronal polyQ, C) muscle polyQ, D) muscle A β 1-42, and E) muscle α -synuclein. Data are represented as the average number of aggregates or TOP (seconds) per worm obtained from at least two independent experiments for a total of 30-60 worms. Error bars represent standard error of the mean (SEM). Statistical significance was calculated using one-way ANOVA followed by

multiple comparison Dunnett's post-hoc test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

[0042] FIG. 4. Graphs illustrating the effect of proteotoxic bacteria on proteins associated with neurodegenerative diseases. A) The effect of gram-negative, aerobic bacteria on *C. elegans* intestinal polyQ aggregation ("Aggregates") and the associated toxicity ("Motility"). Three robust enhancers of polyQ aggregation were tested using intestinal polyQ, B) neuronal polyQ, C) muscle polyQ, D) muscle A β_{1-42} , and E) muscle α -synuclein. Data are represented as the average number of aggregates or TOP (seconds) per worm obtained from at least two independent experiments for a total of 30-60 worms. Error bars represent SEM. Statistical significance was calculated using one-way ANOVA followed by multiple comparison Dunnett's post-hoc test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

[0043] FIG. 5. Image (panel A) illustrating aggregation of A β_{1-42} in worms fed various bacteria and graphs (panel B) illustrating time-off-pick (TOP) in control worms or worms expressing muscle A β_{1-42} .

[0044] FIG. 6. Graphs illustrating age dependence of aggregation of muscle A β_{1-42} (panel A) and α -synuclein (panel B). Data are represented as the average TOP (seconds) per worm. Each data point represents two independent experiments for a total of 20 worms. Error bars represent SEM. Statistical significance was calculated using one-way analysis of variants (ANOVA) followed by multiple comparison Dunnett's post-hoc test (*** $p < 0.001$, **** $p < 0.0001$).

[0045] FIG. 7. Graph illustrating effect of *P. corporis* on motility in worms expressing an endogenous temperature-sensitive mutation that leads to protein misfolding in muscle or neuronal tissue at the restrictive temperature of 25 °C. Wild-type (WT) indicates the N2 control worms. Data are represented as the average TOP (seconds) per worm. Each data point represents three independent experiments for a total of 30 worms. Error bars represent SEM. Statistical significance was calculated using Student's t-test (*** $p < 0.001$, **** $p < 0.0001$).

[0046] FIG. 8. Graph illustrating effect of various enteric bacteria on host proteostasis assessed by polyQ aggregation in the *C. elegans* intestine.

[0047] FIG. 9. Workflow for identification of bacterial proteins that affect host proteostasis.

[0048] FIG. 10. Graphs and images illustrating the effect of *P. corporis* on bacteria-induced polyQ aggregation and activation of the heat-shock response. The effect of co-colonizing intestinal polyQ44 worms with (A) *K. pneumoniae* HM-751 and *P. corporis* HM-1294, (B) *E. coli* OP50 and *P. corporis* HM-12924, and (C) *K. pneumoniae* HM-751 and *E. coli* OP50. Data are represented as the average number of aggregates per intestinal polyQ44 worm obtained

from three independent experiments for a total of 60 worms. Statistical significance was calculated using one-way analysis of variants (ANOVA) followed by multiple comparison Dunnett's post-hoc test (**** $p < 0.0001$). (D) Nomarski and fluorescent (EGFP) images of transgenic worms expressing transcriptional fusion reporter *hsp70p::GFP*, fed *E. coli* OP50, *P. corporis* HM-1294, *K. pneumoniae* HM-751, and as a positive control, heat-shocked worms fed *E. coli* OP50. Scale bar is 200 μm .

[0049] FIG. 11. Graph illustrating the effect of *P. corporis* on pharyngeal pumping. Data are represented as the average number of pharyngeal pumps per 30 seconds for a total of ten data points per worm (N2) and three independent experiments for a total of 20 worms per condition. Mean pumping rates of worms fed *P. corporis* HM-1294 (101.22 pumps/30 sec $\pm$ SEM 1.28) are not significantly different from those fed *E. coli* OP50 control (89.97 $\pm$ 1.68 SEM) as determined by t-test ($p > 0.9999$); distribution of pumping rates of worms fed *P. corporis* HM-1294 are not significantly different from those fed *E. coli* OP50 control as determined by Kolmogorov-Smirnov test ($p = 0.9639$).

[0050] FIG. 12. Graph illustrating the effect of PFA-killed *P. corporis* on intestinal polyQ aggregation. Data are represented as the average number of aggregates per intestinal polyQ44 worm. Each bar represents two independent experiments for a total of 60 worms. Error bars represent SEM. Statistical significance was calculated using Student's t-test (**** $p < 0.0001$).

[0051] FIG. 13. Graph illustrating colonization of proteotoxic bacteria in the *C. elegans* intestine. Data are represented as the average bacterial load per N2 worm [Log(CFU/worm)]. Each bar represents three independent experiments for a total of 30 worms. Error bars represent SEM.

[0052] FIG. 14. Graph illustrating the effect of bacterial supernatants on intestinal polyQ aggregation in *C. elegans*. Data are represented as the average number of aggregates per intestinal polyQ44 worm. Each bar represents three independent experiments for a total of 98 worms. Error bars represent SEM. Statistical significance was calculated using one-way analysis of variants (ANOVA) followed by Dunnett's post-hoc test (** $p < 0.01$, *** $p < 0.001$).

DETAILED DESCRIPTION

[0053] The scope of the present invention is defined by the claims appended hereto and is not limited by certain embodiments described herein. Those skilled in the art, reading the present specification, will be aware of various modifications that may be equivalent to such described embodiments, or otherwise within the scope of the claims. In general, terms used herein are in accordance with their understood meaning in the art, unless clearly indicated

otherwise. Explicit definitions of certain terms are provided below; meanings of these and other terms in particular instances throughout this specification will be clear to those skilled in the art from context. Additional definitions for the following and other terms are set forth throughout the specification. Patent and non-patent literature references cited within this specification, or relevant portions thereof, are incorporated herein by reference in their entireties.

[0054] The singular forms of the articles “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “an element” or “at least one element” can include a plurality of elements, including mixtures thereof.

[0055] The term “and/or” refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative (“or”).

[0056] The term “or” refers to any one member of a particular list.

[0057] Designation of a range of values includes all integers within or defining the range, and all subranges defined by integers within the range.

[0058] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur and that the description includes instances in which the event or circumstance occurs and instances in which the event or circumstance does not.

[0059] As used herein, the terms “about” and “approximately,” when used to modify an amount specified in a numeric value or range, indicates the numeric value as well as reasonable deviations from the value known to the skilled person in the art. In some embodiments, the term “about” means within the typical ranges of tolerances in the art. In some embodiments, the term “about” means within 1 or 2 standard deviations from the mean. In some embodiments, the term “about” means $\pm 10\%$. In some embodiments, the term “about” means $\pm 5\%$. When the term “about” is present before a series of numbers or a range, it is understood that “about” can modify each of the numbers in the series or range.

[0060] The term “subject,” “individual,” and “patient,” as used interchangeably herein, refer to a mammal, including but not limited to humans, non-human primates, rodents (e.g., rats, mice, and guinea pigs), rabbits, cows, pigs, horses, and other mammalian species. In some embodiments, the subject is a human.

[0061] A “protein conformational disease” (PCD) (also termed proteinopathy) is a disease where one or more cellular functions are compromised because of misfolded proteins or non-native protein conformations. Disease can be caused by loss of function of the protein and/or

aggregation or accumulation of misfolded proteins. PCD can be genetic, age-related, or infectious (*e.g.*, prion diseases). For some proteins, the misfolded conformation is able to interact with other copies of the same protein and induce their transition into the misfolded state. Inherited genetic defects that result in the misfolding of proteins may lead to recessive disorders if the proteins in question are totally or partly eliminated or to dominant diseases if the misfolded proteins accumulate in the cell. Misfolding may also occur in proteins with an intrinsic ability to aggregate and in oxidatively damaged proteins, which accumulate by aging. Misfolding of proteins is a contributing factor in the development of late onset neurodegenerative disorders.

[0062] “Proteotoxicity” refers to the adverse effects of damaged or misfolded proteins on a cell. Proteotoxicity also refers to the process by which a protein or proteins misfold and exert a toxic effect on cells or cellular metabolism.

[0063] The terms “treat,” “treatment,” and the like, mean the methods or steps taken to provide relief from, or amelioration or alleviation of the number, severity, adverse effect, and/or frequency of one or more symptoms or pathological consequences of a disease, disorder, or condition in a subject. Treatment can be prophylactic in terms of preventing or partially preventing a disease, or a symptom or condition of the disease. Preventing includes providing prophylaxis with respect to the occurrence or recurrence of a disease in a subject that may be predisposed to the disease but has not yet been diagnosed with the disease. Preventing also includes providing prophylaxis with respect to the occurrence or recurrence of a symptom or pathological consequence of a disease in a subject that may be predisposed symptom or pathological consequence of the disease but has not yet been diagnosed with the symptom or pathological consequence the disease. Treatment can also be prophylactic in terms of delaying onset of a disease, or a symptom or condition of the disease. Delaying development of a disease or symptom or pathological consequence of the disease indicates deferring, hindering, slowing, retarding, stabilizing, suppressing, and/or postponing development of the disease or symptom or pathological consequence of the disease. The delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. Treating can include inhibiting the disease, disorder, or condition, *e.g.*, impeding its progress; and relieving the disease, disorder, or condition, *e.g.*, causing regression of the disease, disorder and/or condition. Treatment can also mean prolonging survival as compared to expected survival in the absence of treatment. Treatment can be therapeutic in terms of a partial or complete cure of a disease, condition, symptom, or adverse effect attributed to the disease, disorder, or

condition. The term treatment can include: (a) preventing the disease from occurring in a subject who may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, *i.e.*, arresting its development; and (c) relieving the disease, *i.e.*, mitigating or ameliorating the disease and/or its symptoms or conditions. Treating can refer to both therapeutic treatment alone, prophylactic treatment alone, or both therapeutic and prophylactic treatment. Those in need of treatment (subjects in need thereof) can include those previously diagnosed with a disease, disorder, or condition, or those identified as being at risk of developing a disease, disorder, or condition. Treating the disease, disorder, or condition can include ameliorating at least one symptom of the particular disease, disorder, or condition, even if the underlying pathophysiology is not affected.

[0064] The term “pharmaceutically acceptable excipient” refers to a non-active pharmaceutical ingredient that is biologically or pharmacologically compatible for use in humans or animals, such as but not limited to a buffer, carrier, or preservative.

[0065] An “effective amount” of an agent, e.g., a dual transporter or a pharmaceutical formulation containing a dual transporter, in the context of administration, refers to an amount effective, at dosages/amounts and for periods of time necessary, to achieve a desired result, such as a therapeutic or prophylactic result.

[0066] A “therapeutically effective amount” of an agent, e.g., a dual transporter or a pharmaceutical formulation containing a dual transporter, refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result, such as for treatment of a disease, condition, or disorder, and/or pharmacokinetic or pharmacodynamic effect of the treatment. The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the subject, and the populations of cells administered.

[0067] A “prophylactically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. A prophylactically effective amount may be less than the therapeutically effective amount of the same drug.

[0068] A “dose,” “unit dose,” or “dosage” refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of active pharmaceutical ingredient and/or a pharmaceutical composition.

[0069] The term “administer” refers to a method of delivering agents, compounds, or compositions to the desired site of biological action. These methods include, but are not limited to, oral delivery, topical delivery, parenteral delivery, intravenous delivery, intradermal

delivery, intramuscular delivery, intrathecal delivery, colonic delivery, rectal delivery, or intraperitoneal delivery. In one embodiment, the compositions described herein are administered intravenously. A molecule that is “administered peripherally” means that the molecule is not administered directly to CNS (e.g., not administered intrathecally or directly into the brain, such as intracerebroventricularly). Thousands of bacterial species colonize the human body. Genetic analyses have identified 1473 genomes in the human mouth and 2182 genomes in the human gut. Bacterial species have also been identified on skin, vagina, and other body parts. In addition, the human microbiota is affected by lifestyle, diet, drugs, and aging.

[0070] A pharmaceutically acceptable excipient (excipient) is a substance other than an active pharmaceutical ingredient (API, therapeutic product) that is intentionally included with the API. Excipients do not exert or are not intended to exert a therapeutic effect at the intended dosage. Excipients may act to a) aid in processing of the API during manufacture, b) protect, support, or enhance stability, bioavailability or subject acceptability of the API, c) assist in product identification, and/or d) enhance any other attribute of the overall safety, effectiveness, of delivery of the API during storage or use. A pharmaceutically acceptable excipient may or may not be an inert substance. Excipients include, but are not limited to: absorption enhancers, anti-adherents, anti-foaming agents, anti-oxidants, binders, buffering agents, carriers, coating agents, colors, delivery enhancers, delivery polymers, dextran, dextrose, diluents, disintegrants, emulsifiers, extenders, fillers, flavors, glidants, humectants, lubricants, oils, polymers, preservatives, saline, salts, solvents, sugars, suspending agents, sustained release matrices, sweeteners, thickening agents, tonicity agents, vehicles, water-repelling agents, and wetting agents

[0071] Described are compositions and methods of using the compositions to treat PCDs in a host. The compositions include formulations that increase beneficial bacteria (bacteria that enhance proteostasis in the host) in the gut, formulations comprising a component of a bacterial species that enhances proteostasis, and/or formulations that decrease detrimental bacteria (bacteria that disrupt or decrease proteostasis in the host) in the gut.

[0072] Described are methods of decreasing protein misfolding in a subject, the methods comprising administering to the subject one or more compositions that specifically increase the abundance or growth, in the gut of the subject, of one or more bacterial species that enhances proteostasis in the subject; one of more compositions comprising a component of a bacterial species that enhances proteostasis in the subject, and/or one or more compositions that

specifically decrease the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject.

[0073] In some embodiments, the bacterial species that enhances proteostasis in the subject is a *Prevotella* species. Compositions that increase the abundance of a *Prevotella* sp. in the gut include but are not limited to, isolated *Prevotella* sp. bacteria, a composition comprising the isolated *Prevotella* sp. bacteria, or a composition that increases or supports growth of the *Prevotella* species in the gut of the subject. Compositions comprising a component of a bacterial species that enhances proteostasis in the subject include, but are not limited to, a purified *Prevotella* sp. protein, killed *Prevotella* sp. bacteria, a *Prevotella* sp. lysate or a fraction thereof, or a *Prevotella* sp. extract or fraction thereof. In some embodiments, the *Prevotella* sp. is *Prevotella corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogencia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

[0074] In some embodiments, the bacterial species that disrupts proteostasis in the subject is a *Pseudomonas* species and/or a *Shigella* species. In some embodiments, a composition that decreases the abundance of a *Pseudomonas* species and/or a *Shigella* species comprises a bacteriophage. In some embodiments, the composition that decreases the abundance of the *Pseudomonas* species comprises a bacteriophage that specifically targets (infects) the *Pseudomonas* species. In some embodiments, the *Pseudomonas* species is *Pseudomonas aeruginosa*. In some embodiments, the composition that decreases the abundance of the *Shigella* species comprises a bacteriophage that specifically targets (infects) the *Shigella* species.

[0075] In some embodiments, the bacterial species that disrupts proteostasis in the subject is a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species. In some embodiments, a composition that decreases the abundance of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, or the *Escherichia* species comprises a bacteriophage. In some embodiments, the composition that decreases the abundance of the *Pseudomonas* species comprises a bacteriophage that specifically targets (infects) the *Pseudomonas* species. In some embodiments, the composition that decreases the abundance of the *Shigella* species comprises a bacteriophage that specifically targets (infects) the *Shigella*

species. In some embodiments, the composition that decreases the abundance of the *Achromobacter* species comprises a bacteriophage that specifically targets (infects) the *Achromobacter* species. In some embodiments, the composition that decreases the abundance of the *Ralstonia* species comprises a bacteriophage that specifically targets (infects) the *Ralstonia* species. In some embodiments, the composition that decreases the abundance of the *Klebsiella* species comprises a bacteriophage that specifically targets (infects) the *Klebsiella* species. In some embodiments, the composition that decreases the abundance of the *Arcobacter* species comprises a bacteriophage that specifically targets (infects) the *Arcobacter* species. In some embodiments, the composition that decreases the abundance of the *Citrobacter* species comprises a bacteriophage that specifically targets (infects) the *Citrobacter* species. In some embodiments, the composition that decreases the abundance of the *Escherichia* species comprises a bacteriophage that specifically targets (infects) the *Escherichia* species.

[0076] In some embodiments, the methods comprise administering to the subject (a) one or more compositions that specifically increases the abundance or growth, in the gut of the subject, of one or more bacterial species that enhances proteostasis in the subject or one of more compositions comprising a component of a bacterial species that enhances proteostasis in the subject, and (b) one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject. In some embodiments, the bacterial species that enhances proteostasis in the subject is a *Prevotella* species. In some embodiments, the *Prevotella* species is *P. corporis*. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises a bacteriophage that specifically targets a *Pseudomonas* species. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises a bacteriophage that specifically targets a *Shigella* species. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises a bacteriophage that specifically targets a *Pseudomonas* species and bacteriophage that specifically targets a *Shigella* species.

[0077] In some embodiments, the methods comprise administering to the subject (a) one or more compositions that specifically increases the abundance or growth, in the gut of the subject, of one or more bacterial species that enhances proteostasis in the subject or one of

more compositions comprising a component of a bacterial species that enhances proteostasis in the subject, and (b) one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject. In some embodiments, the bacterial species that enhances proteostasis in the subject is a *Prevotella* species. In some embodiments, the *Prevotella* species is *P. corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogenia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises a bacteriophage that specifically targets a *Pseudomonas* species. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises one or more bacteriophages that specifically target one or more of a *Shigella* species, a *Pseudomonas* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, an *Escherichia* or combination of two or more thereof.

[0078] Specifically increases the abundance or supports growth of a bacterial species in the gut of a subject indicates the composition increases the abundance or growth of the target bacterial species in the gut of the subject without substantially increasing the abundance or growth of bacteria of a different genus or species in the gut of the subject. In some embodiments, a composition that specifically increases the abundance or growth of a *Prevotella* species in the gut of a subject increases abundance or supports growth of the *Prevotella corporis* relative to other species in the gut, particularly a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species.

[0079] Specifically decreases the abundance or growth of a bacterial species in the gut of a subject indicates the composition decreases the abundance or growth of the target bacterial species in the gut of the subject without substantially decreasing the abundance or growth of bacteria of a different genus or species in the gut of the subject.

[0080] Enhances proteostasis indicates the level or rate of protein misfolding in the subject is less when the bacterial species that enhances proteostasis is present in the gut of the subject,

or present in the gut above a predetermined amount, relative to the level or rate of protein misfolding in the subject is the absence of the bacteria species in the gut or when the abundance of the bacteria species is below a predetermined amount in the gut. Enhances proteostasis indicates ability of a cell to buffer misfolded proteins.

[0081] In some embodiments, enhancing proteostasis comprises increasing expression of heat shock protein (HSP) and/or activation of a heat shock response in a subject. Increasing expression of heat shock protein (HSP) and/or activation of a heat shock response in a subject can comprise administering to the subject: *Prevotella corporis*; a composition containing *Prevotella corporis*; a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof; a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or combinations thereof.

[0082] In some embodiments, enhancing proteostasis comprises increasing expression of mucin-associated membrane proteins MUC3 and/or MUC4 in a subject. Increasing expression of MUC3 and/or MUC4 in a subject can comprise administering to the subject: *Prevotella corporis*; a composition containing *Prevotella corporis*; a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof; a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or combinations thereof.

[0083] Disrupts proteostasis indicates the level or rate of protein misfolding in the subject is greater when the bacterial species that disrupts proteostasis is present in the gut of the subject, or present in the gut above a predetermined amount, relative to the level or rate of protein misfolding in the subject is the absence of the bacteria species in the gut or when the abundance of the bacteria species is below a predetermined amount in the gut.

[0084] Described are methods for treating PCD, the methods comprising administering to the subject one or more compositions that specifically increases the abundance or growth, in the gut of the subject, of one or more bacterial species that enhances proteostasis in the subject; one or more compositions comprising a component of a bacterial species that enhances proteostasis in the subject, and/or one or more compositions that specifically decrease the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject.

[0085] In some embodiments, the bacterial species that enhances proteostasis in the subject is a *Prevotella* species. Compositions that increase the abundance of a *Prevotella* sp. in the gut include but are not limited to, isolated *Prevotella* sp. bacteria, a composition comprising the

isolated *Prevotella* sp. bacteria, or a composition that specifically increases or supports growth of the *Prevotella* species in the gut of the subject. Compositions comprising a component of a bacterial species that enhances proteostasis in the subject include, but are not limited to, killed *Prevotella* sp. bacteria, a composition comprising killed *Prevotella* sp. bacteria, a purified *Prevotella* sp. protein, a *Prevotella* sp. lysate or a fraction thereof, or a *Prevotella* sp. extract or fraction thereof. In some embodiments, the *Prevotella* sp. is *Prevotella corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogencia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

[0086] In some embodiments, the bacterial species that disrupts proteostasis in the subject is a *Pseudomonas* species and/or a *Shigella* species. In some embodiments, a composition that decreases the abundance of a *Pseudomonas* species and/or a *Shigella* species comprises a bacteriophage. In some embodiments, a composition that decreases the abundance of a *Pseudomonas* species and/or a *Shigella* species comprises a lytic bacteriophage. In some embodiments, the composition that decreases the abundance of the *Pseudomonas* species comprises a bacteriophage that specifically targets (infects) the *Pseudomonas* species. In some embodiments, the *Pseudomonas* species is *Pseudomonas aeruginosa*. In some embodiments, the composition that decreases the abundance of the *Shigella* species comprises a bacteriophage that specifically targets (infects) the *Shigella* species.

[0087] In some embodiments, the bacterial species that disrupts proteostasis in the subject is an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species. In some embodiments, a composition that decreases the abundance of the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species comprises a one or more bacteriophages that specifically target (infect) the *Achromobacter*, *Ralstonia*, *Klebsiella*, *Arcobacter*, *Citrobacter*, and/or the *Escherichia* bacterial species. In some embodiments, a composition that decreases the abundance of the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species comprises a one or more lytic bacteriophages that specifically target (infect) the *Achromobacter*, *Ralstonia*, *Klebsiella*, *Arcobacter*, *Citrobacter*, and/or the *Escherichia* bacterial species.

[0088] In some embodiments, the methods for treating a PCD comprise administering to the subject one or more compositions that specifically increases the abundance or growth, in the gut of the subject, of one or more bacterial species that enhances proteostasis in the subject or one of more compositions comprising a component of a bacterial species that enhances proteostasis in the subject. In some embodiments, the bacterial species that enhances proteostasis in the subject is a *Prevotella* species. In some embodiments, the *Prevotella* species is *Prevotella corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogenia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

[0089] In some embodiments, the methods for treating a PCD comprise administering to the subject one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject. In some embodiments, the bacterial species that disrupts proteostasis in the subject is a *Pseudomonas* species and/or a *Shigella* species. In some embodiments, a composition that decreases the abundance of a *Pseudomonas* species and/or a *Shigella* species comprises a bacteriophage (e.g., a lytic bacteriophage). In some embodiments, the composition that decreases the abundance of the *Pseudomonas* species comprises a bacteriophage that specifically targets (infects) the *Pseudomonas* species. In some embodiments, the *Pseudomonas* species is *Pseudomonas aeruginosa*. In some embodiments, the composition that decreases the abundance of the *Shigella* species comprises a bacteriophage that specifically targets (infects) the *Shigella* species.

[0090] In some embodiments, the methods for treating a PCD comprise administering to the subject one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject. In some embodiments, the bacterial species that disrupts proteostasis in the subject is a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species. In some embodiments, a composition that decreases the abundance of the bacterial species that disrupts or decreases proteostasis in the subject comprises one or more bacteriophage (e.g., a lytic bacteriophage) that infects one or more of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, or the *Escherichia* species.

[0091] In some embodiments, the methods for treating a PCD comprise administering to the subject one or more compositions that inhibits the proteotoxicity of one or more bacterial species that disrupts or decreases proteostasis in the subject. In some embodiments, the bacterial species that disrupts proteostasis in the subject is a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species. In some embodiments, a composition that inhibits the proteotoxicity caused by a bacterial species (e.g., a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species) comprises a composition comprising *Prevotella corporis*; a composition containing *Prevotella corporis*; a composition comprising killed *Prevotella corporis* or a *Prevotella corporis* lysate or an extract or a fraction thereof; a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or combinations thereof.

[0092] In some embodiments, the methods for treating a PCD comprise administering to the subject (a) one or more compositions that specifically increases the abundance or growth, in the gut of the subject, of one or more bacterial species that enhances proteostasis in the subject or one of more compositions comprising a component of a bacterial species that enhances proteostasis in the subject, and (b) one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject. In some embodiments, the bacterial species that enhances proteostasis in the subject is a *Prevotella* species. In some embodiments, the *Prevotella* species is *P. corporis*. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises a bacteriophage that specifically targets a *Pseudomonas* species. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises a bacteriophage that specifically targets a *Shigella* species. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises a bacteriophage that specifically targets a *Pseudomonas* species and bacteriophage that specifically targets a *Shigella* species.

[0093] In some embodiments, the methods for treating a PCD comprise administering to the subject (a) one or more compositions that specifically increases the abundance or growth, in the gut of the subject, of one or more bacterial species that enhances proteostasis in the subject or one of more compositions comprising a component of a bacterial species that enhances proteostasis in the subject, and (b) one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject. In some embodiments, the bacterial species that enhances proteostasis in the subject is a *Prevotella* species. In some embodiments, the *Prevotella* species is *P. corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogencia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*. In some embodiments, the one or more compositions that specifically decreases the abundance or growth, in the gut of the subject, of one or more bacterial species that disrupts or decreases proteostasis in the subject comprises one or more bacteriophages that specifically target one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species.

[0094] In some embodiments, methods for increasing expression of HSP in a subject are described, the methods comprising administering to the subject one or more compositions that specifically increase the abundance or growth of a *Prevotella* species in the gut of the subject. Compositions that increase the abundance of *Prevotella* sp. in the gut include but are not limited to, isolated *Prevotella* sp. bacteria, a composition comprising the isolated *Prevotella* sp. bacteria, or a composition that specifically increases or supports growth of the *Prevotella* species in the gut of the subject. In some embodiments, methods for increasing expression of HSP in a subject are described, the methods comprising: administering to the subject killed *Prevotella* sp. bacteria, a composition comprising killed *Prevotella* sp. bacteria, a purified *Prevotella* sp. protein, a *Prevotella* sp. lysate or a fraction thereof, or a *Prevotella* sp. extract or fraction thereof, or combinations thereof. In some embodiments, the *Prevotella* species is *Prevotella corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogencia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

[0095] In some embodiments, methods for increasing expression of MUC3 and/or MUC4 in a subject are described, the methods comprising: administering to the subject one or more compositions that specifically increases the abundance or growth of a *Prevotella* species in the gut of the subject. Compositions that increase the abundance of a *Prevotella* sp. in the gut include but are not limited to, isolated *Prevotella* sp. bacteria, a composition comprising the isolated *Prevotella* sp. bacteria, or a composition that specifically increases or supports growth of the *Prevotella* species in the gut of the subject. In some embodiments, methods for increasing expression of MUC3 and/or MUC4 in a subject are described, the methods comprising: administering to the subject killed *Prevotella* sp. bacteria, a composition comprising killed *Prevotella* sp. bacteria, a purified *Prevotella* sp. protein, a *Prevotella* sp. lysate or a fraction thereof, or a *Prevotella* sp. extract or fraction thereof, or combinations thereof. In some embodiments, the *Prevotella* species is *Prevotella corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogenia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

[0096] In some embodiments, methods for activating or inducing a heat shock response in a subject are described, the methods comprising: administering to the subject one or more compositions that specifically increases the abundance or growth of a *Prevotella* species in the gut of the subject. Compositions that increase the abundance of a *Prevotella* sp. in the gut include but are not limited to, isolated *Prevotella* sp. bacteria, a composition comprising the isolated *Prevotella* sp. bacteria, or a composition that specifically increases or supports growth of the *Prevotella* species in the gut of the subject. In some embodiments, methods for activating a heat shock response in a subject are described, the methods comprising: administering to the subject killed *Prevotella* sp. bacteria, a composition comprising killed *Prevotella* sp. bacteria, a purified *Prevotella* sp. protein, a *Prevotella* sp. lysate or a fraction thereof, or a *Prevotella* sp. extract or fraction thereof, or combinations thereof. In some embodiments, the *Prevotella* species is *Prevotella corporis*. In some embodiments, the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogenia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

[0097] Described are compositions use in treating a PCD in a subject, the composition comprising: (a) isolated *Prevotella* species bacteria; (b) a composition containing *Prevotella* species bacteria; (c) a composition comprising killed *Prevotella* species bacteria; (d) a

composition comprising a *Prevotella* species lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella* species in the gut of the subject; or (f) combinations of two or more of (a)-(e). In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient.

[0098] Described are compositions use in treating a PCD in a subject, the composition comprising: (a) isolated *Prevotella corporis* bacteria; (b) a composition containing *Prevotella corporis* bacteria; (c) a composition comprising killed *Prevotella corporis* bacteria; (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or (f) combinations of two or more of (a)-(e). In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient.

[0099] Described are compositions use in increasing expression of HSP in a subject, the composition comprising: (a) isolated *Prevotella corporis* bacteria; (b) a composition containing *Prevotella corporis* bacteria; (c) a composition comprising killed *Prevotella corporis* bacteria; (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or (f) combinations of two or more of (a)-(e). In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient.

[0100] Described are compositions use in increasing expression of MUC3 and/or MUC4 in a subject, the composition comprising: (a) isolated *Prevotella corporis* bacteria; (b) a composition containing *Prevotella corporis* bacteria; (c) a composition comprising killed *Prevotella corporis* bacteria; (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or (f) combinations of two or more of (a)-(e). In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient.

[0101] Described are compositions use in activating or inducing a heat shock response in a subject, the compositions comprising: (a) isolated *Prevotella corporis* bacteria; (b) a composition containing *Prevotella corporis* bacteria; (c) a composition comprising killed *Prevotella corporis* bacteria; (d) a composition comprising a *Prevotella corporis* lysate or an

extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or (f) combinations of two or more of (a)-(e). In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient.

[0102] In some embodiments, the isolated *Prevotella* species bacteria or the composition containing *Prevotella* species bacteria can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, or a granular powder. The isolated *Prevotella* species bacteria can be cultured bacteria. The *Prevotella* species can be genetically modified.

[0103] In some embodiments, the isolated *Prevotella corporis* bacteria or the composition containing *Prevotella corporis* bacteria can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, or a granular powder. The isolated *Prevotella corporis* bacteria can be cultured bacteria. The *Prevotella corporis* can be genetically modified.

[0104] In some embodiments, the composition comprising killed *Prevotella* species bacteria or the composition containing *Prevotella* species bacteria can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, or a granular powder. The *Prevotella* species can be genetically modified.

[0105] In some embodiments, the isolated *Prevotella corporis* bacteria or the composition containing *Prevotella corporis* bacteria can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, or a granular powder. The *Prevotella corporis* can be genetically modified.

[0106] In some embodiments, the composition comprising the *Prevotella* species lysate or an extract or a fraction thereof, or the composition that increases abundance or supports growth of *Prevotella* species in the gut of the subject, can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, or a nutraceutical, or a supplement. The *Prevotella* species can be genetically modified.

[0107] In some embodiments, the composition comprising the *Prevotella corporis* lysate or an extract or a fraction thereof, or the composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject, can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, or a nutraceutical, or a supplement. The *Prevotella corporis* can be genetically modified.

[0108] In some embodiments, the composition comprises one or more additional active ingredients. The one or more additional active ingredients can comprise an agent or composition that decreases the abundance or inhibits the growth of a *Pseudomonas* species and/or a *Shigella* species in the gut of the subject. In some embodiments, the agent or composition comprises a bacteriophage.

[0109] In some embodiments, the composition comprises one or more additional active ingredients. The one or more additional active ingredients can comprise an agent or composition that decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject. In some embodiments, the agent or composition comprises a bacteriophage.

[0110] Described are compositions for use in treating a PCD in a subject, the compositions comprising: a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject and/or a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject. In some embodiments, the compositions comprise a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject and a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject. In some embodiments, the composition comprises at least one bacteriophage. In some embodiments, the composition comprises a bacteriophage that specifically targets the *Pseudomonas* species. In some embodiments, the composition comprises a bacteriophage that specifically targets the *Shigella* species. In some embodiments, the composition comprises a bacteriophage that specifically targets the *Pseudomonas* species and a bacteriophage that specifically targets the *Shigella* species. In some embodiments, the *Pseudomonas* species is *Pseudomonas aeruginosa*. The composition can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, or a nutraceutical, or a supplement. In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition further comprises one or more additional active ingredients. The one or more additional active ingredients can be, but is not limited to: *Prevotella corporis*, a composition containing *Prevotella corporis*, a

composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof, or a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject.

[0111] Described are compositions for use in treating a PCD in a subject, the compositions comprising: a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject. In some embodiments, the composition comprises at least one bacteriophage. In some embodiments, the composition comprises one or more bacteriophage that specifically target one or more of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species. The composition can be provided or formulated as a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, or a nutraceutical, or a supplement. In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition further comprises one or more additional active ingredients. The one or more additional active ingredients can be, but is not limited to: a *Prevotella* species, a composition containing *Prevotella* species, a composition comprising a *Prevotella* species lysate or an extract or a fraction thereof, or a composition that increases abundance or supports growth of *Prevotella* species in the gut of the subject.

[0112] A bacteriophage is virus that infects bacteria. In some embodiments, the bacteriophage specifically infects a *Pseudomonas* species. In some embodiments, the bacteriophage specifically infects a *Shigella* species. In some embodiments, the bacteriophage specifically infects an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species. In some embodiments, the bacteriophage is a lytic bacteriophage. The bacteriophage can be a genetically modified bacteriophage. The bacteriophage can be genetically modified to increase killing of the target bacteria. Lytic bacteriophages have been identified for several bacterial species, including, but not limited to, *Achromobacter xylosoxidans*, *Bacteroides dorei*, *Bacteroides finegoldii*, *Bacteroides fragilis*, *Citrobacter portucalensis*, *Citrobacter* sp., *Clostridiales* bacterium, *Clostridioides difficile*, *Clostridium cadaveris*, *Enterococcus faecalis*, *Escherichia coli*,

Klebsiella pneumoniae, *Neisseria flavescens*, *Pseudomonas* sp., *Pseudomonas aeruginosa*, *Ralstonia* sp., *Shigella* sp., and *Treponema denticola*. Bacteriophage that target *Pseudomonas aeruginosa* have been described by Chegini Z et al. (“Bacteriophage therapy against *Pseudomonas aeruginosa* biofilms: a review.” *Annals of Clinical Microbiology and Antimicrobials* 2020 19(45). Bacteriophage that target *Shigella* species have been described by Goodridge LD (“Bacteriophages for managing *Shigella* in various clinical and non-clinical settings.” *Bacteriophage*. 2013 3(1):e25098.) Bacteriophage that target an *Achromobacter* species have been described by Wittmann et al. 2014 (“Isolation and Characterization of Numerous Novel Phages Targeting Diverse Strains of the Ubiquitous and Opportunistic Pathogen *Achromobacter xylosoxidans*” *PLoS One* 9(1):e86935) and Lebeaux et al. 2021 (“A Case of Phage Therapy against Pandrug-Resistant *Achromobacter xylosoxidans* in a 12-Year-Old Lung-Transplanted Cystic Fibrosis Patient” *Viruses* 13(1):60). Bacteriophage that target a *Ralstonia* species have been described by Fujiwara et al. 2011 (“Biocontrol of *Ralstonia solanacearum* by Treatment with Lytic Bacteriophages” *Appl. Environ. Microbiol.* 77(12):4155-4162). Bacteriophage that target a *Klebsiella* species have been described by Cao et al. 2015 (“Evaluation of the Efficacy of a Bacteriophage in the Treatment of Pneumonia Induced by Multidrug Resistance *Klebsiella pneumoniae* in Mice” *BioMed Research International*, Article ID 752930). Bacteriophage that target a *Citrobacter* species have been described by Tikhe et al. 2015 (“Complete Genome Sequence of *Citrobacter* Phage CVT22 Isolated from the Gut of the Formosan Subterranean Termite, *Coptotermes formosanus* Shiraki” *Genome Announc.* 3(4):e00408). Bacteriophage that target a *Escherichia* species have been described by Cieplak et al. 2018 (“A bacteriophage cocktail targeting *Escherichia coli* reduces *E. coli* in simulated gut conditions, while preserving a non-targeted representative commensal normal microbiota” *Gut Microbes* 9(5):391-399). Bacteriophage that target a *Escherichia* species have been described by

[0113] Described are methods of treating a subject suffering from a PCD or at risk of developing a PCD, the methods comprising: administering to the subject one or more of:

- (a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprising killed *Prevotella* species bacteria, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;
- (b) a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject; and

(c) a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject.

[0114] Described are methods of treating a subject suffering from a PCD or at risk of developing a PCD, the methods comprising: administering to the subject one or more of:

(a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprising killed *Prevotella* species bacteria, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;

(b) a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject.

[0115] In some embodiments, the methods comprise administering to the subject a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprising killed *Prevotella* species bacteria, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject.

[0116] In some embodiments, the methods comprise administering to the subject a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject.

[0117] In some embodiments, the methods comprise administering to the subject a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject.

[0118] In some embodiments, the methods comprise administering to the subject a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject.

[0119] In some embodiments, the methods comprise administering to the subject (a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprising killed *Prevotella* species bacteria, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; and (b) a composition that specifically

decreases the abundance or inhibits the growth of a *Pseudomonas* species or a *Shigella* species in the gut of the subject.

[0120] In some embodiments, the methods comprise administering to the subject (a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprising killed *Prevotella* species bacteria, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; and (b) a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species and a *Shigella* species in the gut of the subject.

[0121] In some embodiments, subjects suitable for treatment with the described compositions, or using the described methods, are identified by having a low relative abundance of *Prevotella* species in the gut. In some embodiments, subjects suitable for treatment with the described compositions, or using the described methods, are identified by having a high relative abundance of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species in the gut. In some embodiments, subjects suitable for treatment with the described compositions, or using the described methods, are identified by having a low relative abundance of *Prevotella* species in the gut and a high relative abundance of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, or an *Escherichia* species in the gut.

[0122] A low relative abundance of the *Prevotella* species (e.g., *Prevotella corporis*) in the gut of a subject indicates the abundance of the *Prevotella* species in the subject is lower relative to the abundance of the *Prevotella* species in the gut of a control population (e.g., a population of healthy subjects) or is lower than a predetermined control. A high relative abundance of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, or the *Escherichia* species in the gut of a subject indicates the abundance of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, or the *Escherichia* species in the subject is higher relative to the abundance of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter*

species, or the *Escherichia* species in the gut of a control population (e.g., a population of healthy subjects) or is higher than a predetermined control.

[0123] In some embodiments, the method further comprises monitoring the abundance of one or more of the *Prevotella* species, *Pseudomonas* species, and the *Shigella* species in the gut of the subject. In some embodiments, if the abundance of *Prevotella* species in the gut of the subject is below a predetermined value, then the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the killed *Prevotella* species bacteria, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject is administered to the subject. In some embodiments, if the abundance of the *Pseudomonas* species in subject is above a predetermined value, then the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject is administered to the subject. In some embodiments, if the abundance of the *Shigella* species in the gut of the subject is above a predetermined value, then the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject is administered to the subject. In some embodiments, the *Prevotella* species is *Prevotella corporis*. In some embodiments, the *Pseudomonas* species is *Pseudomonas aeruginosa* or *Pseudomonas stutzeri*. In some embodiments, the *Shigella* species is *Shigella flexneri*, *Shigella sonnei*, *Shigella dysenteriae*, or *Shigella boydii*.

[0124] In some embodiments, the method further comprises monitoring the abundance of one or more of a *Prevotella* species, a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject. In some embodiments, if the abundance of *Prevotella* species in the gut of the subject is below a predetermined value, then the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the killed *Prevotella* species bacteria, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject is administered to the subject. In some embodiments, if the abundance of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species in subject is above a predetermined value, then the composition that specifically decreases the abundance or

inhibits the growth of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species in the gut of the subject is administered to the subject.

[0125] In some embodiments, the methods further comprise analyzing a sample of a microbiota from a gut or a stool sample from the subject to determine an amount of one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample and comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample to a predetermined control; and (i) if the amount of the *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the killed *Prevotella* species bacteria, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; (ii) if the amount of the *Pseudomonas* species in the gut of subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject; and/or (iii) if the amount of the *Shigella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject. The sample can be, but is not limited to, a gut microbial sample, a mucosal biopsy, an intestinal fluid, or a fecal sample.

[0126] In some embodiments, the methods further comprise analyzing a sample of a microbiota from a gut or a stool sample from the subject to determine an amount of one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the sample and comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the sample to a predetermined control; and (i) if the amount of the *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the killed *Prevotella* species bacteria, the composition comprising the *Prevotella* species lysate or the extract or the fraction

thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; (ii) if the amount of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species in the gut of subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species that is above the predetermined value in the gut of the subject. The sample can be, but is not limited to, a gut microbial sample, a mucosal biopsy, an intestinal fluid, or a fecal sample.

[0127] Any method available in the art for detecting, measuring, or monitoring bacterial levels in the gut can be used to determine the amount the *Prevotella* species, the *Pseudomonas* species, and/or the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species in the sample. The relative abundance of microbial taxa can be measured using techniques based on DNA sequencing, quantitative PCR, DNA microarray, by using test beds utilizing arrays or other suitable platforms, including microfluidic solutions, techniques based on droplet PCR, or any other suitable method wherein the abundance of taxa is expressed as read count, percentage, cell count, or value expressing intensity of any other suitable signal. Exemplary methods include, but are not limited to, analyzing nucleic acid in the sample.

[0128] Described are methods for determining a risk of developing a PCD or one or more symptoms of a PCD comprising: analyzing a sample of a microbiota from a gut or a stool sample of a subject to determine an amount of one or more of a *Prevotella* species, a *Pseudomonas* species, and a *Shigella* species in the sample; and comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample to a predetermined control; wherein an amount of the *Prevotella* species in the sample lower than the predetermined control, and/or an amount of *Pseudomonas* species and/or the *Shigella* species in the sample that is higher than the predetermined control, indicates the subject is at increased risk of developing the PCD.

[0129] Described are methods for determining a risk of developing a PCD or one or more symptoms of a PCD comprising: analyzing a sample of a microbiota from a gut or a stool sample of a subject to determine an amount of one or more of a *Prevotella* species, a *Pseudomonas* species, and a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species,

a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* in the sample; and comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the sample to a predetermined control; wherein an amount of the *Prevotella* species in the sample lower than the predetermined control, and/or an amount of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species in the sample that is higher than the predetermined control, indicates the subject is at increased risk of developing the PCD.

[0130] In some embodiments, the predetermined value comprises a standard derived from a population of subjects known to suffer from a protein folding disease (e.g., Alzheimer's disease or Parkinson's disease) or a population of subjects known to not suffer from the protein folding disease (i.e., healthy subjects). The abundance of *Prevotella* species. (e.g., *Prevotella corporis*), *Pseudomonas* species, (e.g., *Pseudomonas aeruginosa*), *Shigella* species, *Achromobacter* species, *Ralstonia* species, *Klebsiella* species, *Arcobacter* species, *Citrobacter* species, and/or *Escherichia* species as determined for the population is measured using the same or substantially the same method as used to measure the abundance of *Prevotella* species. (e.g., *Prevotella corporis*), *Pseudomonas* species, (e.g., *Pseudomonas aeruginosa*), *Shigella* species, *Achromobacter* species, *Ralstonia* species, *Klebsiella* species, *Arcobacter* species, *Citrobacter* species, and/or *Escherichia* species in an individual subject or subject to be treated. An abundance of *Prevotella* species (e.g., *Prevotella corporis*) in the gut of a subject that is the lower relative to the abundance of the *Prevotella* species (e.g., *Prevotella corporis*) determined for a population of healthy subjects indicates the subject is likely to respond to composition comprising: a *Prevotella* species (e.g., *Prevotella corporis*), a composition containing the *Prevotella* species (e.g., *Prevotella corporis*), a composition comprising lysate of the *Prevotella* species (e.g., *Prevotella corporis*) or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species (e.g., *Prevotella corporis*) in the gut of the subject. An abundance of *Achromobacter* species, *Ralstonia* species, *Klebsiella* species, *Arcobacter* species, *Citrobacter* species, and/or *Escherichia* species in the gut of a subject that is the higher relative to the abundance of the *Pseudomonas* species, *Shigella* species, *Achromobacter* species, *Ralstonia* species, *Klebsiella* species, *Arcobacter* species, *Citrobacter* species, and/or *Escherichia* species determined for a

population of healthy subjects indicates the subject is likely to respond to composition comprising: a composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species, *Shigella* species, *Achromobacter* species, *Ralstonia* species, *Klebsiella* species, *Arcobacter* species, *Citrobacter* species, and/or *Escherichia* species in the gut of the subject.

[0131] The described compositions and methods can be used to treat or prevent a PCD in a subject. In some embodiments, the PCD is a neurodegenerative disease. Protein conformational diseases include, but are not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, cystic fibrosis, amyotrophic lateral sclerosis, alpha1-antitrypsin deficiency liver disease, cerebral β -amyloid angiopathy, tauopathies, frontotemporal lobar degeneration, CADASIL, Alexander disease, Pelizaeus-Merzbacher disease, seipinopathies, familial amyloidotic neuropathy, serpinopathies, amyloidosis, hereditary cerebral hemorrhage with amyloidosis, senile systemic amyloidosis, aortic medial amyloidosis, ApoAI amyloidosis, ApoAII amyloidosis, ApoAIV amyloidosis, familial amyloidosis of the Finnish type (FAF), lysozyme amyloidosis, fibrinogen amyloidosis, dialysis amyloidosis, cardiac atrial amyloidosis, cutaneous lichen amyloidosis, corneal lactoferrin amyloidosis, apolipoprotein C2 amyloidosis, apolipoprotein C3 amyloidosis, Lect2 amyloidosis, insulin amyloidosis, galectin-7 amyloidosis, corneodesmosin amyloidosis, enfuvirtide amyloidosis, type II diabetes, inclusion body myositis/myopathy, cataracts, retinitis pigmentosa with rhodopsin mutations, retinal ganglion cell degeneration, medullary thyroid carcinoma, pituitary prolactinoma, hereditary lattice corneal dystrophy, mallory bodies, pulmonary alveolar proteinosis, odontogenic tumor amyloid, seminal vesicle amyloid, sickle cell disease, plasma cell dyscrasias, exfoliation syndrome, autism, Creutzfeldt–Jakob disease, multiple system atrophy, Lewy body dementia, and certain dementias.

[0132] In some embodiments, the subject is a human subject.

[0133] In some embodiments, the subject has or has been diagnosed with a PCD or is at increased risk of developing a PCD.

[0134] Treating a PCD include, but is not limited to, reducing or ameliorating the severity of the disease, reducing or ameliorating the severity of one or more symptoms associated with the disease, slowing progression of the disease, slowing progression of one or more symptoms associated with the disease, reducing severity of the disease, reducing severity of one or more symptoms of the disease, delaying onset of the disease, delaying onset of one or more symptoms associated with the disease, preventing the disease, preventing one or more

symptoms associated with the disease, reduce the duration of a symptom associated with a disease, regressing the disease, regressing one or more symptoms associated with the disease, reducing recurrence of one or more symptom associated with the disease, or increasing or prolonging survival of a subject with a disease.

[0135] The one or more symptoms of a PCT include, but are not limited to: anosmia, hyposmia, bradykinesia, ataxia, tremor, muscle rigidity, impaired gait, impaired posture and balance, loss of automatic movements, dysarthria or other speech changes, handwriting changes, orthostatic hypotension, memory deficit, dysphagia, incontinence, sleep disruption, cardiac arrhythmia, visual disturbance, psychiatric problems including depression and visual, auditory, olfactory, or tactile hallucinations, vertigo, cognitive dysfunction, altered dopamine levels, altered serotonin levels, altered kynurenine levels, and/or any combination thereof.

[0136] Also described are compositions and methods that can used to identify bacterial signals that disrupt host proteostasis, characterize bacterial genes that disrupt host proteostasis; and analyze bacterial influence on host stress responses and lifetime.

EXAMPLES

Example 1. Methods

[0137] *A. C. elegans maintenance and strains.* For experiments that generated the data represented in the heat-map (FIG. 2), nematodes were kept on *E. coli* OP50 for two days at 20°C, washed three times and transferred to indicated bacteria, where they were kept at 22.5°C for three days. For all other experiments, nematodes were plated on indicated bacteria as L1s at 22.5°C, where they remained until the time of assay, except for the experiment in FIG. 7, in which worms were cultured in temperatures indicated in the figure.

[0138] *B. Bacterial culture conditions.* All bacteria were cultured at 37°C. Bacteria were grown: 1) anaerobically in reinforced clostridial broth (RCB) with Oxyrase; 2) in facultative conditions (no shaking, tube filled to top) in brain heart infusion broth (BHI), 3) in aerobic conditions, shaking at 220 revolutions per minute (RPM) in BHI; 4) in anaerobic conditions on tryptic soy agar (TSA) supplemented with 5% defibrinated sheep's blood; or 5) in aerobic conditions on TSA supplemented with 5% defibrinated sheep's blood. *E. coli* OP50 controls were grown in a manner consistent with which experiment was performed. Bacteria were washed and resuspended in M9 before being seeded on NGM. All follow-up experiments were performed with bacteria grown on TSA supplemented with 5% defibrinated sheep's blood at 37°C except for the intestinal confirmation experiment of the proteotoxic bacteria (FIG. 4 Panel

A, “Aggregates”). Except for *Prevotella* species which were grown under anaerobic conditions, bacteria were grown aerobically in follow-up experiments.

[0139] *C. Aggregate quantification.* Fluorescent aggregates were quantified using Leica MZ10F Modular Stereo Microscope equipped with CoolLED pE300lite 365 dir mount STEREO with filter set ET GFP-MZ10F. Fluorescent aggregates in worms used to generate data for the heat-map (FIG. 2) were manually quantified after having been cultured as indicated in “*C. elegans* maintenance and strains”. For all other experiments, worms were plated on indicated bacteria as L1s and fluorescent aggregates were manually quantified after four days (intestinal polyQ44) or three days (muscle polyQ35, 40) of life. Aggregates of worms that were quantified to generate the data used in the heat map were quantified blind.

[0140] *D. Motility assays.* All motility assays were performed at room temperature as described in Walker AC et al. 2021 (“Colonization of the *Caenorhabditis Elegans* Gut with Human Enteric Bacterial Pathogens Leads to Proteostasis Disruption That Is Rescued by Butyrate. PLOS Pathog. 2021, 17(5):e1009510) and Walker AC et al. 2022 (Time-off-Pick Assay to Measure *Caenorhabditis Elegans* Motility. Bio-Protoc. 2022, 12(12):e4436). In brief, the time-off-pick (TOP) assay entailed sliding a worm pick made with an eyebrow hair under the mid-section of the worm and using a ticking second timer to count the number of seconds it took for the worm to crawl off entirely. TOP (seconds) of transgenic nematodes harboring tissue-specific aggregating protein species was assessed at three days (muscle polyQ, muscle A β ₁₋₄₂, *unc-54(ts)*, *dyn-1(ts)*, TSA, and respective controls) or four days (intestine polyQ, neuron polyQ, muscle α -synuclein and control) after having been plated on indicated bacteria as L1s. Worms carrying the temperature-sensitive mutation in *dyn-1(ts)* were assayed before and after a one-hour shift to the restrictive temperature.

[0141] *E. Live imaging.* Nematodes expressing muscle-specific A β ₁₋₄₂ were plated as L1s on NGM containing *E. coli* OP50, *P. corporis* HM-1294, and *P. aeruginosa* PAO1 for three days were mounted on a 3% agarose pad, frozen to reduce background fluorescence, and imaged. Nematodes expressing *hsp70p::GFP* were plated as L1s onto NGM containing *E. coli* OP50 for two days, washed with M9 and transferred onto NGM containing indicated bacteria for 24 h, and were paralyzed with 2 mM levamisole, mounted on a 3% agarose pad, and imaged. Fluorescent and Nomarski images were taken using Zeiss Axio Observer 7 microscope equipped with AxioCam 503 mono camera, Solid-State Light Source Colibri 7, and a 10 $\times$ EC Plan-Neofluar objective (0.3 NA) and were processed using ZEN Tiles & Positions Module in Zeiss ZenPro Software.

[0142] *F. Gel electrophoresis and western blotting.* Worms were prepared for gel electrophoresis and western blotting. In brief, M9 was used to lift worms from NGM which were washed until superficial bacteria was removed. Worms were plated on unseeded NGM, were allowed to dry briefly and 50 worms were picked into 10 μ L M9 with 1 mM phenylmethylsulfonyl fluoride (PMSF) in non-skirted screw-cap microcentrifuge tubes and frozen overnight or longer at -80°C . Tubes were pulse-centrifuged and three, 1.5mm zirconium beads were added to each tube. The following two steps were repeated a minimum of two times; if large worm particulates were observed, these steps were repeated again with the entire sample set until no tubes contained worm pieces that were visible under a dissecting microscope. Samples were homogenized by placing tubes in a Bead Bug homogenizer at 280×10 rates per minute (RPM) for 90 seconds. Tubes were cooled on ice and centrifuged for 1-2 minutes at a low speed to re-settle worms and worm particulates. Samples were prepped for gel electrophoresis and entire samples were loaded on 4-12% gradient sodium dodecylsulfate-polyacrylamide gels (SDS-PAGE) to separate proteins through electrophoresis. Proteins were transferred onto polyvinyl difluoride (PDVF) membrane, blocked with 5% nonfat milk powder in PBS-Tween-20 (PBST) and probed with Living Colors JL-8 monoclonal primary antibody (1:1000) for 48 h at 4°C on an orbital shaker and underwent three, five-minute washes with 0.1% PBST followed by incubation with a 1:10,000 dilution of goat-anti-mouse horse-radish peroxidase (HRP) conjugated secondary antibody for at least two h followed by three, ten-minute washes with 0.1% PBST. Chemiluminescence was achieved by incubation with Clarity Western ECL substrate. Image J (v1.52) or ChemiDox XRS+System with Image Lab Image Capture and Analysis Software was used to analyze insoluble fractions.

[0143] *G. Quantification and statistical analysis.* Quantification of aggregate counts per worm in FIG. 2 were performed on a cohort of ten worms to corroborate the findings from the western blot analysis. In the rest of the figures, data are represented as the average number of aggregates, TOP (seconds), or otherwise specified per worm obtained from two independent experiments for a total of 60 worms (FIG. 3 Panel A “Aggregates”), 45-60 worms normalized to the control (FIG. 4 Panel A “Aggregates”); three independent experiments for a total of 98 worms (FIG. 14) or 60 worms (FIG. 5) or 45 worms (FIG. 3 Panel A “Motility”, FIG. 3 Panel A “Motility” (polyQ44, polyQ33), FIG. 3 Panels B and C, FIG. 4 Panel A “Motility”, FIG. 4 Panel C “Aggregates”) or 30 worms (FIG. 3 Panel A “Motility” (N2), FIG. 3 Panels D and E, FIG. 4 Panels B and C “Motility”, FIG. 4 Panels D and E, FIG. 5, FIG. 7) or 20 worms (FIG. 11); two independent experiments for a total of 20 worms (FIG. 6). Data are described as

statistically significant when $p < 0.05$ as determined by Student's t-test or one-way ANOVA followed by multiple comparison Dunnett's post-hoc test (statistical tests used are indicated in figure legends) performed using Graphpad Prism 8.4.3 or later. Degrees of significance are denoted by the use of asterisks such that * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. The heat map (FIG. 2) is represented as data normalized to the control *E. coli* OP50. Error bars represent standard error of the mean.

[0144] *H. Heat map generation.* Heatmap was constructed in R-studio using the ComplexHeatmap package from the Bioconductor project. The experimental data were fed into R-studio as an organized .CSV file. The heatmap is the graphical representation of this data, clustering the bacteria by phylum.

[0145] *I. Phylogenetic tree generation.* Whole genome sequences were assembled using the Bacterial and Viral Bioinformatics Resources Center (BV-BCR) via Unicycler. All genomes were annotated in BV-BRC using Prokka. Phylogenetic analysis was conducted in BV-BRC based on concatenated alignments of 100 single-copy genes using mafft, and the results were assessed for maximum likelihood using RAxML. Sequences that did not have 100 complete single-copy genes due to poor sequencing quality were excluded.

[0146] *J. Feeding worms PFA-killed bacteria.* Bacteria were cultured on TSA-blood plates under aerobic (*E. coli* OP50) or anaerobic (*P. corporis*) conditions. Bacterial lawns were washed and resuspended in M9 and adjusted to $OD_{600} = 2$. PFA was added at a final concentration of 0.5% and incubated at 37°C, shaking at 220 RPM for 1 h. After incubation, samples were washed 4× by centrifugation at 5,000×g for 10 min and resuspension in M9. Bacterial killing was confirmed by spotting 20 µL of each sample onto TSA-blood plates and incubating under the above-specified conditions. Dead bacterial samples were seeded onto NGM and allowed to dry overnight. Once dried, age-synchronized L1 worms expressing intestinal polyQ44 were plated onto them and maintained for four days in a 22.5°C incubator. PolyQ aggregates were quantified as described in "Aggregate quantification".

[0147] *K. Pharyngeal pumping.* Pharyngeal pumping was assessed using a modified protocol from Raizen et al. ("Methods for Measuring Pharyngeal Behaviors." In *WormBook*; The *C. elegans* Research Community, Ed.; WormBook, 2012). Bacteria were cultured on TSA-blood plates in anaerobic conditions and seeded. Age-synchronized L1 N2s were plated onto NGM containing indicated bacteria and kept at 22.5°C for four days until the assay. After four days, each worm was picked onto a fresh plate of NGM seeded with the indicated bacteria and was given 10-15 min to acclimate. The number of pharyngeal pumps was counted over a 30-second

period. A single pump was scored as a complete backward motion of the terminal bulb grinder. This was repeated on the same worm for a total of 10 times per worm.

[0148] *L. Exposing worms to bacterial supernatants.* Bacteria were grown on TSA-blood plates under aerobic (*E. coli* OP50, *K. pneumoniae*, *A. xylosoxidans*) or anaerobic (*P. corporis*) conditions. *E. coli* OP50 pellets and bacterial supernatants were obtained as follows: bacterial lawns were resuspended in M9, adjusted to OD₆₀₀ = 2, centrifuged at 5,000 ×g for 15 minutes and sterile filtered. *E. coli* OP50 pellets were washed and resuspended in M9 (No SN) or supernatants from indicated bacteria. Suspensions were seeded onto NGM and allowed to dry overnight prior to having worms (intestinal polyQ44) plated on them.

[0149] *M. Co-colonization assays.* Bacteria were grown on TSA-blood plates under aerobic (*E. coli* OP50, *K. pneumoniae*) or anaerobic (*P. corporis*) conditions. Bacterial lawns were resuspended in M9 and indicated bacteria were mixed 1:1 (CFU/mL) and seeded on NGM. The seeded plates were allowed to dry for 6-8 h in ambient conditions prior to having worms (intestinal polyQ44) plated on them.

[0150] *N. Quantification of intestinal bacteria.* Bacterial loads in the *C. elegans* intestine (N2, WT) were quantified as previously. *C. elegans* were lysed using the BeadBug. Bacteria were cultured on TSA-blood plates in aerobic conditions. Age-synchronized L1 N2s were plated onto NGM containing indicated bacteria and kept at 22.5°C for four days until the assay.

Example 2. Characterization of the human microbiome on host proteostasis.

[0151] We obtained a comprehensive Human Microbiome Project collection of 229 unique bacterial isolates from BEI Resources and assessed their effect on *C. elegans* proteostasis. The method used to conduct this experiment is illustrated in FIG. 1. In brief, anaerobic bacteria were cultured on TSA-blood plates using anaerobic gas packs or in liquid broth supplemented with oxyrase for 2-7 days, while aerobic bacteria were cultured on TSA-blood plates or in liquid broth for one day. Cultured bacteria were transferred to nematode growth media (NGM) plates and incubated overnight with (for anaerobic bacteria) or without (aerobic bacteria) anaerobic gas packs. Worms were synchronized by the bleaching method and cultured on control *E. coli* OP50 until young adults (2 d), washed and transferred to NGM plates containing anaerobically or aerobically grown test bacteria, and cultured for an additional three days. Intestinal polyQ aggregates were quantified by manual counting and western blotting the insoluble fractions.

[0152] The collection encompasses isolates from a range of diverse phyla and a variety of anatomical sites (FIG. 2). In a previous study, we used aggregation-prone polyQ tracts as a

sensor of the protein folding environment to demonstrate that gram-negative pathogens disrupt host proteostasis (Walker AC et al. 2021). Among animals carrying intestine-, muscle-, and neuron-specific polyQ::YFP, we previously found that proteostasis in the intestine was significantly affected by the colonizing bacteria (Walker AC et al. 2021). As such, we performed our initial screen using the intestinal polyQ model (FIG. 2). To eliminate the possibility that bacteria will affect *C. elegans* development, worms were grown to adulthood prior to being transferred to the bacterial strains of interest. polyQ aggregation was assessed by fluorescent microscopy. To ensure the validity of our results, we also assessed polyQ aggregation by western blotting. Validating our approach, both quantitative methods yielded similar results.

[0153] Bacteria from the isolate collection exhibited a differential effect on *C. elegans* proteostasis as indicated by increases and decreases in polyQ aggregation compared to worms fed control *E. coli* OP50 (FIG. 2). FIG. 2 summarizes the screen revealing bacteria that most robustly affected host proteostasis. For example, *Prevotella* was the only genus that consistently resulted in low polyQ aggregation across all 229 strains tested (FIG. 2). Conversely, significant host proteotoxicity was observed in nematodes that were fed *Achromobacter xylosoxidans* and *Arcobacter butzleri*, as well as *Citrobacter*, *Escherichia*, *Klebsiella*, *Pseudomonas*, and *Ralstonia* species (FIG. 2). A detailed list of all bacterial strains and their effect on polyQ aggregation is summarized in Table 1.

[0154] We screened a collection of 229 unique bacterial isolates from the Human Microbiome Project for their ability to affect host proteostasis from within the intestinal milieu. Our follow-up experiments on the most robust beneficial and detrimental bacteria confirmed their influence on proteostasis across host tissues, affecting the stability of proteins associated with Alzheimer's, Parkinson's, and Huntington's diseases. The phylogenetic analysis revealed clustering of select proteotoxic and proteoprotective bacteria, indicating that genetically related bacteria affect host proteostasis in a similar manner, but with a different magnitude. To our knowledge, this is the first comprehensive characterization of bacteria from human microbiomes on host proteostasis. Surprisingly, our data suggest that bacteria do not selectively target any specific host proteins associated with PCDs, but rather affect proteostasis in general, leading to the aggregation and proteotoxicity of any destabilized proteins present within the proteome, such as exogenous polyQ, A β ₁₋₄₂, and α -synuclein, tested in our experiments. While this is a generalized mechanism, there could be microbes that exclusively affect a specific disease.

Example 3. Prevotella species mitigate the proteotoxic aggregation of diverse culprit proteins.

[0155] Out of the 229 strains tested, the *Prevotella* genus had the highest number of members that suppressed polyQ aggregation. We further retested 17 *Prevotella* species using the intestinal polyQ44 model. To increase the robustness of the response, we started feeding animals test bacteria immediately after hatching. Although we observed an enhanced suppression of aggregation for most retested strains, there were few isolates that did not significantly inhibit polyQ aggregation, likely due to the timing of feeding. Furthermore, as expected, feeding worms test bacteria beginning at the L1 larval stage affected development (FIG. 3 Panel A, “Aggregates”). Out of all strains, *P. buccae*, *P. oris*, and *P. corporis* significantly suppressed polyQ aggregation without causing any detectable developmental delay (FIG. 3 Panel A, “Aggregates”). Motility defects are associated with neurodegenerative PCDs. As such, we assessed whether the three *Prevotella* species alleviated aggregate-dependent motility defects caused by culprit proteins expressed in the intestine and distal tissues. We used our well-established and validated time-off-pick (TOP) assay that relies on *C. elegans* motility as a readout of proteotoxicity. Consistent with their suppression of polyQ aggregation, all three strains alleviated aggregate-dependent motility defects with *P. corporis* having the strongest effect (FIG. 3 Panel A, “Motility”). To determine whether the observed suppression is dependent on polyQ, we used N2 wild-type worms and a model expressing a shorter polyglutamine tract, polyQ33. The results revealed no effect on the N2 worms and a less robust suppression of the motility defect for polyQ33, indicating that *Prevotella* suppressed proteotoxicity.

[0156] To determine whether *Prevotella* also affects polyQ in distal tissues, we employed the neuronal and muscle models. Because worms expressing the neuronal polyQ do not exhibit quantifiable aggregates, we used the TOP assay as a motility readout. Our results show that of the three strains, only *P. corporis* showed significant suppression of the motility defect in worms expressing neuronal polyQ40 (FIG. 3 Panel B). Unexpectedly, *P. buccae*, *P. oris*, and *P. corporis* increased motility defects in the neuronal empty vector control (polyQ0); the reason for this is unknown, but importantly does not diminish the observed beneficial effects of *Prevotella* on neuronal polyQ. In a manner similar to the intestinal polyQ, we observed *Prevotella*-mediated suppression of aggregation and proteotoxicity in worms expressing muscle-specific polyQ (FIG. 3 Panel C).

[0157] The association between the low abundance of gut *Prevotella* and diverse neurodegenerative PCDs suggests that the bacterial influence on these diseases is independent of the culprit protein species. As such, we hypothesized that bacteria might affect protein aggregation by modulating host proteostasis, and if this is the case, *Prevotella* species should enhance proteostasis in worms expressing various aggregation-prone proteins. To test the effect of *Prevotella* on other disease-associated proteins, we chose three muscle-specific models: one expressing A β ₁₋₄₂, and two expressing α -synuclein. These culprit proteins model Alzheimer's and Parkinson's diseases, respectively. Additionally, these models exhibit age-dependent proteotoxicity, which is consistent with the age-dependent progression of neurodegenerative diseases. To investigate progressive proteotoxicity in the A β ₁₋₄₂ and α -synuclein models, we assessed their motility between days three to five post-hatching (FIG. 6). Nematodes expressing A β ₁₋₄₂ and α -synuclein had age-dependent motility defects that were markedly greater than those of the controls (FIG. 6). We examined the effect of *P. buccae*, *P. oris*, and *P. corporis* on proteotoxicity associated with each of these three models. In a manner similar to the polyQ models, *P. buccae*, *P. oris*, and *P. corporis* reduced aggregate-dependent toxicity compared to wild-type control (FIG. 3 Panel A), particularly with *P. corporis* having the strongest effect (FIG. 3 Panels D and E). Bacteria that strongly enhanced or suppressed host proteostasis induced notable differences in the aggregation of A β ₁₋₄₂, which parallels the extent of the motility defect (FIG. 5). Both A β ₁₋₄₂ aggregation and the associated toxicity were suppressed by *P. corporis* and enhanced by *Pseudomonas aeruginosa* (FIG. 5), a bacterium that strongly disrupted host proteostasis in our previous studies (Walker et al. 2021 and Walker AC et al; 2022b ("Bacteria-Derived Protein Aggregates Contribute to the Disruption of Host Proteostasis." Int. J. Mol. Sci. 2022, 23(9): 4807)). All of our transgenic worms expressed exogenous proteins. To determine whether *Prevotella* can also provide protection against misfolding of endogenous proteins, we used a strain that carried a temperature-sensitive mutation in myosin heavy chain (UNC-54) that leads to its misfolding and paralysis at the restrictive temperature (25°C) ("Muscle") and DYN-1, featuring a modified GTPase domain that is highly expressed in motor neurons, resulting in loss of coordination at the restrictive temperature (25°C) ("Neuronal"). In agreement with the proteoprotective effect against misfolding and aggregation of exogenous proteins, *Prevotella* suppressed the temperature-dependent motility defect at the restrictive temperature, further supporting its beneficial role (FIG. 7). Collectively, our findings indicate that *Prevotella* can mitigate the pathogenesis of PCDs, including neurodegenerative diseases.

[0158] Given that dietary restriction enhances proteostasis and suppresses polyQ aggregation, we assessed pharyngeal pumping to determine whether the proteoprotective effect mediated by *P. corporis* was the result of caloric restriction. The results showed no significant difference in pharyngeal pumping between worms fed *E. coli* OP50 and those fed *P. corporis* (FIG. 11), indicating that the observed proteoprotection was not caused by caloric restriction.

Example 4. Proteotoxic bacteria enhance the aggregation and toxicity of PCD-associated proteins.

[0159] To confirm the effect of the most robust proteotoxic strains identified in our original screen (FIG. 2), we assessed polyQ44 aggregation in animals fed gram-negative aerobes (FIG. 4A, “Aggregates”). We concentrated on these specific bacteria because they did not affect worm development, which is known to influence proteostasis. We found that *Ralstonia* sp., *Achromobacter xylosoxidans*, *Pseudomonas* sp., and *K. pneumoniae* were the strongest inducers of polyQ aggregation (FIG. 4 Panel A). As we have already demonstrated the proteotoxic potential of *P. aeruginosa* in our previous work, we focused on the three remaining species in follow-up experiments. To assess the proteotoxic effect of these bacteria, we employed the TOP assay to measure the motility of worms expressing aggregating polyQ44 and non-aggregating polyQ33. While we detected a significant enhancement in the motility defect in animals expressing polyQ44, no significant changes were observed in wild-type or in animals expressing polyQ33 (FIG. 4 Panel A). These results indicate that the impairment of motility induced by bacteria is contingent on polyQ aggregation rather than general bacterial pathogenicity. The aggregate-dependent motility defects were also observed in worms expressing neuronal and muscle-specific polyQ; although, the phenotype was less robust as we did detect some decrease in motility in control animals (FIG. 4 Panels B and C). *K. pneumoniae*, *Ralstonia* sp., and *A. xylosoxidans* also elevated muscle-specific polyQ aggregation (FIG. 4 Panel C). To test the microbial influence on other disease-associated proteins, we employed worms expressing muscle-specific A β ₁₋₄₂ and α -synuclein. In agreement with the intestinal polyQ model, all of these bacterial isolates also induced proteotoxicity associated with these additional culprit proteins (FIGs. 4 Panels D and E). These results demonstrate that bacteria can enhance the proteotoxicity of diverse disease-associated proteins, supporting their role in the pathogenesis of neurodegenerative PCDs.

[0160] To determine whether the observed proteotoxicity is attributed to increased bacterial colonization, we quantified intestinal bacteria. The results indicated that *K. pneumoniae*, *Ralstonia* sp., and *A. xylosoxidans* colonized less than *E. coli* OP50 (FIG. 13), indicating that

the proteotoxicity mediated by these strains was not explained by their colonization efficiencies.

[0161] Worms were exposed to spent culture supernatants from *K. pneumoniae* and *A. xylosoxidans*. The results demonstrated that supernatants from these bacteria significantly increased polyQ aggregation, whereas supernatants from *P. corporis* and *E. coli* OP50 had no effect (FIG. 14).

Example 5. Analysis

[0162] Numerous studies that employed genomic analyses of microbial compositions in affected patients revealed a connection between comparable gut dysbioses and diverse neurodegenerative PCDs (Fang P et al. The Microbiome as a Modifier of Neurodegenerative Disease Risk. *Cell Host Microbe* 2020, 28(2):201–222 and Walker A et al. “Oh My Gut! Is the Microbial Origin of Neurodegenerative Diseases Real?” *Infect. Immun.* 2023).

[0163] We screened a collection of 229 unique bacterial isolates from the Human Microbiome Project for their ability to affect host proteostasis from within the intestinal milieu. Follow-up experiments on the most robust beneficial and detrimental bacteria confirmed their influence on proteostasis across host tissues, affecting the stability of proteins associated with Alzheimer’s, Parkinson’s, and Huntington’s diseases. The phylogenetic analysis revealed clustering of select proteotoxic and proteoprotective bacteria, indicating that genetically related bacteria affect host proteostasis in a similar manner, but with a different magnitude. Surprisingly, our data suggest that bacteria do not selectively target any specific host proteins associated with PCDs, but rather affect proteostasis in general, leading to the aggregation and proteotoxicity of any destabilized proteins present within the proteome, such as exogenous polyQ, A β ₁₋₄₂, and α -synuclein, tested in our experiments.

[0164] In our screen (FIG. 2), *Prevotella* stood out as the only genus devoid of any species that exhibit proteotoxicity towards the host. Furthermore, our findings indicate that *Prevotella* species have a broad and suppressive effect on host protein aggregation, regardless of the specific disease-associated protein (FIG. 3). Sequencing data suggest that a low abundance of *Prevotella* in the guts of patients with PCDs enhances disease pathogenesis. Our data indicate that various *Prevotella* species exhibit a differential effect on host proteostasis (FIG. 3 panel A). Such various effects of individual species could be explained by large variability in their genomes (Tett A et al. “Prevotella Diversity, Niches and Interactions with the Human Host. *Nat. Rev. Microbiol.* 2021, 19 (9), 585–599).

[0165] The robust induction of proteotoxicity by *K. pneumoniae* across all *C. elegans* models expressing different aggregation-prone protein species (FIG. 4), is in agreement with a previous study that identified an overabundance of *K. pneumoniae* in the gut microbiota of individuals with AD (Haran JP et al. “Alzheimer’s Disease Microbiome Is Associated with Dysregulation of the Anti-Inflammatory P-Glycoprotein Pathway. mBio 2019, 10(3)). *A. xylosoxidans* induced proteotoxicity in all our disease models (FIG. 4), along with *Pseudomonas*, which displayed a notable increase in polyQ aggregation (FIG. 4 Panel A, “Aggregates”). Furthermore, we previously demonstrated that *P. aeruginosa* exerts robust proteotoxic effects on *C. elegans* (Walker AC et al. 2022 and Walker AC 2022b). It is remarkable that the various bacteria induce proteotoxicity consistently across all our *C. elegans* models expressing distinct disease proteins.

Example 6. Effect of bacteria on host protein folding

[0166] To decipher the effect of individual microbes on host proteostasis, we employed *Caenorhabditis elegans* models that express fluorescent polyglutamine (polyQ) tracts across different tissues, including intestine, muscle, and neurons. A polyglutamine aggregation model has been used as a sensor for changes in proteostasis in various tissue (Muscle (Morley et al 2002); Intestine (Mohri-Shiomi, Garsin 2008); and neurons (Brignull et al. 2006)) for various proteins, including, A β 1-42, Tau, α -Syn, and TDP-43. We use these reporters as proxies to detect bacteria-induced changes in the folding environment. We used *C. elegans* as a model organism for studying the effect of gut bacteria on host organism protein folding. We found that colonization of the *C. elegans* intestine with gram-negative enteropathogenic bacteria led to disruption of the folding environment and consequently aggregation of polyQ not only in that tissue but in the muscle and neuronal tissues as well. We demonstrated that bacteria-derived aggregates contribute to the observed disruption of proteostasis. Co-colonization with butyrogenic bacteria or the presence of butyrate inhibited polyQ aggregation and alleviated the associated proteotoxicity. Genetic experiments revealed that the protective response mediated by butyrate required SKN-1/Nrf2 and DAF-16/FOXO transcription factors. We further deciphered the effect of all culturable bacterial isolates from the Human Microbiome Project on host proteostasis and found species that either disrupt or enhance host proteostasis. We tested the most robust bacterial isolates using *C. elegans* models expressing A β 1-42, α -syn, and a novel tauopathy model. Our results indicate that bacteria do not discriminate between different metastable proteins but rather generally affect host proteostasis. Collectively, our

study characterized the effect of the culturable microbiome on host proteostasis revealing proteoprotective and proteotoxic species.

[0167] By analyzing the effect of culturable bacterial isolates from the Human Microbiome Project on protein folding homeostasis, we have identified bacteria that disrupt the protein folding environment and contribute to the pathogenesis of neurodegenerative diseases by inducing toxic protein aggregation. We observed that bacteria-derived protein aggregates contribute to the disruption of host proteostasis. Protein aggregates could migrate from the gut into the brain and contribute to the disruption of host proteostasis.

[0168] We looked at the effect of various enteric bacteria on host proteostasis. The enteric bacteria included: Enterobacteriaceae (*E. coli*, *Klebsiella* species, *Proteus* species, *Citrobacter* species, *Shigella* species, and *Salmonella* species) and other pathogenic species (*Pseudomonas* species and *Acinetobacter* species) (FIG. 8).

[0169] We then examined whether bacteria or their products contribute to the pathogenesis of neurodegenerative PCDs. We observed that bacteria-derived protein aggregates contributed to the disruption of host proteostasis. We further showed that protein aggregates could migrate from the gut into the brain and contribute to the disruption of host proteostasis.

[0170] To analyze how bacteria-derived protein aggregates affect host proteostasis, we performed a genome-wide screen for bacterial signals that affect host proteostasis. A screen of about 10,000 *P. aeruginosa* mutants revealed bacterial genes and pathways that affect host proteostasis (FIG. 9).

Example 7. Mitigation of proteotoxicity by P. corporis.

[0171] The human microbiota is comprised of a diverse array of bacterial species that coexist and interact within a complex polymicrobial community. We investigated the potential of a proteoprotective species to mitigate bacterial proteotoxicity by co-colonizing worms with *P. corporis* and either *K. pneumoniae* or *E. coli* OP50. Our findings demonstrated that *P. corporis* suppressed the polyQ aggregation associated with *K. pneumoniae* and *E. coli* OP50 (FIG. 10 Panels A and B). We tested whether the same suppressive effect would result from co-colonizing worms with *K. pneumoniae* and *E. coli* OP50 and found that the resulting aggregation profile was an integrative reflection of the individual effects observed when each strain was introduced in isolation (FIG. 10 Panel C). *P. corporis* completely inhibited the proteotoxicity of *K. pneumoniae* (FIG. 10 Panel A) and *E. coli* (FIG. 10 Panel B). Collectively, these results indicate that, in addition to suppressing proteotoxicity from intrinsic factors like

aging and host-encoded metastable proteins, *P. corporis* also suppresses host proteotoxicity mediated by extrinsic factors such as proteotoxic bacteria.

Example 8. P. corporis activates heat shock response.

[0172] To investigate the mechanistic basis behind the ability of *P. corporis* to safeguard against host proteotoxicity, we investigated its potential to activate the heat shock response (HSR), a critical and evolutionary conserved cellular defense mechanism that responds to protein misfolding and proteotoxic stress. Using *C. elegans* expressing a transcriptional fluorescent reporter, *hsp70p::GFP*, we monitored HSR activation in worms fed *P. corporis*. While control *E. coli* OP50 and proteotoxic *K. pneumoniae* did not elicit any detectable response, *P. corporis* induced the reporter, indicating HSR activation (FIG. 10 Panel D).

[0173] The results demonstrate that *P. corporis* can be used to induce expression of Heat Shock proteins and heat shock response. The results reinforce the ability of bacteria such as *P. corporis* to target components of the host proteostasis network.

Example 9. Killed P. corporis retain proteoprotective properties.

[0174] Because *Prevotella* spp. are anaerobic and may not thrive well in the ambient conditions in which *C. elegans* are cultured, we investigated whether dead bacteria retain their proteoprotective properties. To accomplish this, we fed worms paraformaldehyde (PFA)-killed bacteria and found that *P. corporis* still significantly suppressed polyQ aggregation relative to *E. coli* OP50 control (FIG. 12), indicating that live bacteria are not necessary to elicit protection. The data also indicate that *Prevotella* lysate, extract, or fraction will also elicit protection.

Table 1. Bacterial strains and their effect on polyQ aggregation.

Bacteria	Strain	Aggregates		Bacteria	Strain	Aggregates	
		Western	Count			Western	Count
<i>Acetobacteraceae</i> sp.	AT-5844	1.59	1.89	<i>Lactobacillus gasseri</i>	EX336960VC02	1.15	1.02
<i>Achromobacter xylosoxidans</i>	C54	2.76	2.70	<i>Lactobacillus gasseri</i>	224-1	0.80	1.02
<i>Acidaminococcus</i> sp.	D21	0.57	0.66	<i>Lactobacillus iners</i>	Lactin V 09 (V1)-c	0.85	0.83
<i>Acidaminococcus</i> sp.	HPA0509	0.10	0.47	<i>Lactobacillus jensenii</i>	208-1	1.12	1.00
<i>Acinetobacter radiorisistens</i>	SK82	0.72	0.59	<i>Lactobacillus johnsonii</i>	135-1-CHN	1.16	0.98
<i>Actinomyces cardiffensis</i>	F0333	2.27	1.60	<i>Lactobacillus parafarraginis</i>	F0439	1.12	1.09
<i>Actinomyces gerencseriae</i>	F0344	1.12	0.97	<i>Lactobacillus rhamnosus</i>	LMS2-1	1.86	1.33
<i>Actinomyces graevenitzi</i>	C83	1.47	1.73	<i>Leptotrichia goodii</i>	F0264	0.21	0.78
<i>Actinomyces israelii</i>	F0345	0.19	0.18	<i>Listeria monocytogenes</i>	CC70B	2.15	1.83
<i>Actinomyces johnsonii</i>	F0510	1.30	1.00	<i>Mageibacillus indolicus</i>	S7-24-11	1.50	1.20
<i>Actinomyces massiliensis</i>	F0489	4.60	2.07	<i>Megasphaera micromuciformis</i>	DNF00954	3.30	1.85
<i>Actinomyces neuii</i>	MJR8396A	2.27	2.13	<i>Microbacterium</i> sp.	F0373	0.07	0.22
<i>Actinomyces odontolyticus</i>	F0309	0.83	0.96	<i>Micrococcus luteus</i>	SK58	0.86	0.93
<i>Actinomyces</i> sp.	S6-Spd3	1.80	1.31	<i>Mobiluncus mulieris</i>	UPII 28-1	0.23	0.60
<i>Actinomyces</i> sp.	F0338	1.32	1.16	<i>Neisseria flavescens</i>	SK114	1.90	2.22
<i>Actinomyces urogenitalis</i>	S6-C4	0.59	0.65	<i>Neisseria mucosa</i>	C102	0.35	0.51
<i>Actinomyces viscosus</i>	C505	1.64	1.86	<i>Neisseria</i> sp.	F0314	0.63	0.70
<i>Aggregatibacter aphrophilus</i>	F0387	0.65	0.73	<i>Olsenella</i> sp.	DNF00959	1.36	1.09
<i>Akkermansia</i> sp.	KLE1605	0.39	0.53	<i>Olsenella uli</i>	MSTE5	1.75	1.31
<i>Alloscardovia omnicolens</i>	CMW7705A	2.42	3.43	<i>Oribacterium sinus</i>	F0268	0.31	0.44
<i>Anaerococcus hydrogenalis</i>	MJR7738A	0.59	0.57	<i>Oscillibacter</i> sp.	KLE 1728	0.85	0.80
<i>Anaerococcus lactolyticus</i>	CC31C	0.17	0.53	<i>Oxalobacter formigenes</i>	OxCC13	0.21	0.45
<i>Anaerostipes</i> sp.	3_2_56t-AA	5.84	1.94	<i>Paenibacillus barengoltzii</i>	CC33_002B	0.15	0.55
<i>Arcobacter butzleri</i>	JV22	1.98	2.03	<i>Paenisporsarcina</i> sp.	HGH0030	0.47	0.97
<i>Arthrobacter albus</i>	DNF00011	1.20	2.11	<i>Parabacteroides goldsteinii</i>	CC87F	6.77	4.29
<i>Atopobium parvulum</i>	CC14Z	1.66	1.57	<i>Parabacteroides merdae</i>	CL09T00C40	1.10	1.10

<i>Atopobium parvulum</i>	DNF00906	0.19	0.29		<i>Parvimonas micra</i>	CC57A	0.54	0.70
<i>Atopobium</i> sp.	F0494	2.54	1.74		<i>Parvimonas</i> sp.	KA00067	0.86	0.95
<i>Bacteroides caccae</i>	CL03T12C61	0.89	0.86		<i>Parvimonas</i> sp.	F0139	0.27	0.52
<i>Bacteroides cellulosilyticus</i>	CL02T12C19	1.53	1.22		<i>Peptoniphilus lacrimalis</i>	DNF00528	0.21	0.54
<i>Bacteroides dorei</i>	CL02T00C15	28.27	4.35		<i>Peptoniphilus</i> sp.	BV3AC2	0.97	0.97
<i>Bacteroides eggerthii</i>	1_2_48FAA	0.97	1.03		<i>Peptoniphilus</i> sp.	F0141	0.16	0.51
<i>Bacteroides finegoldii</i>	CL09T03C10	3.38	4.35		<i>Peptostreptococcaceae</i> <i>bacterium</i>	ACC19a	0.98	1.00
<i>Bacteroides fragilis</i>	3_1_12	63.50	4.35		<i>Peptostreptococcus</i> sp.	CC14N	0.11	0.53
<i>Bacteroides fragilis</i>	CL07T00C01	61.59	4.35		<i>Phascolarctobacterium</i> sp.	3_1_syn4	1.25	1.68
<i>Bacteroides ovatus</i>	3_8_47FAA	1.59	1.41		<i>Plesiomonas</i> sp.	HP00020	0.31	0.83
<i>Bacteroides salyersiae</i>	CL02T12C01	0.49	0.80		<i>Porphyromonas gingivalis</i>	F0568	0.08	0.26
<i>Bacteroides</i> sp.	2_1_22	0.34	0.58		<i>Porphyromonas gingivalis</i>	F0570	0.36	0.57
<i>Bacteroides stercoris</i>	CC31F	0.31	0.73		<i>Porphyromonas</i> sp.	W7784	1.24	1.33
<i>Bacteroides vulgatus</i>	CL09T03C04	0.49	0.79		<i>Porphyromonas</i> sp.	KLE1280	0.42	0.54
<i>Bacteroidetes</i>	F0058	0.19	0.38		<i>Porphyromonas uenonis</i>	UPII 60-3	0.90	0.83
<i>Bifidobacterium adolescentis</i>	L2-32	0.88	1.28		<i>Prevotella amnii</i>	CRIS 21A-A	0.77	0.63
<i>Bifidobacterium angulatum</i>	F16_22	0.73	0.72		<i>Prevotella bivia</i>	DNF00650	0.93	0.92
<i>Bifidobacterium breve</i>	HPH0326	2.81	3.84		<i>Prevotella bivia</i>	GED7880	0.83	0.44
<i>Bifidobacterium longum</i>	1-6B	0.47	0.92		<i>Prevotella bivia</i>	GED7760C	0.49	0.70
<i>Bifidobacterium</i> sp.	12_1_47BFAA	1.20	2.17		<i>Prevotella buccae</i>	DI7	0.87	0.61
<i>Campylobacter coli</i>	JV20	0.68	0.95		<i>Prevotella corporis</i>	MJR7716	0.69	0.49
<i>Campylobacter upsaliensis</i>	JV21	0.35	0.95		<i>Prevotella denticola</i>	DNF00960	0.68	0.43
<i>Capnocytophaga ochracea</i>	F0287	0.30	0.46		<i>Prevotella denticola</i>	F0289	0.10	0.54
<i>Capnocytophaga</i> sp.	F0502	0.56	0.75		<i>Prevotella disiens</i>	DNF00882	0.28	0.48
<i>Capnocytophaga sputigena</i>	CC21_001D	1.60	1.26		<i>Prevotella hisitcola</i>	F0411	0.64	0.57
<i>Cardiobacterium valvarum</i>	F0432	0.78	1.08		<i>Prevotella melaninogenica</i>	DI8	0.51	0.60
<i>Catabacter hongkongensis</i>	AB8_9	0.07	0.33		<i>Prevotella nigrescens</i>	F0103	1.33	1.44
<i>Citrobacter portucalensis</i>	4_7_47CFAA	3.09	3.74		<i>Prevotella oralis</i>	CC98A	0.08	0.44
<i>Citrobacter</i> sp.	30_2	8.17	6.45		<i>Prevotella oralis</i>	HGA0225	0.09	0.41
<i>Clostridiales bacterium</i>	S5-A14a	2.16	1.94		<i>Prevotella oris</i>	F0302	0.25	0.36

<i>Clostridiales bacterium</i>	HP00074	2.94	3.10	<i>Prevotella</i> sp.	S7-1-8	1.72	1.17
<i>Clostridiales</i> sp.	S9 PR-1	1.48	1.19	<i>Prevotella</i> sp.	F0295	0.68	0.59
<i>Clostridium bolleae</i>	WAL-14578	1.06	1.01	<i>Prevotella</i> sp.	F0108	0.81	0.72
<i>Clostridium cadaveris</i>	CC40_001C	2.12	3.02	<i>Prevotella timonensis</i>	CRIS 5C-B1	1.20	1.01
<i>Clostridium cadaveris</i>	CC88A	0.65	0.84	<i>Prevotella veroralis</i>	F0319	0.31	0.56
<i>Clostridium citroniae</i>	WAL-17108	0.48	0.74	<i>Propionibacterium acidifaciens</i>	F0233	0.72	1.22
<i>Clostridium clostridioforme</i>	2_1_49FAA	0.36	0.48	<i>Propionibacterium acnes</i>	HL002PA3	2.07	1.60
<i>Clostridium difficile</i>	70-100-2010	5.06	3.98	<i>Propionibacterium propionicum</i>	F0230	2.66	1.84
<i>Clostridium difficile</i>	002-P50-2011	0.91	1.03	<i>Propionibacterium</i> sp.	F0372	6.30	2.11
<i>Clostridium difficile</i>	NAP07	0.85	1.26	<i>Pseudomonas</i> sp.	HPB0071	8.56	4.49
<i>Clostridium innocuum</i>	6_1_30	1.24	1.11	<i>Psychrobacter</i> sp.	1501	2.19	1.85
<i>Clostridium orbiscindens</i>	CC43_001K	0.53	0.74	<i>Ralstonia</i> sp.	5_2_56FAA	15.33	6.45
<i>Clostridium orbiscindens</i>	1_3_50FAA	0.63	0.60	<i>Rhodococcus erythropolis</i>	SK121	1.16	1.14
<i>Clostridium</i> sp.	HGF2	2.41	1.68	<i>Rothia aeria</i>	F0474	0.75	0.73
<i>Clostridium</i> sp.	7_2_43FAA	0.63	0.82	<i>Rothia dentocariosa</i>	M567	0.69	0.85
<i>Clostridium symbiosum</i>	WAL-14163	2.31	1.67	<i>Rothia mucilaginosa</i>	CC87LB	2.03	1.74
<i>Collinsella</i> sp.	4_8_47FAA	0.13	0.28	<i>Ruminococcaceae</i> sp.	D16	2.19	1.76
<i>Coprobacillus</i> sp.	D6 (29_1)	2.10	1.54	<i>Ruminococcus gnavus</i>	CC55_001C	0.88	0.85
<i>Coprococcus</i> sp.	HP00048	0.33	0.65	<i>Ruminococcus lactaris</i>	CC59_002D	0.15	0.53
<i>Corynebacterium amycolatum</i>	SK46	1.21	1.41	<i>Scardovia wiggisiae</i>	F0424	0.12	0.67
<i>Corynebacterium</i> sp.	CMW7794	0.13	0.62	<i>Selenomonas noxia</i>	F0398	0.64	0.68
<i>Corynebacterium</i> sp.	HFH0082	0.27	0.61	<i>Selenomonas</i> sp.	F0430	1.48	1.27
<i>Corynebacterium tuscaniense</i>	DNF00037	0.67	1.43	<i>Shigella</i> sp.	D9	0.88	1.00
<i>Deinococcus grandis</i>	SK125	1.62	1.46	<i>Shuttleworthia</i> sp.	MSX8B	0.24	0.42
<i>Dermabacter</i> sp.	HFH0086	2.26	1.66	<i>Sneathia amnii</i>	Sn35	0.09	0.38
<i>Dorea formicigenerans</i>	4_6_53FAA	0.26	0.65	<i>Solobacterium moorei</i>	CC14Y	1.19	1.09
<i>Eggerthella</i> sp.	MVA1	0.97	1.01	<i>Solobacterium moorei</i>	CC57E	0.60	0.90
<i>Enterococcus faecalis</i>	TX2137	2.16	3.18	<i>Sporosarcina</i> sp.	2681	0.30	0.59
<i>Enterococcus faecium</i>	ERV102	0.08	0.57	<i>Staphylococcus aureus</i>	MRSA131	0.26	0.80

<i>Erysipelotrichaceae</i> sp.	6_1_45	2.05	1.51	<i>Staphylococcus capitis</i>	SK14	0.08	0.35
<i>Escherichia coli</i>	MS 124-1	6.00	4.68	<i>Staphylococcus caprae</i>	M23864.W1	0.19	0.48
<i>Escherichia coli</i>	MS 145-7	2.11	3.23	<i>Staphylococcus epidermidis</i>	BCM0060	0.24	0.36
<i>Escherichia</i> sp.	3_2_53FAA	2.02	3.39	<i>Staphylococcus haemolyticus</i>	DNF00585	1.69	1.53
<i>Eubacterium infernum</i>	F0142	0.17	0.63	<i>Staphylococcus hominis</i>	SK119	1.27	2.00
<i>Eubacterium</i> sp.	AS15	0.48	0.68	<i>Staphylococcus lugdunensis</i>	M23590	0.31	0.64
<i>Facklamia</i> sp.	HFG4	1.58	1.41	<i>Staphylococcus warneri</i>	SK66	0.27	0.41
<i>Faecalibacterium prausnitzii</i>	KLE1255	2.14	1.76	<i>Stomatobaculum longum</i>	ACC2	1.10	1.05
<i>Fingoldia magna</i>	GED7760A	1.34	1.02	<i>Streptococcus anginosus</i>	F0211	1.21	1.75
<i>Fusobacterium gonidiaformans</i>	CMW8396	2.34	1.59	<i>Streptococcus cristatus</i>	F0329	1.40	2.18
<i>Fusobacterium nucleatum</i>	D11	0.70	0.90	<i>Streptococcus downei</i>	F0415	3.71	3.90
<i>Fusobacterium nucleatum</i>	F0401	0.08	0.45	<i>Streptococcus gallolyticus</i>	TX20005	0.98	0.97
<i>Fusobacterium</i> sp.	CM21	1.36	1.08	<i>Streptococcus intermedius</i>	F0413	0.45	0.84
<i>Fusobacterium ulcerans</i>	12_1B	0.18	0.63	<i>Streptococcus mitis</i>	F0392	0.15	0.52
<i>Gardnerella vaginalis</i>	JCP7275	0.70	0.83	<i>Streptococcus parasanguinis</i>	CC87K	2.69	2.18
<i>Gemella asaccharolytica</i>	KA00071	1.30	1.33	<i>Streptococcus pneumoniae</i>	TCH843	1.28	1.04
<i>Gemella haemolysans</i>	M341	0.90	0.64	<i>Streptococcus salivarius</i>	SK126	0.75	0.82
<i>Gemella morbillorum</i>	M424	2.70	3.19	<i>Streptococcus sobrinus</i>	W1703	1.87	1.22
<i>Gemella sanguinis</i>	M325	2.03	2.27	<i>Streptococcus</i> sp.	CM7	0.23	0.50
<i>Granulicatella adiacens</i>	CC94D	2.00	1.53	<i>Streptococcus vestibularis</i>	F0396	0.36	0.41
<i>Helicobacter pullorum</i>	MIT 98-5489	0.30	0.69	<i>Sutterella wadsworthensis</i>	HGA0223	1.60	0.18
<i>Helicobacter pylori</i>	83	0.24	0.60	<i>Tissierella bacterium</i>	S5-A11	2.34	1.52
<i>Hungateella hathewayi</i>	WAL-18680	0.34	0.53	<i>Treponema denticola</i>	SP37	5.10	2.25
<i>Klebsiella oxytoca</i>	MIT 10-5243	1.15	2.00	<i>Treponema denticola</i>	AL-2	3.65	3.76
<i>Klebsiella pneumoniae</i>	WGLW2	4.65	3.73	<i>Varibaculum cambriense</i>	AB12_3	0.42	0.51
<i>Klebsiella</i> sp.	MS 92-3	2.53	3.69	<i>Veillonella atypica</i>	CMW7756B	0.27	0.44
<i>Klebsiella</i> sp.	1_1_55	2.85	3.32	<i>Veillonella montpellierensis</i>	DNF00314	1.62	1.14
<i>Lachnoanaerobaculum</i> sp.	OBRC5-5	1.40	1.22	<i>Veillonella</i> sp.	ACP1	0.66	0.70
<i>Lactobacillus oris</i>	F0423	1.40	1.13	<i>Weissella cibaria</i>	F16_1	0.93	0.95
<i>Lactobacillus crispatus</i>	EX849587VC07	1.27	1.02				

Claims:

1. A composition for use in treating a protein conformational disease (PCD) in a subject, the composition comprising:
 - (a) *Prevotella corporis*;
 - (b) a composition containing *Prevotella corporis*;
 - (c) a composition comprises killed *Prevotella corporis* bacteria;
 - (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof;
 - (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or
 - (f) combinations of two or more of (a)-(e).
2. The composition of claim 1, wherein the *Prevotella corporis* or the composition containing *Prevotella corporis* comprises, a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, or a granular powder.
3. The composition of claim 1, wherein the composition comprising the killed *Prevotella corporis* bacteria, composition comprising the *Prevotella corporis* lysate or an extract or a fraction thereof, or the composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject, comprises a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, or a nutraceutical, or a supplement.
4. The composition of any one of claims 1-3, wherein the composition comprises a pharmaceutical composition.
5. The composition of claim 4, wherein the pharmaceutical composition comprises an excipient and/or one or more additional active ingredients.
6. The composition of claim 5, wherein the one or more additional active ingredients comprises a second composition that decreases the abundance or inhibits the growth of a *Pseudomonas* species and/or a *Shigella* species in the gut of the subject.

7. The composition of claim 6, wherein the second composition comprises one or more bacteriophages.
8. A composition for use in treating a PCD in a subject, the composition comprising: a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject and/or specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject.
9. The method of claim 8, wherein the composition comprises at least one bacteriophage.
10. The composition of claim 8 or 9, wherein the composition comprises a liquid, a suspension, a solid dosage form, a pill, a capsule, a tablet, a granular powder, a food additive, a food composition, or a nutraceutical, or a supplement.
11. The composition of claim 10, wherein the composition comprises a pharmaceutical composition.
12. The composition of claim 11, wherein the pharmaceutical composition comprises an excipient and/or one or more additional active ingredients.
13. The composition of claim 12, wherein the one or more additional active ingredients comprises: *Prevotella corporis*, a composition containing *Prevotella corporis*, a composition comprising killed *Prevotella corporis* bacteria, a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof, or a composition that increases abundance or supports growth of a *Prevotella corporis* in the gut of the subject.
14. The method of claim of any one of claims 1-13, wherein the PCD comprises a neurodegenerative disease.
15. The method of claim 14, wherein the neurodegenerative disease comprises Alzheimer's disease, Parkinson's disease, or Huntington's disease, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.
16. A method of treating a subject suffering from a PCD or at risk of developing a PCD, the method comprising: administering to the subject one or more of:

- (a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprises killed *Prevotella* species bacteria, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;
- (b) a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject; and
- (c) a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject.

17. The method of claim 16, wherein the method further comprises: monitoring the abundance of one or more of the *Prevotella* species, *Pseudomonas* species, and the *Shigella* species in the gut of the subject and

- (a) if the abundance of *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the killed *Prevotella* species bacteria, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; and/or

- (b) if the abundance of the *Pseudomonas* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject; and/or

- (c) if the abundance of the *Shigella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject.

18. The method of claim 16, wherein the method further comprises:

- (a) analyzing a sample of a microbiota from a gut or a stool sample from the subject to determine an amount of one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample;

- (b) comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample to a predetermined control; and

(i) if the amount of the *Prevotella* species in the gut of the subject is below a predetermined value, then administering to the subject the *Prevotella* species, the composition containing *Prevotella* species, the composition comprising the killed *Prevotella* species bacteria, the composition comprising the *Prevotella* species lysate or the extract or the fraction thereof, or the composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;

(ii) if the amount of the *Pseudomonas* species in the gut of subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Pseudomonas* species in the gut of the subject; and/or

(iii) if the amount of the *Shigella* species in the gut of the subject is above a predetermined value, then administering to the subject the composition that specifically decreases the abundance or inhibits the growth of the *Shigella* species in the gut of the subject.

19. The method of claim 18, wherein the sample is a microbial sample or a fecal sample.

20. The method of any one of claims 16-19, wherein monitoring the abundance or analyzing the sample comprises analyzing nucleic acid in the sample.

21. The method of any one of claims 16-20, wherein the *Prevotella* species is *Prevotella corporis*.

22. The method of any one of claims 16-21, wherein the *Pseudomonas* species is *Pseudomonas aeruginosa*, and/or the *Shigella* species is *Shigella flexneri*, *Shigella sonnei*, *Shigella dysenteriae*, or *Shigella boydii*.

23. The method of any one of claims 16-22, wherein subject is human.

24. The method of claim 23, wherein the PCD comprises a neurodegenerative disease.

25. The method of claim 24, wherein the neurodegenerative disease comprises Alzheimer's disease, Parkinson's disease, or Huntington's disease, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

26. The composition of claim 1 or 8, or the method of claim 16, wherein the treating comprising: reducing or ameliorating the severity of the disease, reducing or ameliorating the

severity of one or more symptoms associated with the disease, slowing progression of the disease, slowing progression of one or more symptoms associated with the disease, reducing severity of the disease, reducing severity of one or more symptoms of the disease, delaying onset of the disease, delaying onset of one or more symptoms associated with the disease, preventing the disease, preventing one or more symptoms associated with the disease, reduce the duration of a symptom associated with a disease, regressing the disease, regressing one or more symptoms associated with the disease, reducing recurrence of one or more symptom associated with the disease, or increasing or prolonging survival of a subject with a disease.

27. A method for determining a risk of developing a PCD or one or more symptoms of a PCD comprising:

- (a) analyzing a sample of a microbiota from a gut or a stool sample of a subject to determine an amount of one or more of a *Prevotella* species, a *Pseudomonas* species, and a *Shigella* species in the sample; and
- (b) comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, and the *Shigella* species in the sample to a predetermined control;

wherein an amount of the *Prevotella* species in the sample lower than the predetermined control, and/or an amount of *Pseudomonas* species and/or the *Shigella* species in the sample that is higher than the predetermined control, indicates the subject is at increased risk of developing the PCD.

28. The method of claim 27, wherein the PCD comprises a neurodegenerative disease.

29. The method of claim 28, wherein the neurodegenerative disease comprises Alzheimer's disease, Parkinson's disease, or Huntington's disease, multiple system atrophy, Lewy body dementia, Creutzfeldt–Jakob disease, prion disease, or amyloidosis.

30. A method of decreasing protein misfolding in a subject, the method comprising administering to the subject one or more of:

- (a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition containing killed *Prevotella* species bacteria, a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;

(b) a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject; and

(c) a composition that specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject.

31. A composition for use in treating a protein conformational disease (PCD) in a subject, the composition comprising:

(a) *Prevotella* species;

(b) a composition containing a *Prevotella* species;

(c) a composition containing killed *Prevotella* species bacteria;

(d) a composition comprising a *Prevotella* species lysate or an extract or a fraction thereof;

(e) a composition that increases abundance or supports growth of *Prevotella* species in the gut of the subject; or

(f) combinations of two or more of (a)-(e);

wherein the *Prevotella* species is *Prevotella amnii*, *Prevotella bivia*, *Prevotella buccae*, *Prevotella denticola*, *Prevotella disiens*, *Prevotella histicola*, *Prevotella melaninogencia*, *Prevotella nigrescens*, *Prevotella oralis*, *Prevotella oris*, *Prevotella timonensis*, or *Prevotella veroralis*.

32. A composition for use in treating a PCD in a subject, the composition comprising: a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject.

33. A method of treating a subject suffering from a PCD or at risk of developing a PCD, the method comprising: administering to the subject one or more of:

(a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition containing killed *Prevotella* species bacteria a composition comprising a lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject; and

(b) a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a

Ralstonia species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject.

34. The method of claim 33, wherein the composition comprises one or more lytic bacteriophage that infect one or more of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species.

35. A method for determining a risk of developing a PCD or one or more symptoms of a PCD comprising:

- (a) analyzing a sample of a microbiota from a gut or a stool sample of a subject to determine an amount of one or more of a *Prevotella* species, a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the sample; and
- (b) comparing the amount of the one or more of the *Prevotella* species, the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and the *Escherichia* species in the sample to a predetermined control;

wherein an amount of the *Prevotella* species in the sample lower than the predetermined control, and/or an amount of the *Pseudomonas* species, the *Shigella* species, the *Achromobacter* species, the *Ralstonia* species, the *Klebsiella* species, the *Arcobacter* species, the *Citrobacter* species, and/or the *Escherichia* species in the sample that is higher than the predetermined control, indicates the subject is at increased risk of developing the PCD.

36. A method of decreasing protein misfolding in a subject, the method comprising administering to the subject one or more of:

- (a) a *Prevotella* species, a composition containing the *Prevotella* species, a composition comprising lysate of the *Prevotella* species or an extract or a fraction thereof, or a composition that increases abundance or supports growth of the *Prevotella* species in the gut of the subject;
- (b) a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species a *Shigella* species, an *Achromobacter* species, a

Ralstonia species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject.

37. A method activating or inducing a heat shock response in a subject, the method comprising administering to the subject:

- (a) isolated *Prevotella corporis* bacteria;
- (b) a composition containing *Prevotella corporis* bacteria;
- (c) a composition comprising killed *Prevotella corporis* bacteria;
- (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof;
- (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or
- (f) combinations of two or more of (a)-(e). In some embodiments, the composition comprises a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises an excipient.

38. A method increasing expression of a heat shock protein, mucin-associated membrane protein 3, or mucin-associated membrane protein 4 in a subject, the method comprising administering to the subject:

- (a) isolated *Prevotella corporis* bacteria;
- (b) a composition containing *Prevotella corporis* bacteria;
- (c) a composition comprising killed *Prevotella corporis* bacteria;
- (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof;
- (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or
- (f) combinations of two or more of (a)-(e).

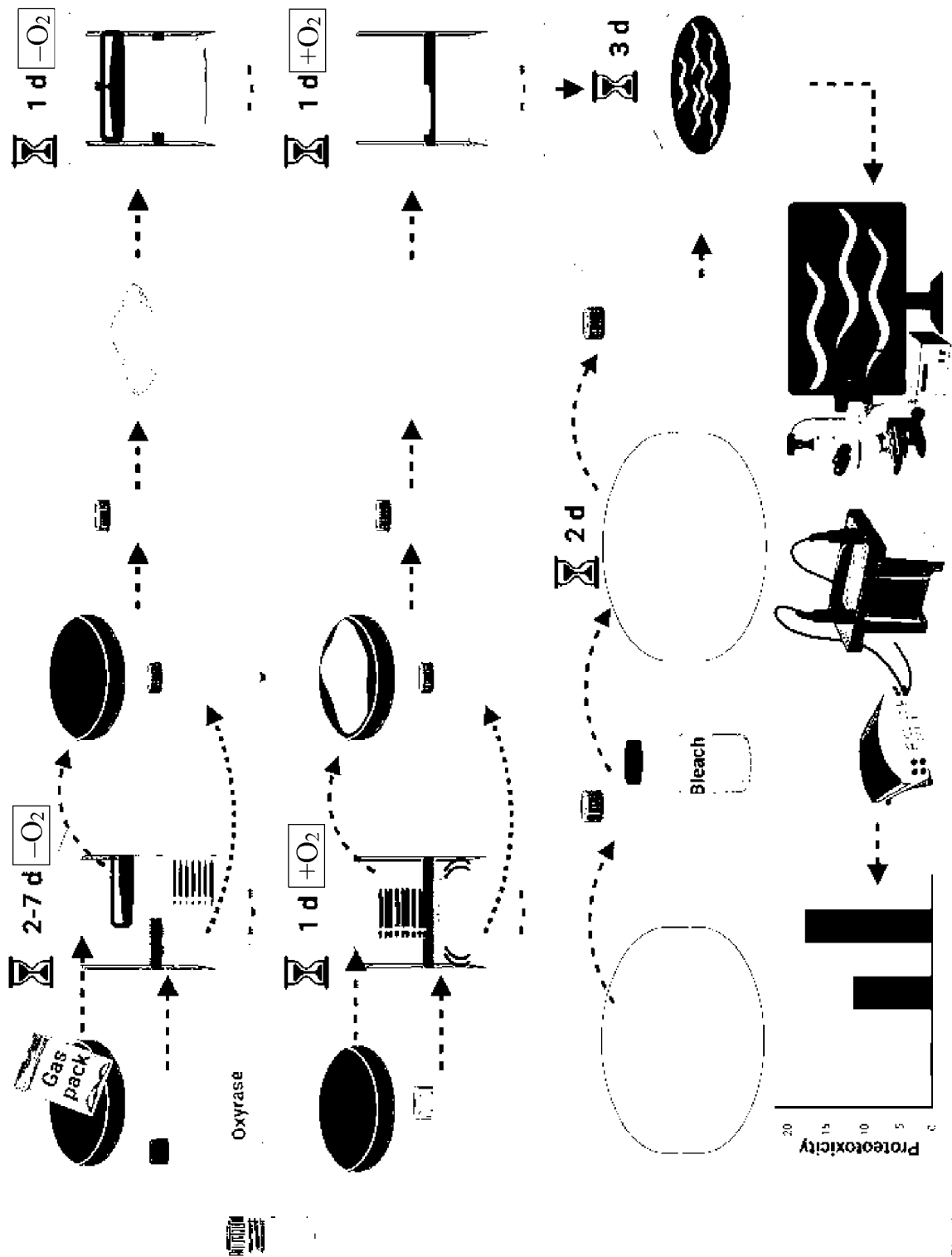


FIG. 1

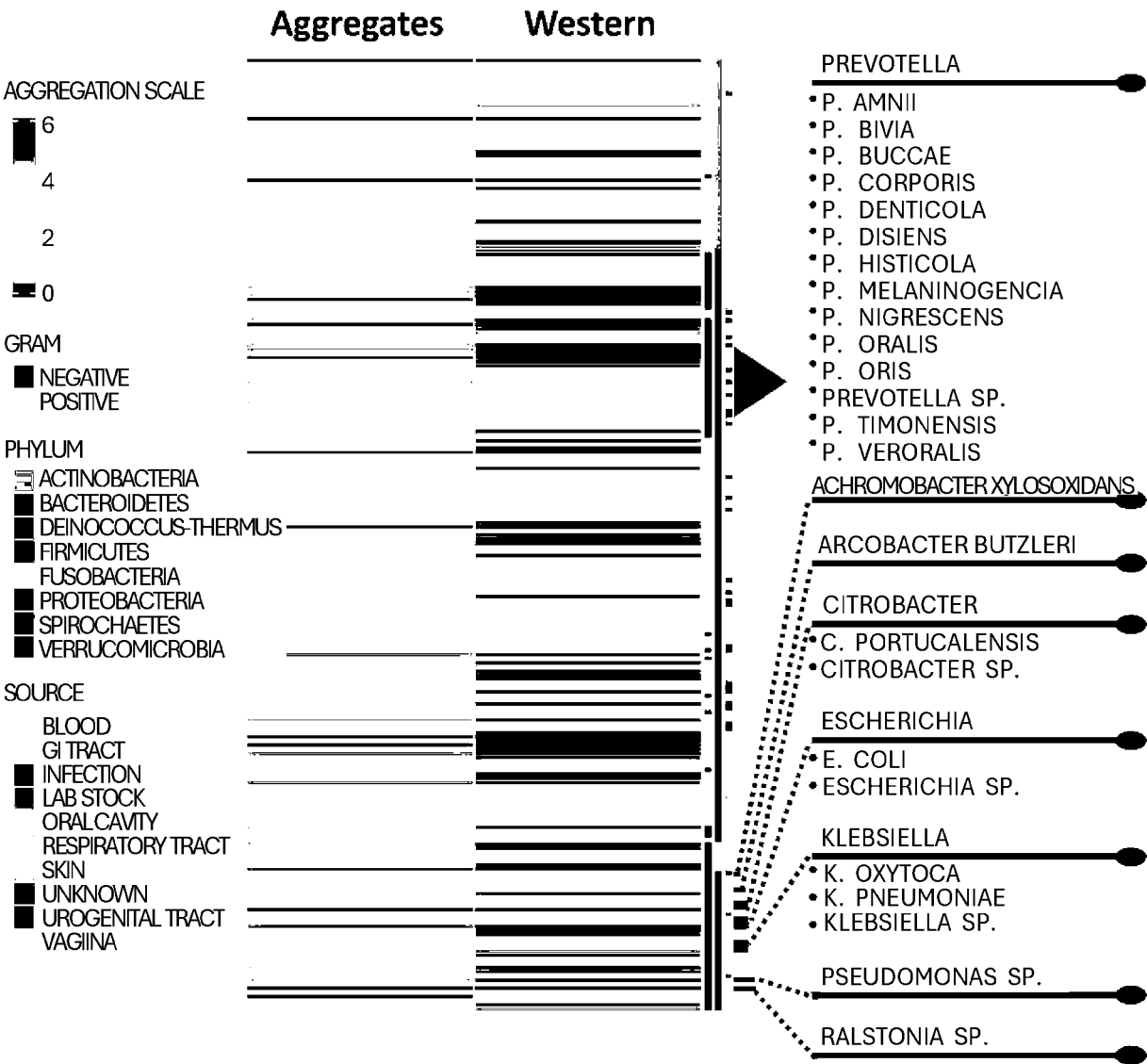


FIG. 2

FIG. 3

B Neuronal polyQ Motility

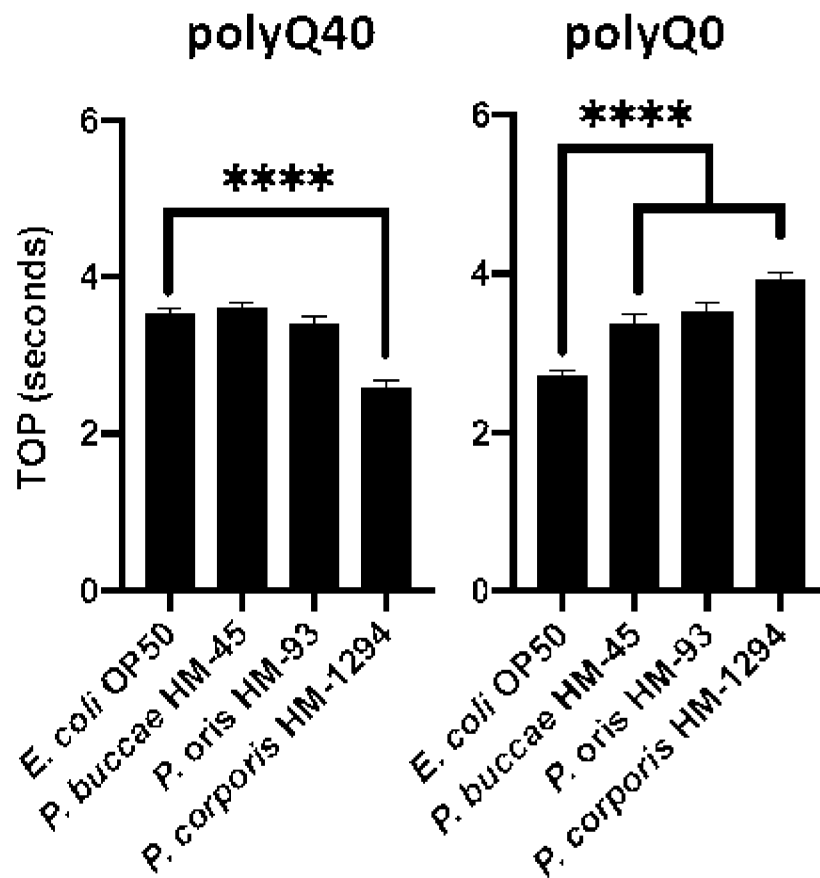


FIG. 3 Cont.

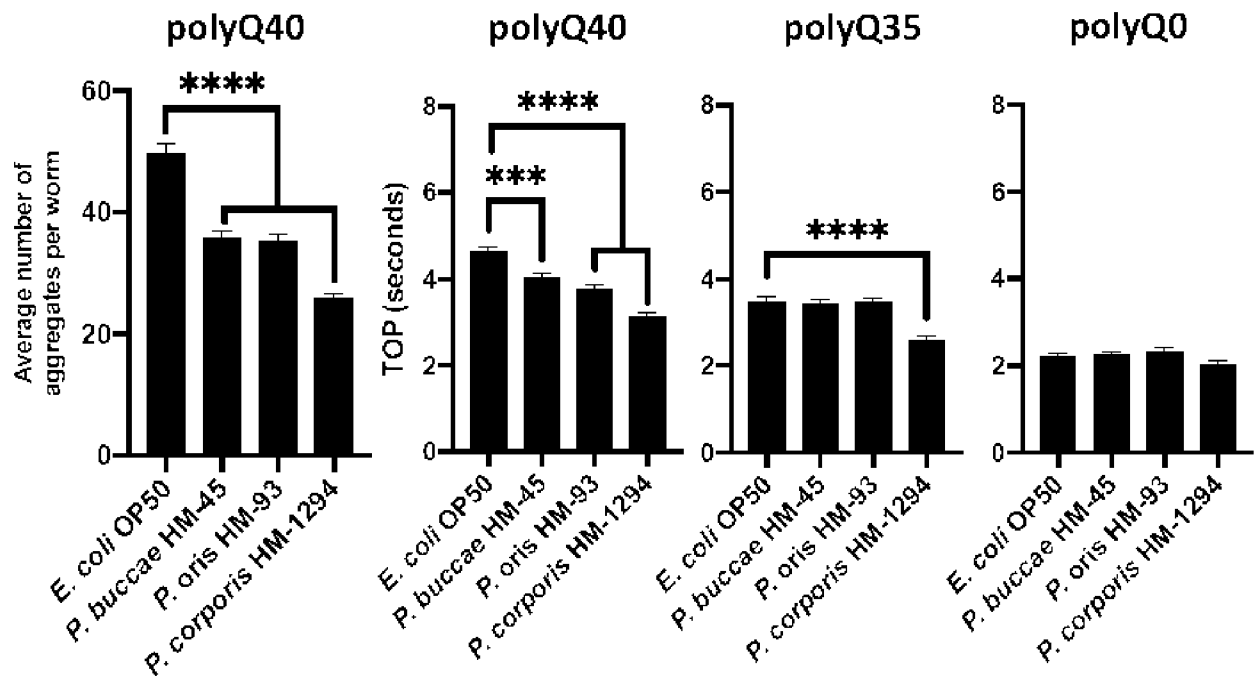
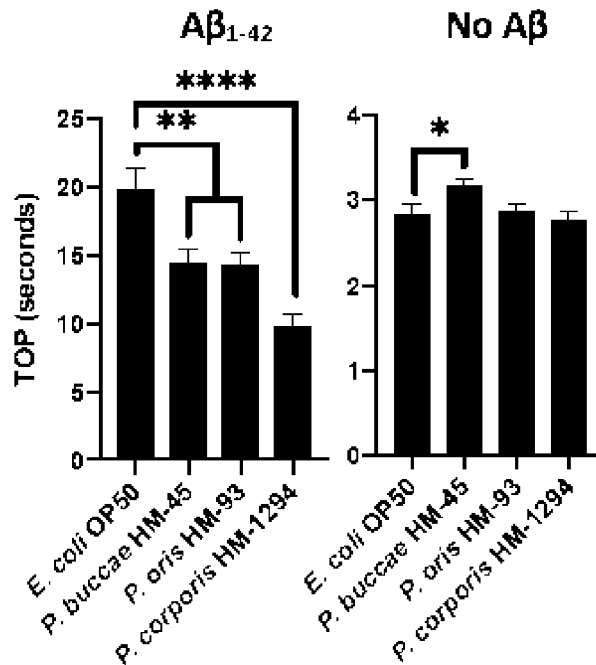
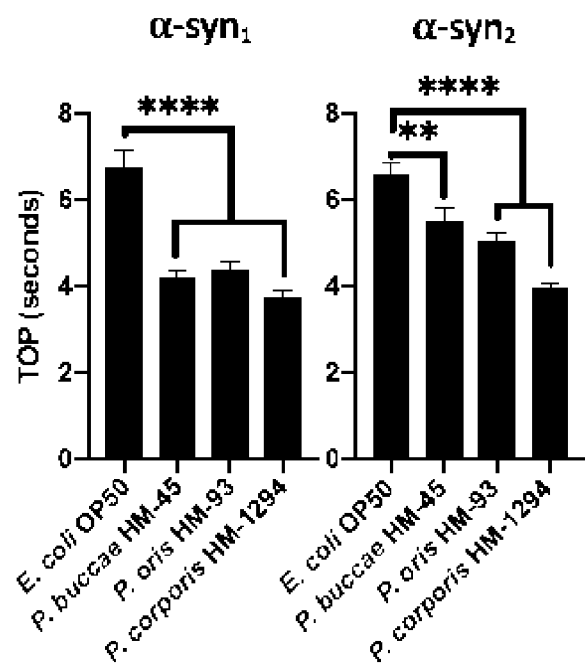
C**Muscle polyQ****Aggregates****Motility****D****Muscle A β** **Motility****E****Muscle α -synuclein****Motility**

FIG. 3 Cont.

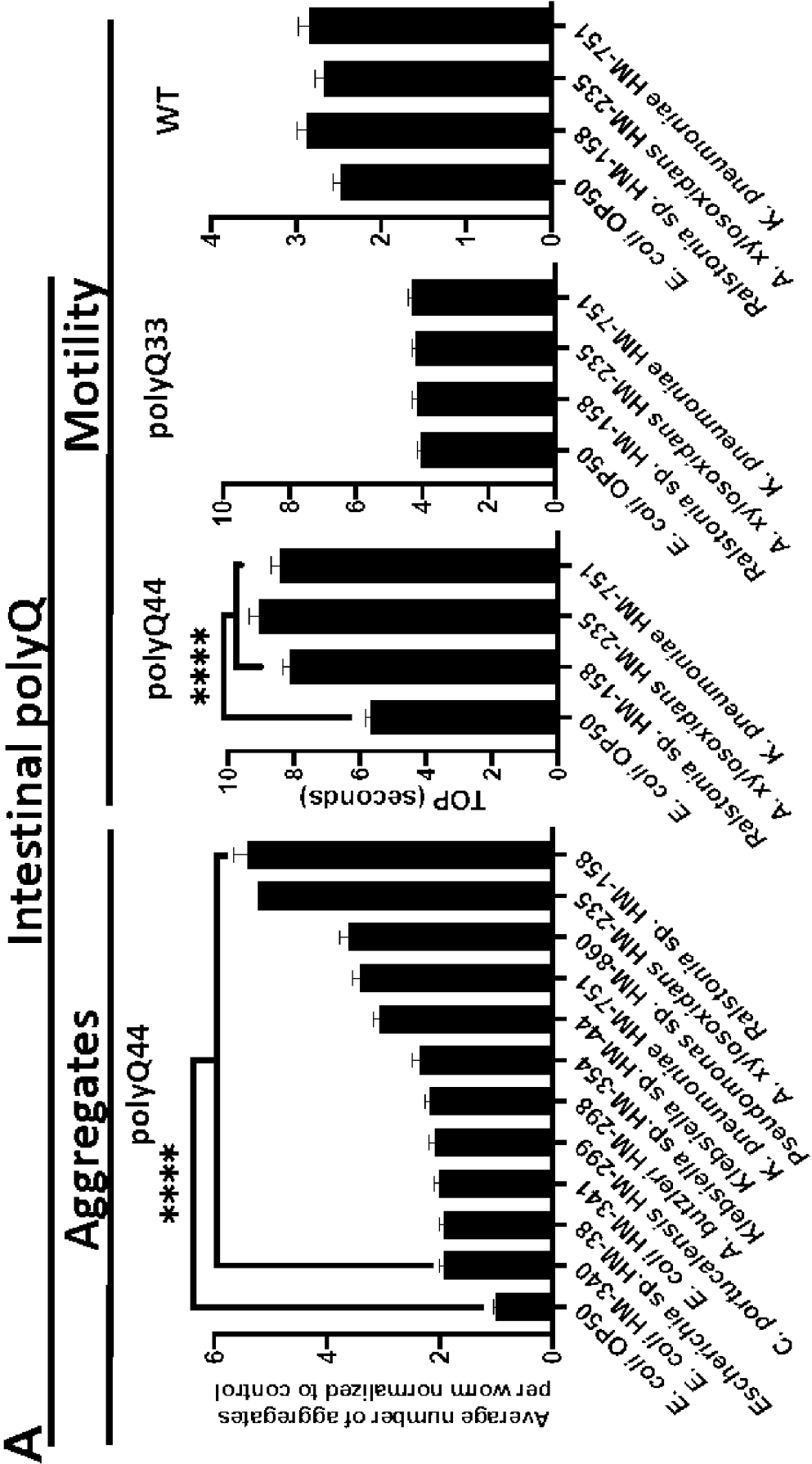


FIG. 4

B Neuronal polyQ Motility

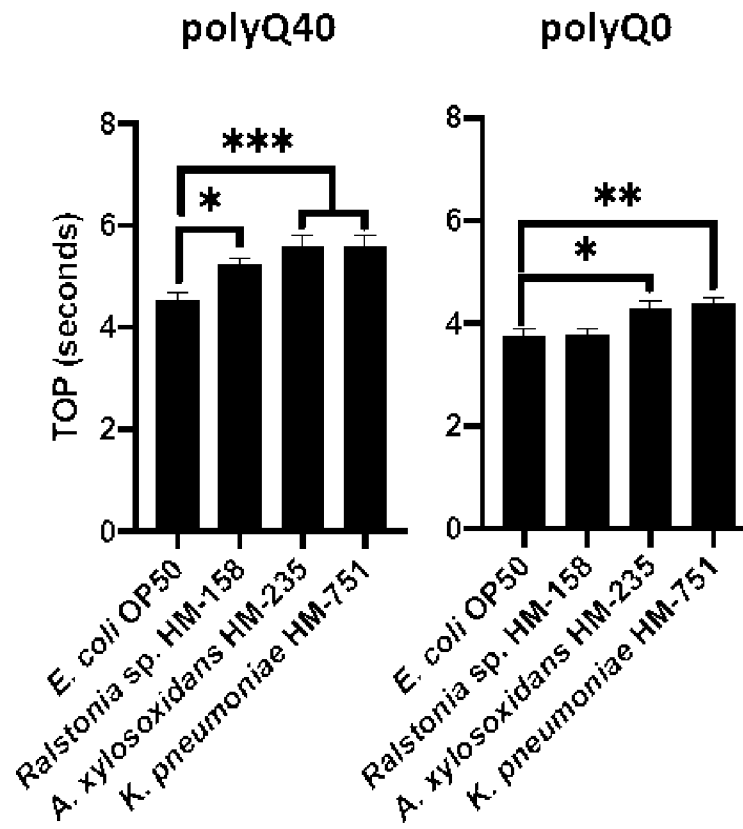


FIG. 4 Cont.

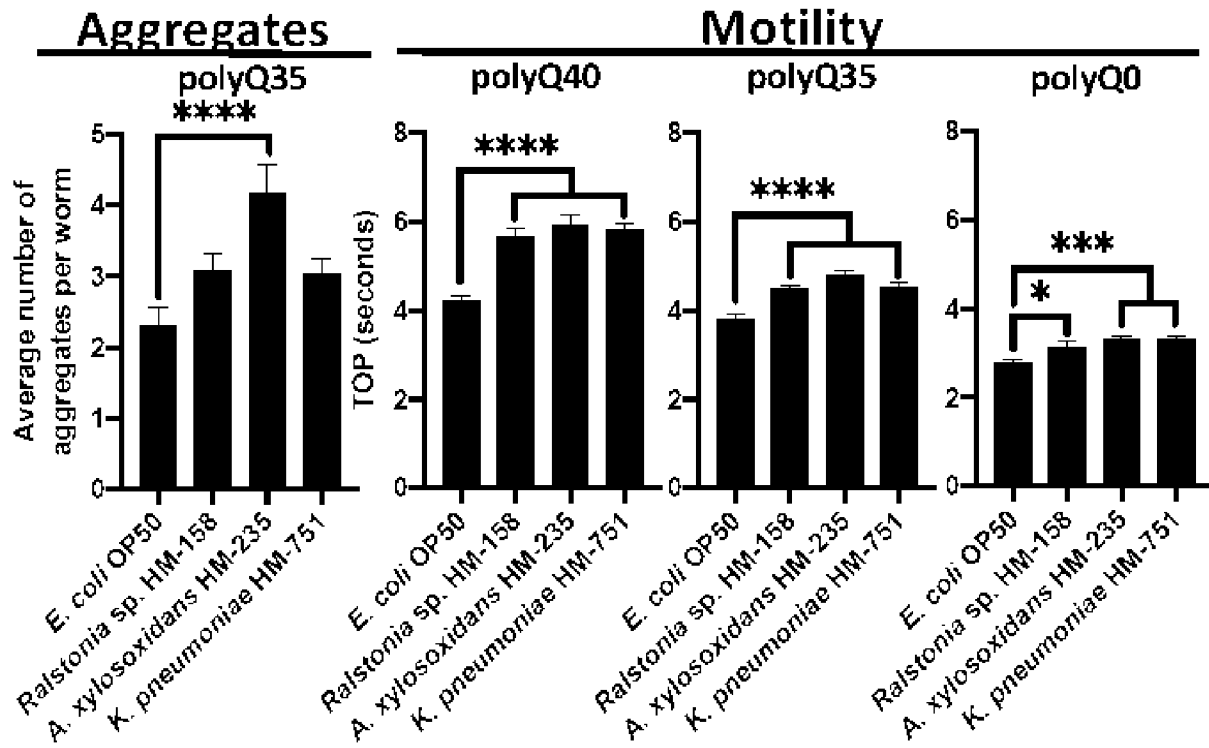
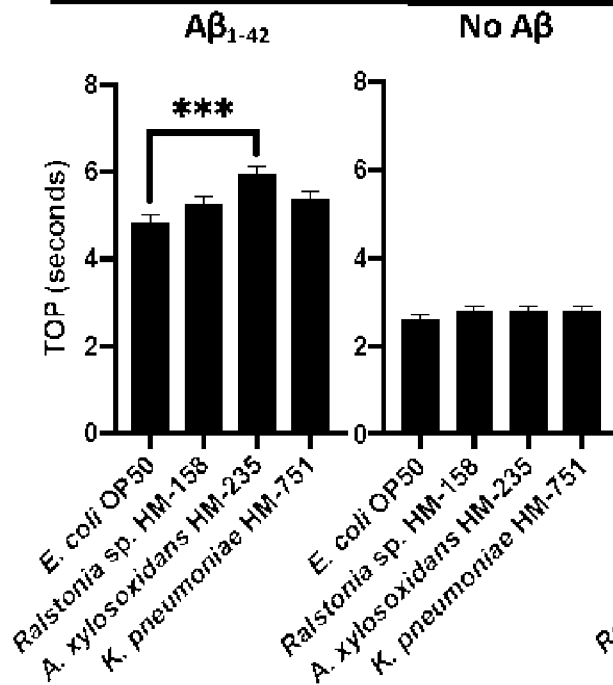
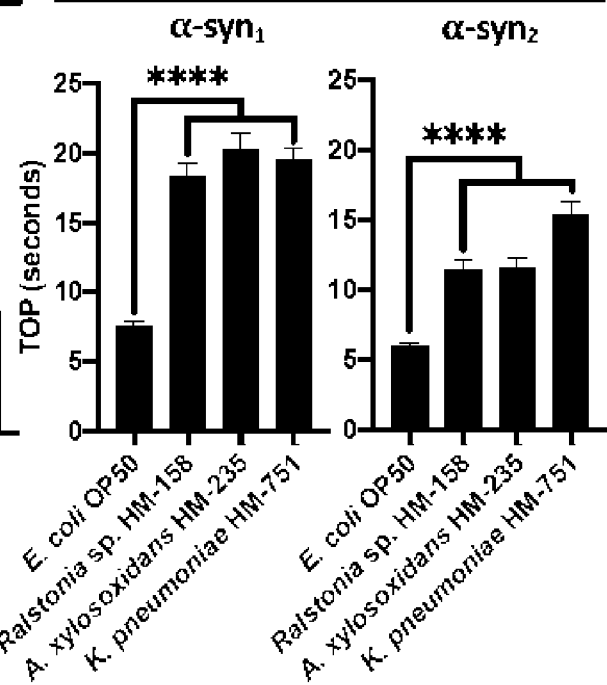
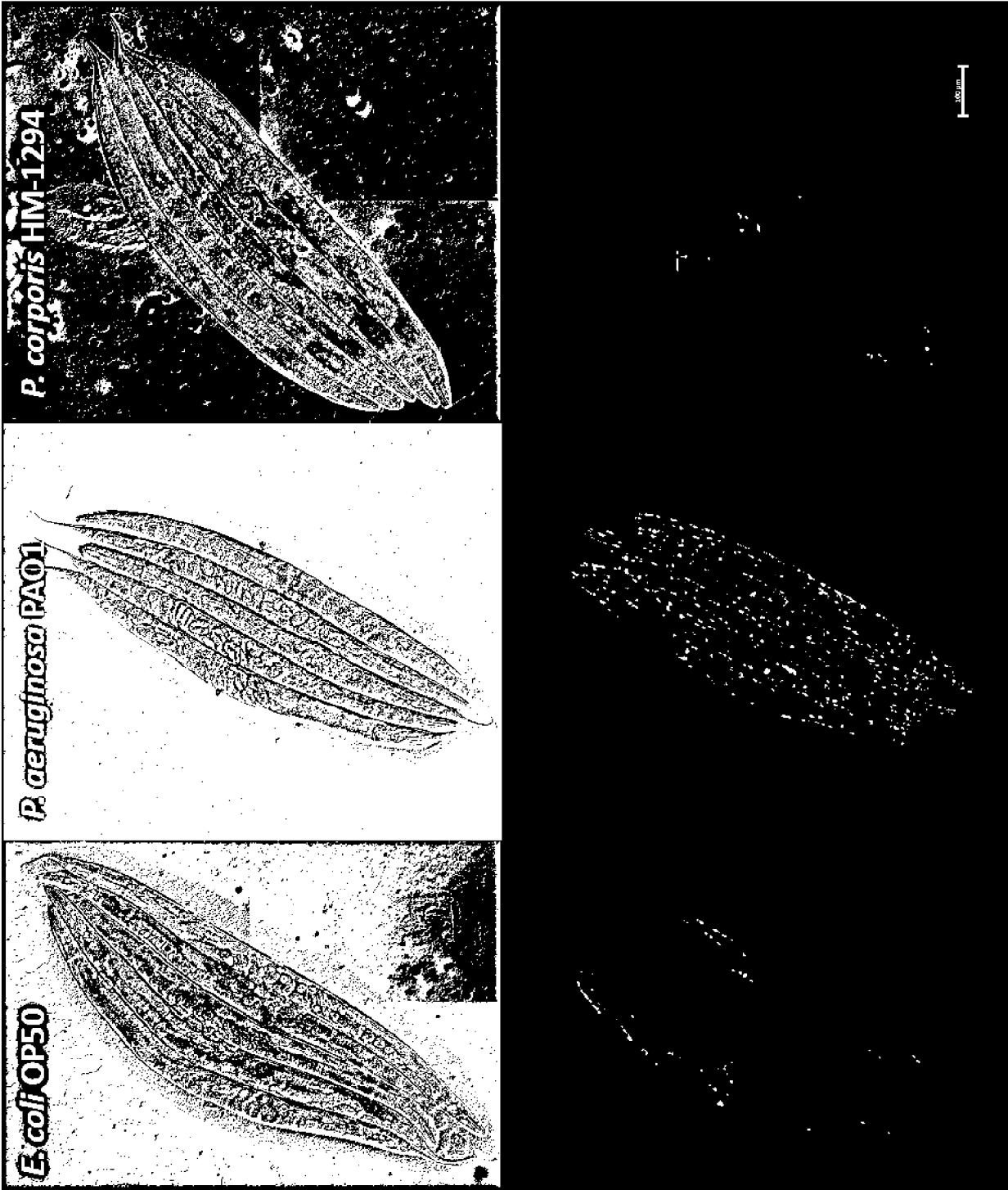
C**Muscle polyQ****D****Muscle A β** **Motility****E Muscle α -synuclein****Motility**

FIG. 4 Cont.



A

FIG. 5

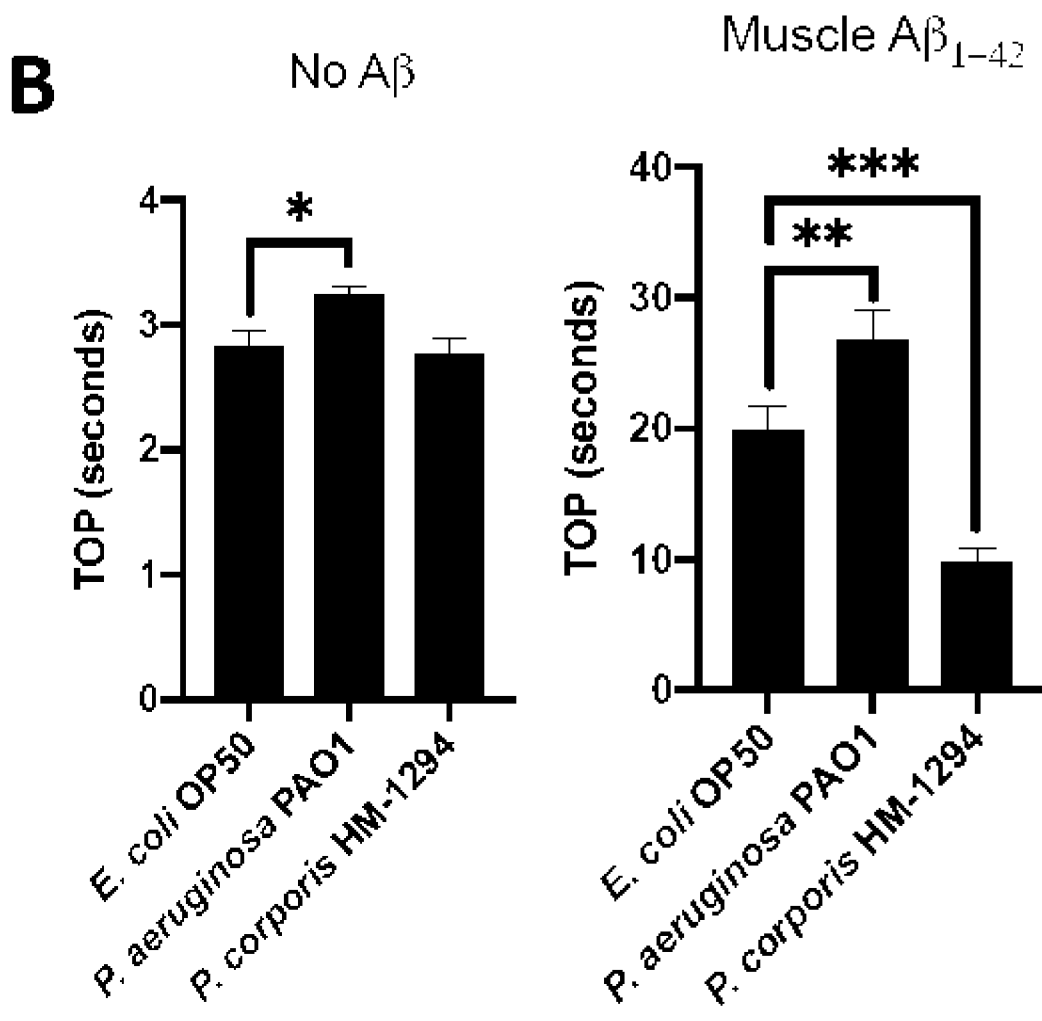


FIG. 5 Cont.

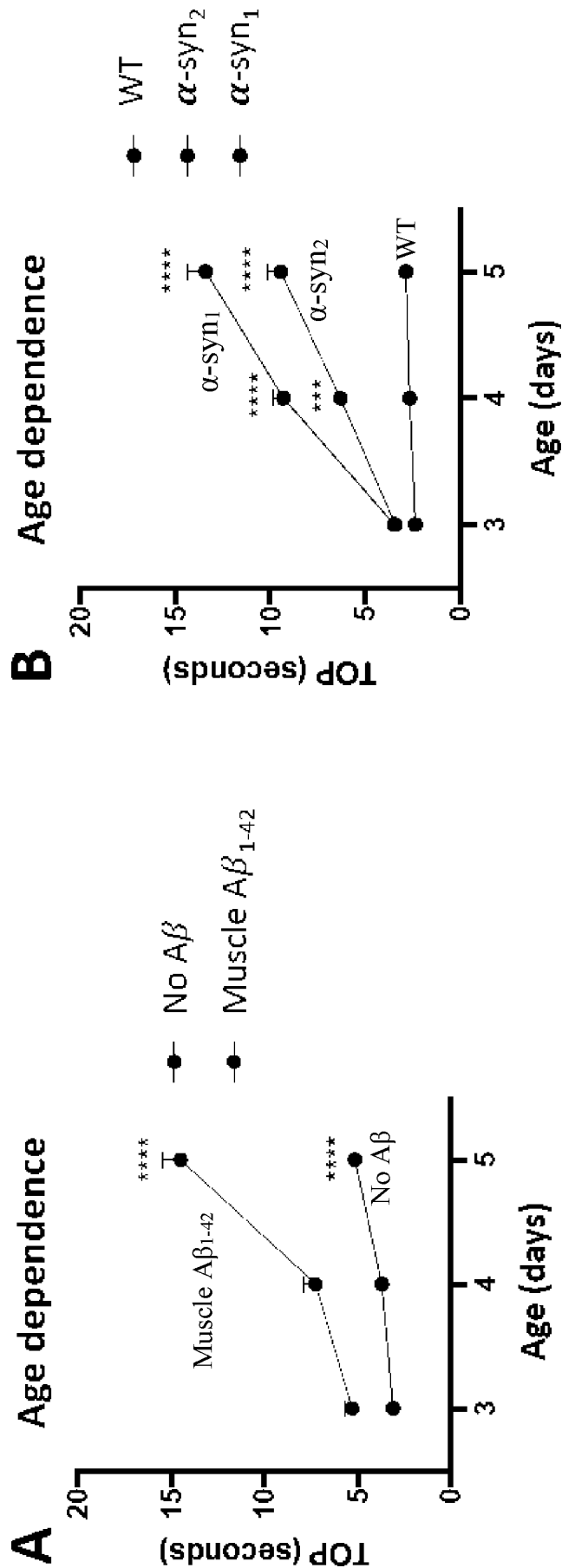


FIG. 6

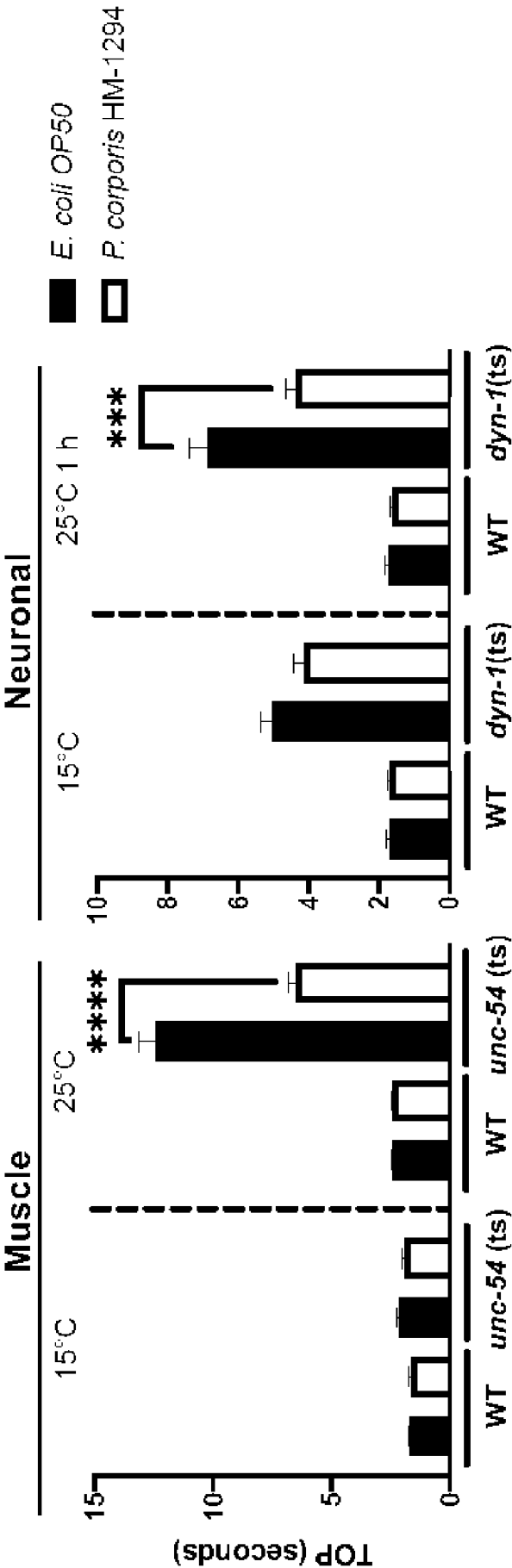


FIG. 7

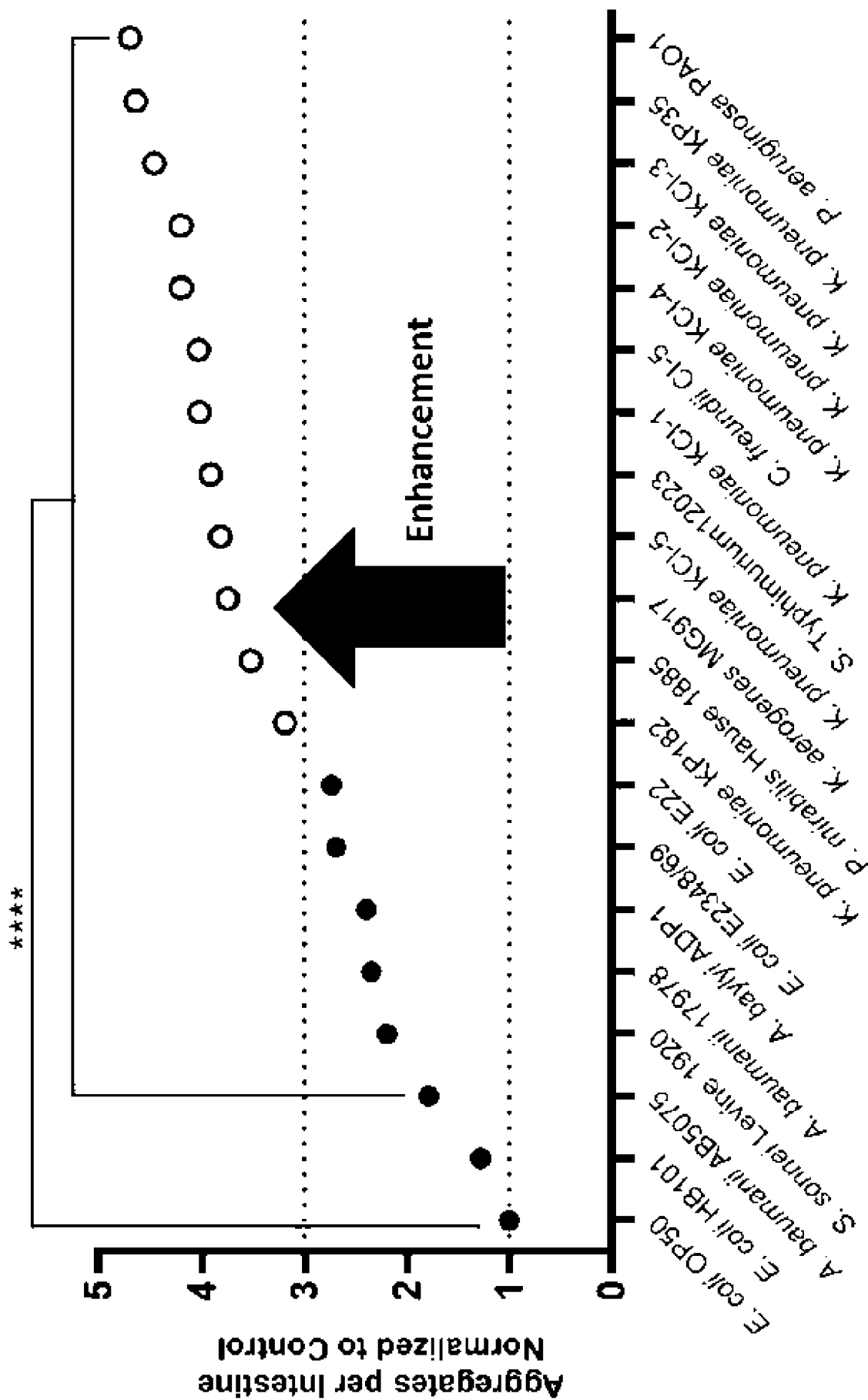


FIG. 8

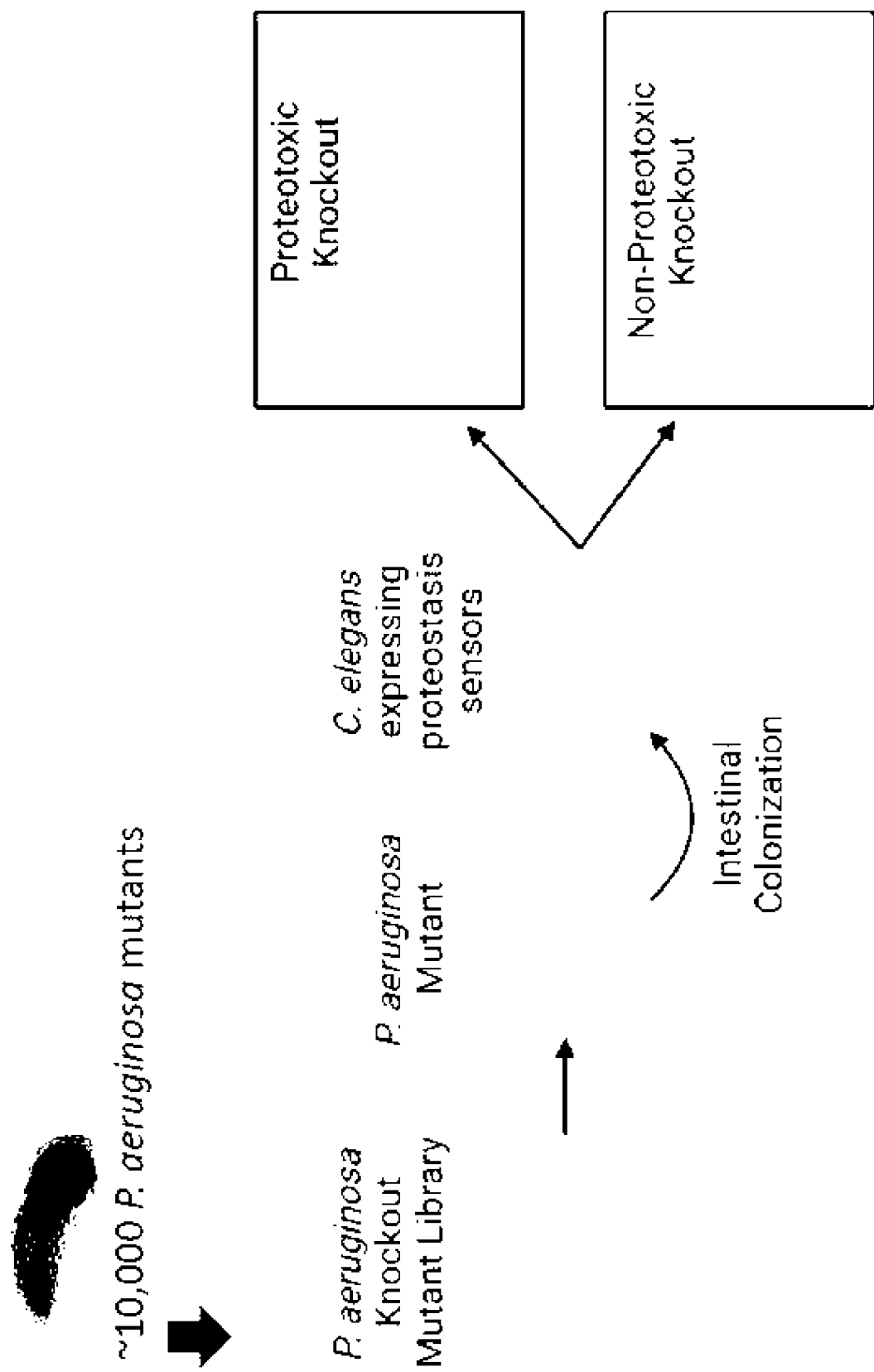


FIG. 9

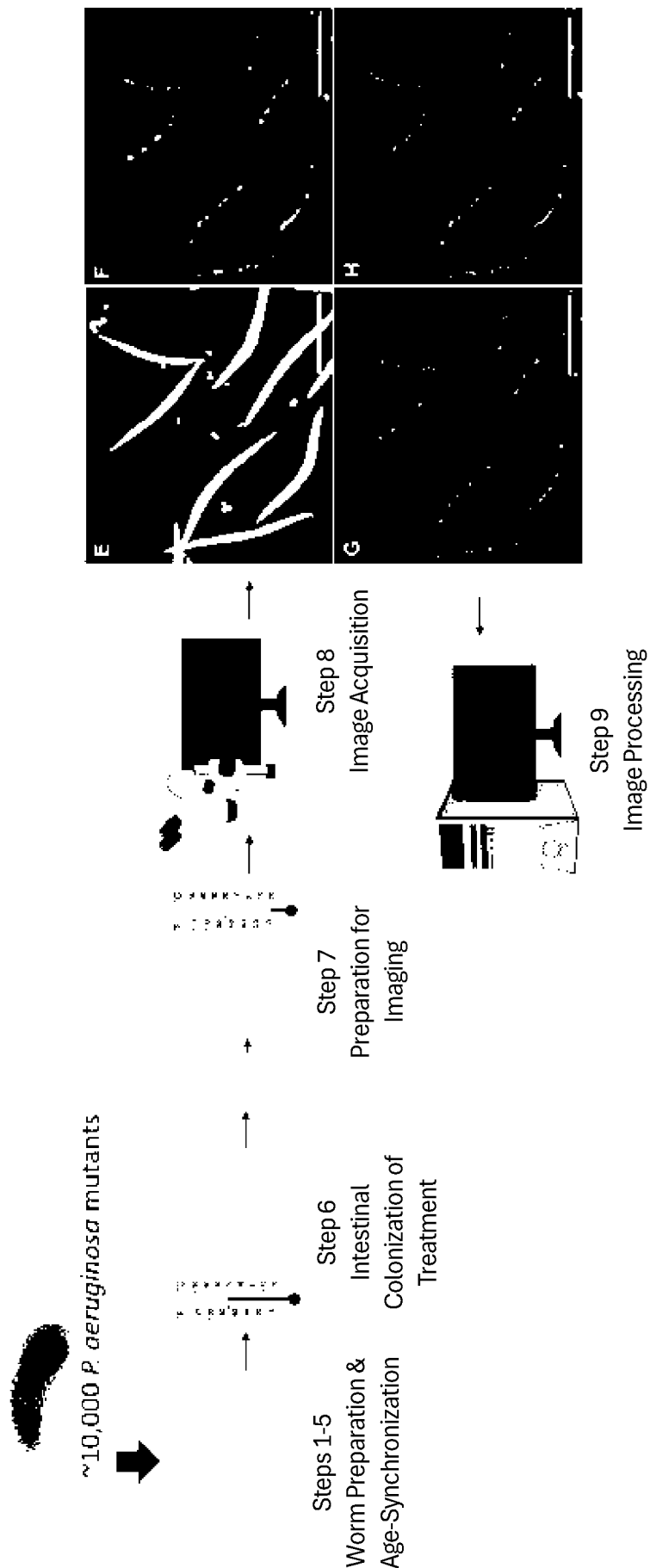


FIG. 9 Cont.

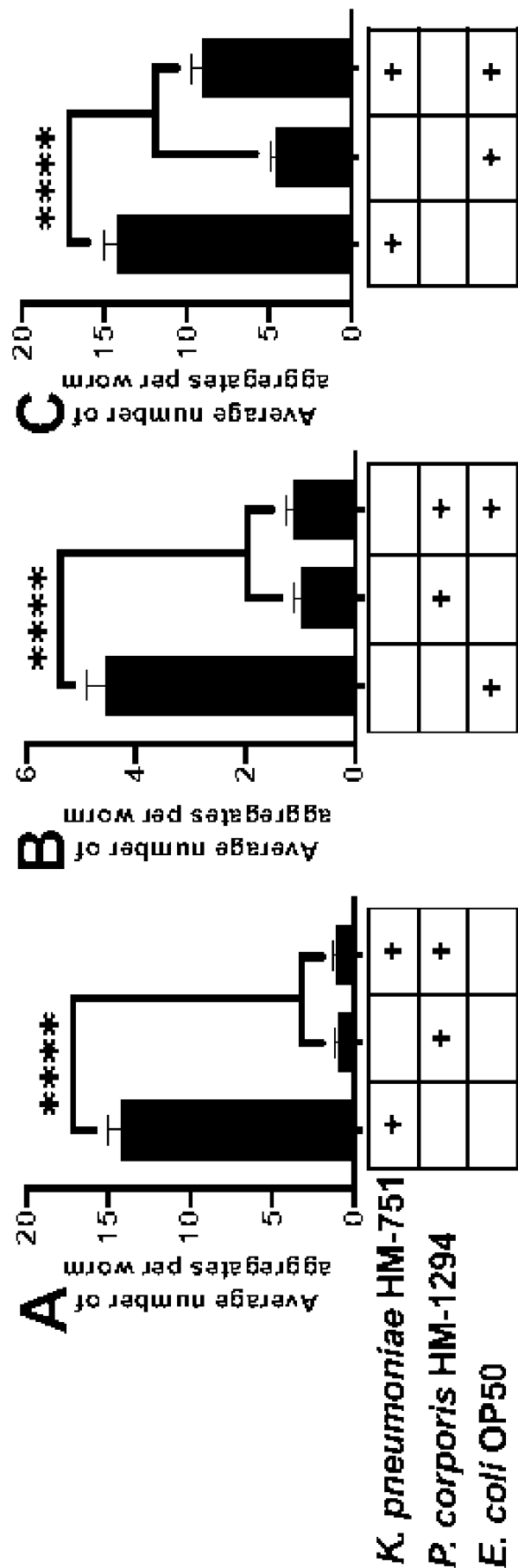


FIG. 10

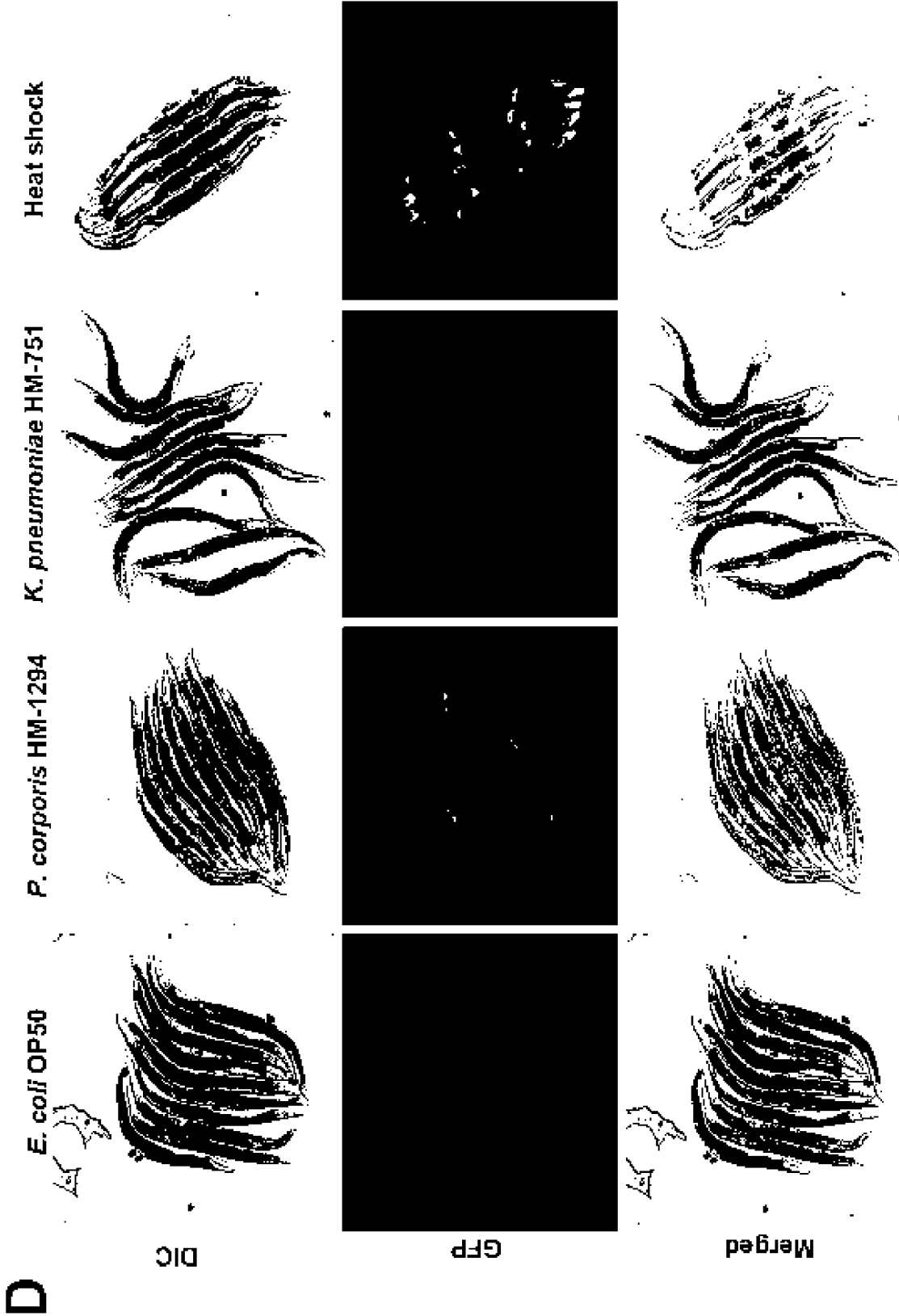


FIG. 10 Cont.

Pharyngeal pumping

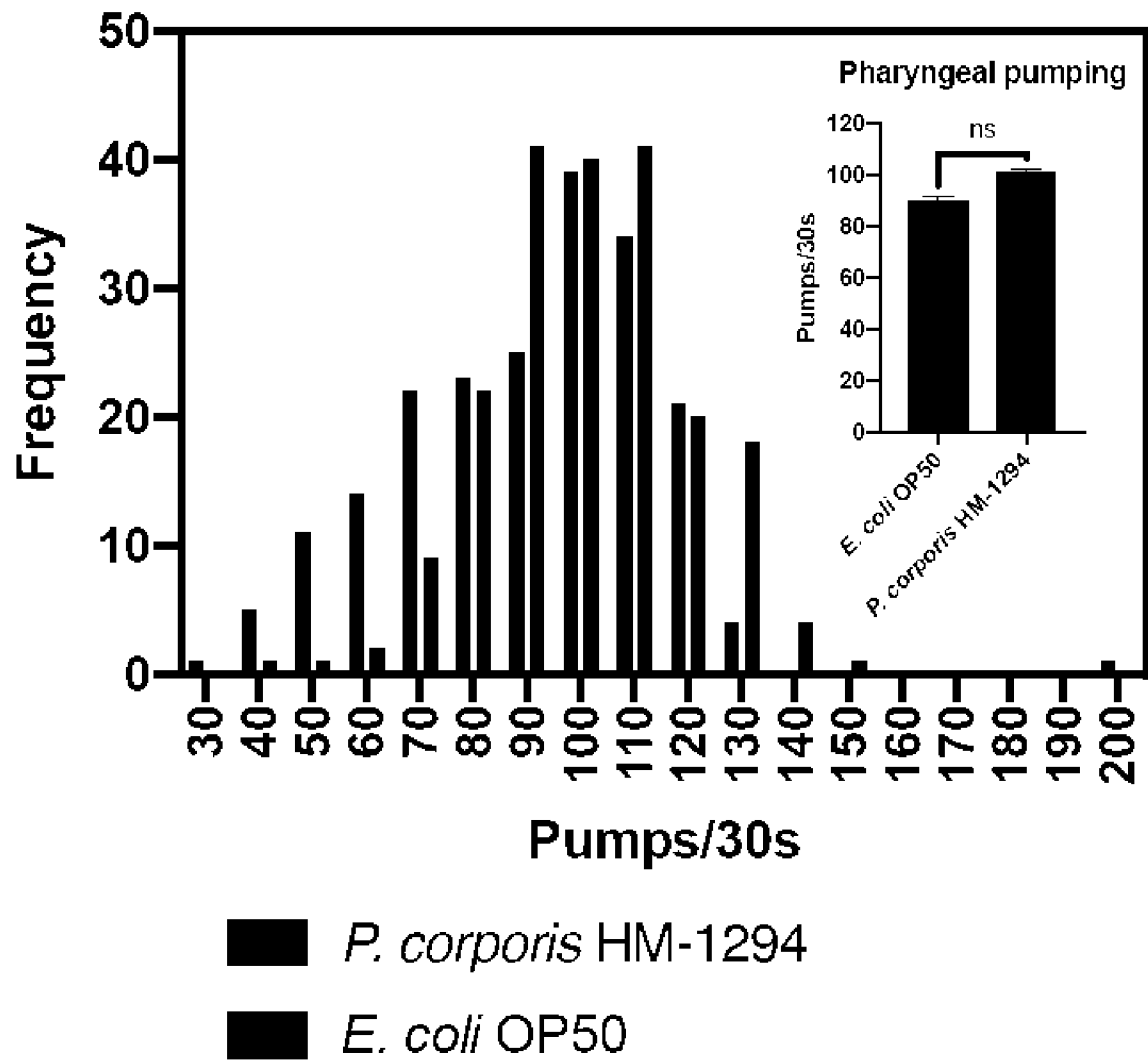


FIG. 11

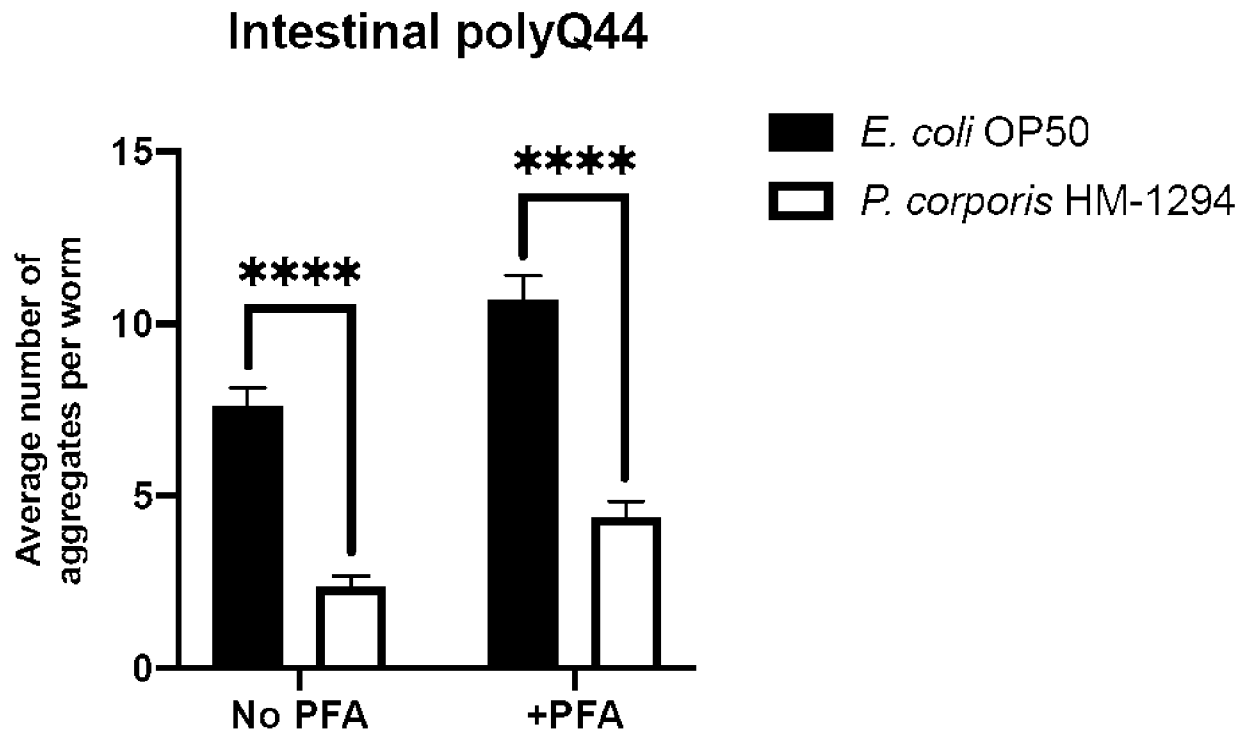


FIG. 12

Quantification of intestinal bacteria

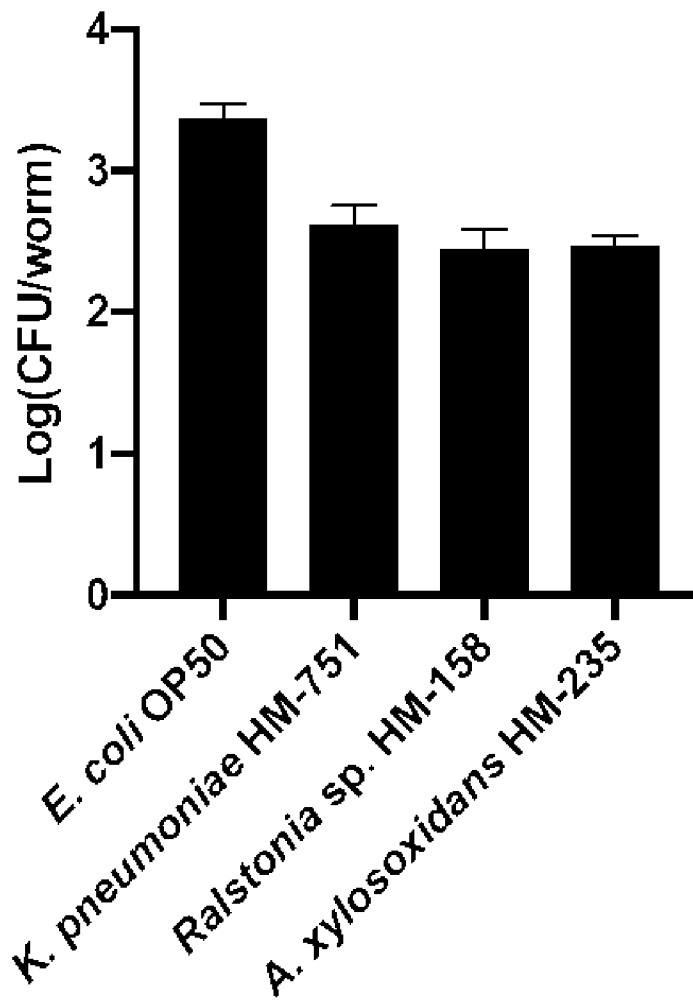


FIG. 13

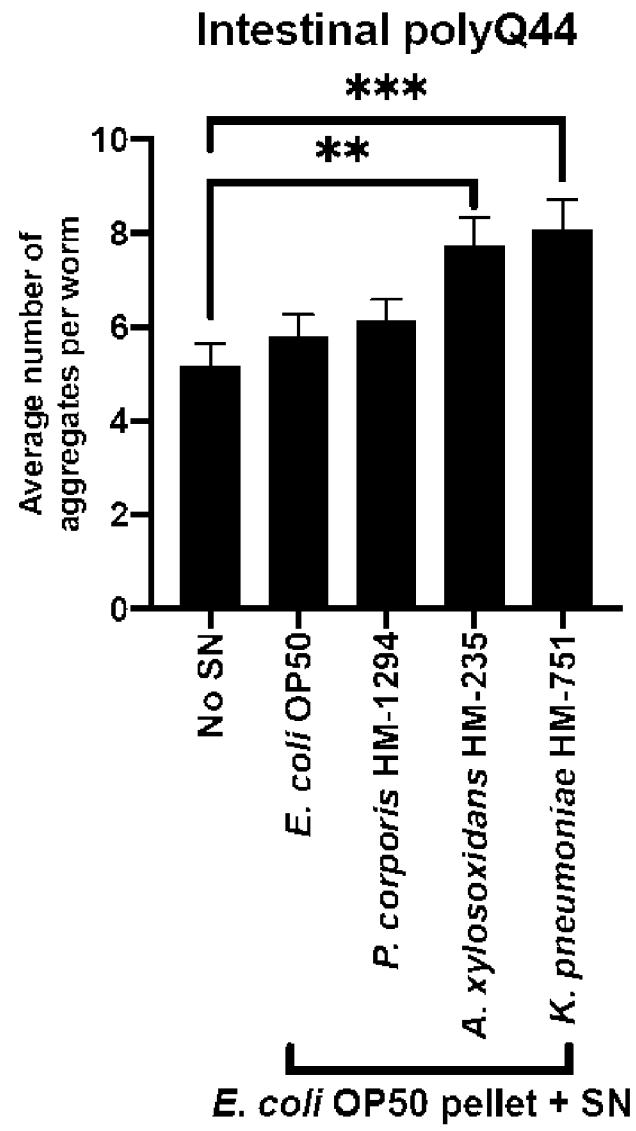


FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/049907

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 35/74** (2024.01); **A61K 35/76** (2024.01); **A61P 25/16** (2024.01); **A61P 31/04** (2024.01); **C12N 1/20** (2024.01); **C12Q 1/689** (2024.01)CPC: **A61K 35/74**; **C12N 1/20**; **A61P 25/16**; **A61P 31/04**; **A61K 35/76**; **C12Q 1/689**; A61K 2121/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2022/098916 A1 (LOCUS BIOSCIENCES INC. et al.) 12 May 2022 (12.05.2022) entire document entire document	8-12, 32 6, 7, 13
X Y	US 2019/0240263 A1 (EVELO BIOSCIENCES INC.) 08 August 2019 (08.08.2019) entire document entire document	31 2-7, 13, 26
A	US 2023/0068960 A1 (PROLACTA BIOSCIENCE INC.) 02 March 2023 (02.03.2023) entire document	1-13, 26, 31, 32
X Y	WALKER et al., Colonization of the Caenorhabditis elegans gut with human enteric bacterial pathogens leads to proteostasis disruption that is rescued by butyrate, PLoS Pathog, Vol. 17, Iss. 5, e1009510 06 May 2021, Pgs. 1-35. [retrieved on 07.11.2024], Retrieved from the internet: <URL:https://doi.org/10.1371/journal.ppat.1009510>. entire document	1 2-7, 26



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

07 November 2024 (07.11.2024)

Date of mailing of the international search report

02 January 2025 (02.01.2025)

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/049907

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WALKER et al., Identification of proteotoxic and proteoprotective bacteria that non-specifically affect proteins associated with neurodegenerative diseases, iScience, Vol. 27, 110828, 20 September 2024, Pgs. 1-24. [retrieved on 07.11.2024], Retrieved from the internet: <URL: https://doi.org/10.1016/j.isci.2024.110828 >. entire document	1-13, 26, 31, 32

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: **14, 15, 21-25**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-13, 31, 32, and also claim 26 (in part) are drawn to compositions for use in treating a protein conformational disease (PCD) in a subject.

Group II: claims 16-20, 30, 33, 34, 36, and also claim 26 (in part) are drawn to methods of treating a subject suffering from a PCD or at risk of developing a PCD and methods of decreasing protein misfolding in a subject.

Group III: claims 27-29 and 35 are drawn to methods for determining a risk of developing a PCD or one or more symptoms of a PCD.

Group IV: claims 37, 37A, 37B, and 38 are drawn to methods activating or inducing a heat shock response in a subject and methods increasing expression of a heat shock protein.

The inventions listed in Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, compositions for use in treating a protein conformational disease (PCD) in a subject, are not present in Groups II-IV; the special technical features of Group II, methods of treating a subject suffering from a PCD or at risk of developing a PCD and methods of decreasing protein misfolding in a subject, are not present in Groups I, II, and III; the special technical features of Group III, methods for determining a risk of developing a PCD or one or more symptoms of a PCD, are not present in Groups I, II, and IV; and the special technical features of Group IV, methods activating or inducing a heat shock response in a subject and methods increasing expression of a heat shock protein, are not present in Groups I-III.

Additionally, even if Groups I-IV were considered to share the technical features of a composition for use in treating a protein conformational disease (PCD) in a subject, the composition comprising: (a) *Prevotella corporis*; (b) a composition containing *Prevotella corporis*; (c) a composition comprising killed *Prevotella corporis* bacteria; (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or (f) combinations of two or more of (a)-(e); a composition for use in treating a PCD in a subject, the composition

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

comprising: a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject and/or specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject; a composition for use in treating a protein conformational disease (PCD) in a subject, the composition comprising: (a) *Prevotella* species; (b) a composition containing a *Prevotella* species; (c) a composition containing killed *Prevotella* species bacteria; (d) a composition comprising a *Prevotella* species lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella* species in the gut of the subject; or (f) combinations of two or more of (a)-(e); a composition for use in treating a PCD in a subject, the composition comprising: a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject, these shared technical features do not represent a contribution over the prior art as disclosed by US 2019/0240263 A1 to Evelo Biosciences Inc (hereinafter, "Evelo") and US 2023/0068960 A1 to Prolacta Bioscience Inc (hereinafter, "Prolacta").

Evelo teaches a composition (methods and compositions related to *Prevotella* EVs useful as therapeutic agents, Abstract), the composition comprising: (a) *Prevotella corporis*; (b) a composition containing *Prevotella corporis* (the pharmaceutical compositions comprise both *Prevotella* EVs and whole *Prevotella* bacteria... e.g.,... killed bacteria.... *Prevotella corporis*, Para. [0002]); (c) a composition comprises killed *Prevotella corporis* bacteria (the pharmaceutical compositions comprise both *Prevotella* EVs and whole *Prevotella* bacteria... e.g.,... killed bacteria.... *Prevotella corporis*, Para. [0002]); (d) a composition comprising a *Prevotella corporis* lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella corporis* in the gut of the subject; or (f) combinations of two or more of (a)-(e); a composition (methods and compositions related to *Prevotella* EVs useful as therapeutic agents, Abstract), the composition comprising: (a) *Prevotella* species; (b) a composition containing a *Prevotella* species (the pharmaceutical compositions comprise both *Prevotella* EVs and whole *Prevotella* bacteria... e.g.,... killed bacteria, Para. [0002]); (c) a composition containing killed *Prevotella* species bacteria (the pharmaceutical compositions comprise both *Prevotella* EVs and whole *Prevotella* bacteria... e.g.,... killed bacteria, Para. [0002]); (d) a composition comprising a *Prevotella* species lysate or an extract or a fraction thereof; (e) a composition that increases abundance or supports growth of *Prevotella* species in the gut of the subject; or (f) combinations of two or more of (a)-(e).

Evelo fails to explicitly disclose a composition for use in treating a PCD in a subject, the composition comprising: a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject and/or specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject; a composition for use in treating a PCD in a subject, the composition comprising: a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species, a *Shigella* species, an *Achromobacter* species, a *Ralstonia* species, a *Klebsiella* species, an *Arcobacter* species, a *Citrobacter* species, and an *Escherichia* species in the gut of the subject.

Prolacta is in the field of treatment of diseases associated with dysbiosis of the intestinal microbiome (Abstract) and teaches a composition for use in treating a PCD in a subject (administration of the at least one probiotic strain and the prebiotic mixture treats or prevents diseases or disorders relating to the "gut-brain axis", including... Parkinson's, Para. [0237], See instant disclosure, Para. [0009], which provides Parkinson's disease as an example of an acceptable PCD), the composition comprising: a composition that specifically decreases the abundance or inhibits the growth of a *Pseudomonas* species in the gut of the subject (administration of the prebiotic mixture and the at least one probiotic strain impairs the growth of one or more pathogens. Such pathogens treated by the provided methods include... *Pseudomonas*, Para. [0231]) and/or specifically decreases the abundance or inhibits the growth of a *Shigella* species in the gut of the subject (administration of the prebiotic mixture and the at least one probiotic strain impairs the growth of one or more pathogens. Such pathogens treated by the provided methods include... *Shigella*, e.g., *Shigella* spp., Para. [0231]); a composition for use in treating a PCD in a subject (administration of the at least one probiotic strain and the prebiotic mixture treats or prevents diseases or disorders relating to the "gut-brain axis", including... Parkinson's, Para. [0237], See instant disclosure, Para. [0009], which provides Parkinson's disease as an example of an acceptable PCD), the composition comprising: a composition that specifically decreases the abundance or inhibits the growth of one or more of a *Pseudomonas* species (administration of the prebiotic mixture and the at least one probiotic strain impairs the growth of one or more pathogens. Such pathogens treated by the provided methods include... *Pseudomonas*, Para. [0231]), a *Shigella* species (administration of the prebiotic mixture and the at

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Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

least one probiotic strain impairs the growth of one or more pathogens. Such pathogens treated by the provided methods include... Shigella, e.g., Shigella spp., Para. [0231]), an Achromobacter species, a Ralstonia species, a Klebsiella species, an Arcobacter species, a Citrobacter species, and an Escherichia species in the gut of the subject.

It would have been obvious to one of ordinary skill in the art before the priority date to modify the composition of Evelo by a composition as taught by Prolacta for the purpose of reducing the presence or colonization of one or more pathogens within the subject's gut (Prolacta, Para. [0268]).

The inventions listed in Groups I-IV therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-13, 26, 31, 32**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.