

Growth rate alterations of human colorectal cancer cells by 157 gut bacteria

Rahwa Taddese^{1,#}, Daniel R. Garza^{2,#}, Lilian N. Ruiter¹, Marien I. de Jonge³, Clara Belzer⁴, Steven Aalvink⁴, Iris D. Nagtegaal¹, Bas E. Dutilh^{2,5,*}, Annemarie Boleij^{1,*}

¹Department of Pathology, Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University Medical Center, Nijmegen, The Netherlands.

²Centre for Molecular and Biomolecular Informatics, Radboud University Medical Center, Nijmegen, The Netherlands.

³Section Pediatric Infectious Diseases, Laboratory of Medical Immunology, Radboud Center for Infectious Diseases (RCI), Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University Medical Center, Nijmegen, The Netherlands

⁴Laboratory of Microbiology, Wageningen University and Research, Wageningen, The Netherlands.

⁵Theoretical Biology and Bioinformatics, Utrecht University, Utrecht, The Netherlands.

^{#,*} Equal contribution

Corresponding authors: BEDutilh@gmail.com, Annemarie.Boleij@radboudumc.nl

Keywords: colorectal cancer, cell proliferation, MTT assay, human microbiome, secretomes

ABSTRACT

Several bacteria in the human gut microbiome have been associated with colorectal cancer (CRC) by high-throughput screens. In some cases, molecular mechanisms have been elucidated that drive tumorigenesis, including bacterial membrane proteins or secreted molecules that interact with the human cancer cells. For most gut bacteria, however, it remains unknown if they enhance or inhibit cancer cell growth. Here, we screened bacteria-free supernatants (secretomes) and inactivated cells of over 150 cultured bacterial strains for their effect on CRC cell growth. We observed family-level and strain-level effects that often differed between bacterial cells and secretomes, suggesting that different molecular mechanisms are at play. Secretomes of *Bacteroidaceae*, *Enterobacteriaceae*, and *Erysipelotrichaceae* bacteria enhanced CRC cell growth, while most *Fusobacteriaceae* cells and secretomes inhibited growth, contrasting prior findings. In some bacteria, the presence of specific functional genes was associated with CRC cell growth rates, including the virulence genes TcdA in *Clostridiales* and FadA in *Fusobacteriaceae*, which both inhibited growth. *Bacteroidaceae* cells that enhanced growth were enriched for genes of the cobalamin synthesis pathway, while *Fusobacteriaceae* cells that inhibit growth were enriched for genes of the ethanolamine utilization pathway. Together, our results reveal how different gut bacteria have wide-ranging effects on cancer cells, contribute a better understanding of the effects of the gut microbiome on the human host, and provide a valuable resource for identifying candidate target genes for potential microbiome-based diagnostics and treatment strategies.

INTRODUCTION

Over the past few decades, thousands of microbial species have been identified in the human gut microbiome. Each person harbors an estimated 3.8×10^{13} bacteria in their guts with a relatively stable species composition (1-3). Changes in the composition of the gut microbiome have been linked with various diseases including colorectal cancer (CRC), the third leading cancer worldwide with an incidence that is estimated to rise in the coming decennium (4, 5). Besides important environmental and genetic factors, the initiation and development of CRC is affected by the human gut microbiome. During tumorigenesis, the bacterial composition on the affected intestinal mucosa changes in a process that is described by the bacterial driver-passenger model (6, 7). Bacterial drivers may facilitate the acquisition of hallmarks of cancer (8) in mucosal cells by generating DNA-damage, reducing the epithelial barrier function, and stimulating pro-carcinogenic immune responses. As the tumor microenvironment changes in the transition from adenoma to carcinoma, bacterial passengers compete with the drivers, further shifting the microbiome towards a CRC signature (9, 10). The newly acquired bacteria may in turn affect tumor development, by potential inhibiting, enhancing, or neutral effects on tumor cell growth (6). These CRC-specific changes offer the opportunity to use the bacterial community for diagnostic, prognostic, preventive, and treatment measures (11-20).

In faeces of CRC patients, the genera *Fusobacterium*, *Peptostreptococcus*, *Ruminococcus*, and *Escherichia/Shigella* are enriched, while *Bacteroides* and *Lachnospiraceae* (*Roseburia*, *Lachnospira*, *Anaerostipes*) have a lower relative abundance (5, 9, 11, 21-25). Even though phyla such as *Bacteroidetes* are depleted,

single species like enterotoxigenic *Bacteroides fragilis* may be enriched in some CRC patients (25-27). Comparing tumor tissue with adjacent normal tissue on the intestinal mucosa of CRC patients revealed that *Fusobacterium*, *Prevotella*, *Streptococcus*, and *Peptostreptococcus* were enriched in tumors while *Blautia*, *Escherichia*, *Pseudomonas*, and *Faecalibacterium* were enriched in the normal mucosa (5, 7, 9, 11, 22-24, 28).

Many different bacteria have been associated with CRC tumors (10), but we are only beginning to understand the different mechanisms that are involved. The effect of bacteria on CRC cell growth may be driven by direct bacterial-to-epithelial cell-cell contact or by secreted products present in the secretome (29, 30). Membrane-bound bacterial proteins that require cell-cell contact can activate epithelial cell signalling. For example, the passenger bacterium *Fusobacterium nucleatum* encodes the membrane protein *Fusobacterium* adhesin A (FadA) that binds to E-cadherin, activating β -catenin signaling and resulting into increased tumor growth (31-33). Specific *E. coli* species with *eae* gene express the adhesin protein intimin on their membrane surface which bind and cause lesions to gut epithelial cells, allowing bacteria to breach the colonic barrier. Once the bacteria are bound to the epithelial cells, this allows them to inhibit DNA repair proteins, further contributing to lasting DNA damage (34-36). Several secreted bacterial toxins are known that can bind to receptors or pass through the cell membrane into the cytoplasm. The driver bacterium enterotoxigenic *B. fragilis* secretes the metalloprotease *B. fragilis* toxin (BFT) which leads to E-cadherin cleavage and increased wnt-signalling in colon epithelial cells and to tumor formation in mice and increased cell proliferation *in vivo*

(37, 38). Bacteria such as *Escherichia coli* containing the *pks* island are able to produce a genotoxin called colibactin. Upon mucosal breach, colibactin reaches the epithelial cells and alkylates DNA, ultimately leading to tumorigenesis (39-41). These examples show that taxonomically diverse bacteria may lead to the acquisition of hallmark capabilities via diverse mechanisms.

The aim of this study was to examine the effects of bacterial cells and their secretomes on the growth rates of epithelial cells. We tested the effect of 157 different gut bacteria on the growth rates of five CRC cell lines and one non-cancerous kidney cell line. Our results revealed that different bacterial families specifically inhibit or enhance CRC cell growth, although contrasting effects could be observed between some closely related strains. Both known virulence genes and novel microbial pathways were associated with the different growth rate changes. These results provide the first large-scale *in vitro* analysis of the effects of different microbial strains on epithelial cell growth.

MATERIALS AND METHODS

Bacterial strains

We selected 116 different gut bacteria, including species that are depleted or enriched in CRC patients whose genome sequences were available in the PATRIC database (42). Additionally, we selected specific bacteria without sequenced genomes (n=39) that were strongly linked to CRC or were isolated from CRC tissue, including *Streptococcus bovis* (43, 44), *Clostridium septicum* (44-46), *Clostridioides*

difficile (47, 48), *Bacteroides* sp. (27), and the two potentially beneficial bacteria *Lactobacillus casei* Shirota (49-51) and *Akkermansia muciniphila* ATCC BAA-835™ (52-55). Together, we analysed 157 bacterial strains isolated from the human gut microbiome (Supplementary Table S1).

We purchased 96 bacterial strains from the reference catalogue of the Human Microbiome Project (HMP, Prof. Dr. Emma Allen-Vercoe from the University of Guelph in Guelph, Canada); 24 bacteria were kindly provided by Prof. Dr. Cynthia L. Sears from Johns Hopkins Medical Institutions, Baltimore, MD, USA; five strains were purchased from DSMZ (*Clostridium septicum* (Macé 1889) Ford 1927 DSM7534, *C. difficile* (Hall and O'Toole 1935) Lawson et al. 2016 DSM27543 (known as *Clostridium difficile* 630, PMID: 6870225), *Fusobacterium nucleatum* Knorr 1922 DSM15643, *Fusobacterium nucleatum* subsp. *polymorphum* (ex Knorr 1922) Dzink et al. 1990 DSM20482, and *Peptostreptococcus stomatis* Downes and Wade 2006 DSM17678); one strain from ATCC (*Streptococcus agalactiae* ATCC13813); and 31 bacteria were in stock at the Radboud University Medical Center in Nijmegen, The Netherlands (56-58). Information about the bacterial strains, their origin, growth media, and their genome sequence is provided in Supplementary Table S1.

Bacteria were cultured in their respective media under anaerobic conditions at 37°C airtight with nitrogen gas (N₂, see Supplementary Table S1). Alternatively, *Ralstonia* sp. 5_2_56FAA, *Ralstonia* sp. 5_7_47FAA and *Pseudomonas* sp. 2_1_26 were grown aerobically at 37°C, and *Bacillus smithii* was grown anaerobically at its preferred temperature of 50°C. Eight media were prepared to culture bacteria

(Supplementary Table S1): brain heart infusion-supplemented (BHI-S, ATCC Medium 1293), BHI-S supplemented with 0.1% Tween 80 at pH 8.0 (BHI-T (59), NADC - 99X medium (ATCC Medium 1804), Desulfovibrio medium (ATCC Medium 2755), Modified Reinforced Clostridial Medium (RCM, ATCC Medium 2107), Reinforced Clostridial medium with sodium lactate (60% solution) at a concentration of 1.5% (RCM+, from ATCC Medium 1252), differential RCM (DRCM), and nutrient broth (NB, ATCC Medium 3). Bacteria were grown until the medium was turbid and the optical density (OD) was at least 1.0. Absorbance was obtained by measuring OD at 600nm.

Obtaining secretomes and bacterial cells

To investigate the effect of secreted molecules, we obtained secretomes from 154 bacterial cultures as follows. After culturing, bacteria were centrifuged at 4,700 rpm for 10 minutes and some bacteria subsequently at a higher speed to settle them down (see Supplementary Table S1). Next, supernatants were spun at 4,700 rpm for 10 minutes to pellet any remaining bacteria and filter-sterilized using 0.2 µm filters (Sigma-Aldrich, USA). Molecules larger than 10 kDa were concentrated using amicon ultra-15 centrifugal filters (Merck Millipore, Merck, USA). Concentrated supernatants were frozen at -80°C until further use and are further referred to as secretomes.

To investigate the effect of bacterial surface-bound molecules, 145 bacteria were inactivated to allow cellular growth rates to be assessed by measuring metabolic activity (see the section “MTT assay” below). Cells of twelve spore-forming bacteria under our experimental conditions were excluded from this analysis (see Supplementary Table S1). Pelleted bacteria were resuspended in 70% ethanol and

incubated for 5 minutes according to our inactivation protocol (60). After centrifugation at 20,000 rcf for 30 seconds, bacteria were washed in PBS twice and inactivated bacteria were frozen at -80°C until further use.

Culturing of cell lines and identification of their mutational landscapes

Five CRC cell lines (Caco-2, HCT15, HCT116, HT29, and SW480) and one non-cancerous embryonic kidney cell line (HEK293T) were selected based on their differences in mutational landscapes (61). Known oncogenes and tumor suppressor genes were confirmed with targeted single molecule molecular inversion probe (smMIP) mutation analysis as described (62), with additional smMIPs targeting CXCR4 (NM_001008540.1) codons 281-357, EZH2 (NM_00004456.4) codons 471-502, 618-645, 679-704, and SF3B1 (NM_012433.2) codons 603-471, 833-906 (smMIP sequences are available upon request), at the Radboud Diagnostics Department, Nijmegen, The Netherlands (Supplementary Table S2). Cells were split twice a week using Dulbecco's Modified Eagle Medium (DMEM, Lonza, Switzerland) supplemented with 10% fetal bovine serum (FBS, Thermo Fisher Scientific, USA) and 1% Penicillin/Streptomycin (Pen/Strep, Thermo Fisher Scientific, USA). Cells used for this study were not split for more than 25 passages.

For MTT assays, optimal cell seeding in 96 well plates (Greiner Bio-One, Austria) was defined at 5,000 cells/well for Caco-2, 4,000 cells/well for HCT15, 1,500 cells/well for HCT116, 10,000 cells/well for HT29, 6,000 cells/well for SW480, and 20,000 cells/well for HEK293T. Cells were incubated overnight to attach before addition of secretomes or bacterial cells.

MTT assay

Secretomes were diluted to their original concentrations in DMEM supplemented with 10% FBS and 1% Pen/Strep. Inactivated bacteria were diluted with DMEM supplemented with 10% FBS and 1% Pen/Strep to an OD of 0.2 and incubated on cell lines up to 72 hours. For secretomes, filter sterilized bacterial culture media used to generate secretomes served as a control for cell growth in the assay, while for bacterial cells, DMEM supplemented with 10% FBS and 1% Pen/Strep served as control for cell growth. MTT assays were performed to measure the cell metabolic activity every 24 hours. These assays involve the conversion of the water-soluble yellow dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] to the insoluble purple formazan by the action of mitochondrial reductase. At 24, 48 and 72 hours 10 µl of MTT (5 mg MTT dissolved per mL PBS) dye was added to the wells and cells were incubated for 3 hours. Formazan was then solubilized with 150 µL MTT solvent (0.5 mL of 10% Nonidet (dissolved in water), 50 mL isopropanol (2-propanol) and 16,7 µL hydrochloric acid fuming 37% together) and the concentration determined by optical density at 570 nm (BioRad microplate reader model 680). Metabolic activity of cell lines was used as a measure for cell growth (63). All experiments were performed in quadruplicate.

Cell growth analysis

Absorbances at optical density of 570 nm were measured by MTT assays at four time points (0, 24, 48, and 72h). Growth rates per hour were calculated by dividing the difference in absorbance by the time interval between measurements (24 h). Results

from four independent experimental replicates were averaged. Growth rates between 24-48 h were selected for comparative analysis because that time window captured the optimal growth for most cell lines (Supplementary Figure S1).

A growth rate score was defined by subtracting the growth of negative controls (cells cultured without bacterial products) from those cultured with bacterial products (secretomes or bacterial cells). Scores greater than 0 refer to enhanced growth, while scores lower than 0 refer to inhibited growth (see Supplementary Tables S3 and S4). To allow comparability between cell lines, normalized growth rate scores were calculated by dividing per cell line the scores (g) of each of the n bacteria by the norm

($|g|$) of the experimental condition ($|g| = \sqrt{\sum_{i=1}^n g_i^2}$). The normalized growth rate

scores were used to evaluate whether the enhancing or inhibiting effect of a bacteria is significantly stronger than the mean effect observed for all other bacteria. For this purpose, growth rate scores were transformed into z-scores and p-values were computed by separate one tailed z-tests for enhancing or inhibiting effects. Based on these p-values, strains were identified as significant enhancers or inhibitors of growth by using a significance cut-off of $p < 0.05$.

The overall effects of bacterial secretomes and inactivated cells were visualized by projecting their normalized growth scores in a two-dimensional space with the t-SNE algorithm (64). To evaluate if bacteria of the same family have a similar overall effect on cell growth relative to bacteria from other families, we applied unsupervised nearest neighbour clustering (65) and evaluated how often bacteria from the same

family were nearest neighbours compared to a random sample without replacement. For this analysis, we only used bacteria from families with more than four representatives. Random groups were evaluated per family and were defined to contain the same number of strains as the family. Fisher's exact test was used to evaluate if the nearest neighbour groups were enriched for bacteria of the same family compared to 1,000 random groups of the same size. The harmonic means of p-values from this comparison are reported.

Association of bacterial virulence genes to growth rate changes

Bacterial genomes were screened for 35 known virulence genes that may be associated with cancer or epithelial cell changes (Supplementary Table S5). The virulence factors Map (Mitochondrial associated protein), Type-3 secretion system (T3SS) effector protein of *Citrobacter rodentium*, Shiga toxin 2A (Stx2A), Shigella enterotoxin 1 (ShEt1), and colibactin (cyclomodulin toxin on polyketide synthase (pks) island of *Enterobacteriaceae*) were identified in the *Enterobacteriaceae* family, *B. fragilis* toxin (BFT) in *B. fragilis* species, FadA in the *Fusobacteriaceae* family and *Clostridium difficile* toxin A (TcdA) in the *Clostridiales* order (Supplementary Table S5). Growth rate changes of strains containing virulence genes (if present in ≥ 3 strains) were compared to those of their non-virulent counterparts within the family or species (in case of *B. fragilis*). Groups were compared using Mann-Whitney U-test of aggregate data of all cell lines. $P < 0.05$ was considered significant.

Genes and subsystems identification

To identify genes that are associated with the inhibiting/enhancing effects of bacterial strains within families, we sorted all strains based on their effect on growth rate scores and used a normalized Kolmogorov-Smirnov statistic to quantify the association of a gene with the observed effect. Significance of the rank-based statistic was estimated by comparing its value to values obtained from 10^3 random permutations of the same list. This provided all genes encoded by the genomes from a family with a p-value which quantified the association of the gene to the inhibiting/enhancing effect. We evaluated genes that belong to the same functional subsystems (42, 66) were more often found to be significantly associated to the inhibiting/enhancing effect than to 103 random groups of genes. We defined this association by modeling the average count of genes belonging to a functional subsystem within the random groups as Poisson distributed variables. We then tested if the count of genes with significant p-values was statistically higher than expected from the Poisson model, with a significance level of 0.05 after Benjamini/Hochberg correction for multiple tests. We used the Poisson distribution as the null distribution since (i) the labels for functional subsystem within the random groups are independent; (ii) Counts are expressed as averages from many random samples; (iii) the mean and variance are equivalent, all features consistent with a Poisson distribution(67)

RESULTS

Reproducibility of growth rate alterations by bacterial cells and secretomes

To identify alterations in the growth rates of CRC cell lines by bacterial cells or their secreted products, inactivated cells or secretomes were added to five CRC cell lines with different mutational landscapes and one non-cancerous kidney cell line (see Methods and Supplementary Table S2). Cell culture and bacterial culture media served as a control for cell growth for cells and secretomes respectively. A total of 7,176 experiments were conducted where we measured the bacterial effect on cell growth. Each experiment was repeated four times. We evaluated reproducibility of these replicates by performing linear regression over all pairwise combinations of replicates. As shown in Supplementary Figure S2, we found high reproducibility between replicates (regression coefficient: 0.87 ± 0.05 , intercept: 0.04 ± 0.02). Based on this reproducibility, we averaged the four experimental replicates for further analysis.

Contrasting effects between bacterial cells and secretomes

Figure 1A summarizes the effect of bacterial cells and secretomes on the growth of human cell lines. Overall, bacterial cells exhibit a stronger inhibiting effect than secretomes ($p=1.02e-75$, Wilcoxon signed rank test, Figure 1B). There was a low correlation between the effects of secretomes and inactivated bacteria on CRC cell growth (Supplementary Table S6), indicating that specific factors within the two compartments (cell wall attached or secreted molecules) are of importance for the observed effects.

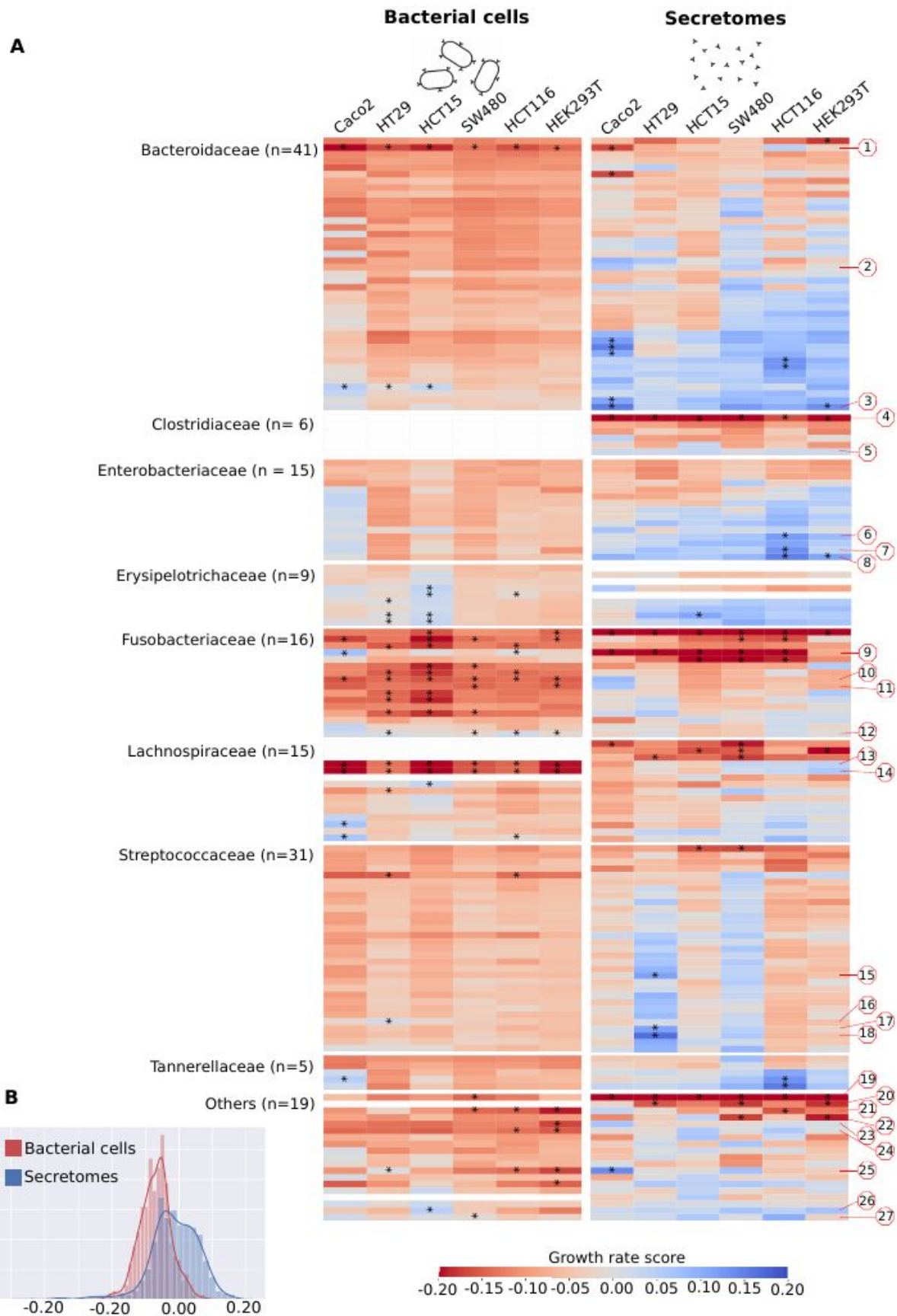


FIGURE 1. Growth rate scores of six human cell lines upon treatment with bacterial cells and secretomes. (A) Heatmap indicating low and high growth rate scores, respectively red and blue. Bacteria are sorted within bacterial families by the average growth rate score. Red numbered octagons highlight the strains discussed in the text: *Bacteroides* sp. 2_1_22 (1), *B. fragilis* K570 clinda R (ETBF) (2), *B. sp.* 4_1_36 (3), *Clostridium septicum* (Mace 1889) Ford 1927 (4), *C. sp.* D5 (5), *Escherichia coli* D9 (6), *Klebsiella* sp. 1_1_55 (7), *E. coli* 4_1_47FAA (8), *F. nucleatum* DSM 15643 (ATCC 25586) (9), *F. nucleatum* DSM 20482 (ATCC 10953) (10), *F. necrophorum* subsp. *funduliforme* 1_1_36S (11), *F. nucleatum* subsp. *animalis* 11_3_2 (12), *Lachnospiraceae bacterium* 8_1_57FAA (13), *L. bacterium* 3_1_46FAA (14), *Streptococcus bovis* 1212 (15), *S. bovis* 1459 (16), *S. bovis* 1417 (17), *S. bovis* 207 (18), *Pediococcus acidilactici* 7_4 (19), *Pseudomonas* sp. 2_1_26 (20), *D. sp.* 6_1_46AFAA (21), *Ralstonia* sp. 5_2_56FAA (22), *Ruminococcaceae bacterium* D16 (23), *Synergistes* sp. 3_1_syn1 (24), *Desulfovibrio* sp. 3_1_syn3 (25), *Propionibacterium* sp. 5_U_42AFAA (26), and *Eubacterium* sp. 3_1_31 (27). Highlighted with asterisks are cases that correspond to the 5% extremes of the z-score distribution. (B) Distribution of the growth rate scores for bacterial cells and secretomes.

Difference in growth rate alterations between CRC cell lines

Growth rates were significantly enhanced or inhibited ($p < 0.05$) in one or more cell lines in 35 out of 145 (24.1%) inactivated bacterial strains (Figure 2A, Supplementary Table S3) and 33 out of 154 (21.4%) secretomes (Figure 2B, Supplementary Table S4). Growth rates of HEK293T cells were affected by the lowest number of bacteria ($n=21$, $n=3$ enhanced and $n=18$ inhibited growth). On the other end of the spectrum were HCT116 cells that were affected by 28 different bacteria ($n=11$ enhanced and $n=17$ inhibited growth) and HCT15 cells that were affected by 27 different bacteria ($n=8$ enhanced and $n=19$ inhibited; Figure 2C). These two cell lines had microsatellite instability (MSI) and harbored the greatest number of pathogenic mutations in known tumor suppressor and oncogenes ($n=3$ and $n=4$ respectively, see Supplementary Table S2). In general, the number of pathogenic mutations of a cell line correlated with the number of bacteria that significantly affected its growth (Pearson $r=0.931$,

$p < 0.01$, see Figure 2D), suggesting that acquiring hallmark mutations might make cells more susceptible to growth rate changes by bacteria.

Some strains significantly enhanced or inhibited the growth rate of specific cell lines (Figure 1). *Streptococcaceae* cells generally had a neutral effect on cell growth, however, some *Streptococcaceae* secretomes specifically enhanced growth of HT29 and SW480 cells (Figure 1). Three *Streptococcus bovis* secretomes (strains 207, 1212 and 1417) and one inactivated bacterium (strain 1459) selectively enhanced growth in HT29 cells, while no effects were observed in other cell lines (Figure 1 and Figure 2C). The genomes of these enhancing *Streptococcus bovis* strains cluster together in a phylogenetic tree with *Streptococcus gallolyticus* subsp. *gallolyticus* (SGG) and subsp. *pasteurianus* (SGP) (Supplementary Figure 3). These effects of *Streptococcus bovis* may be cancer-specific since HEK293T was not affected. Other notable cell-line specific effects include *Erysipelotrichaceae* cells, and *Tannerellaceae* secretomes that significantly enhance growth of HCT15 and HCT116 cells, respectively.

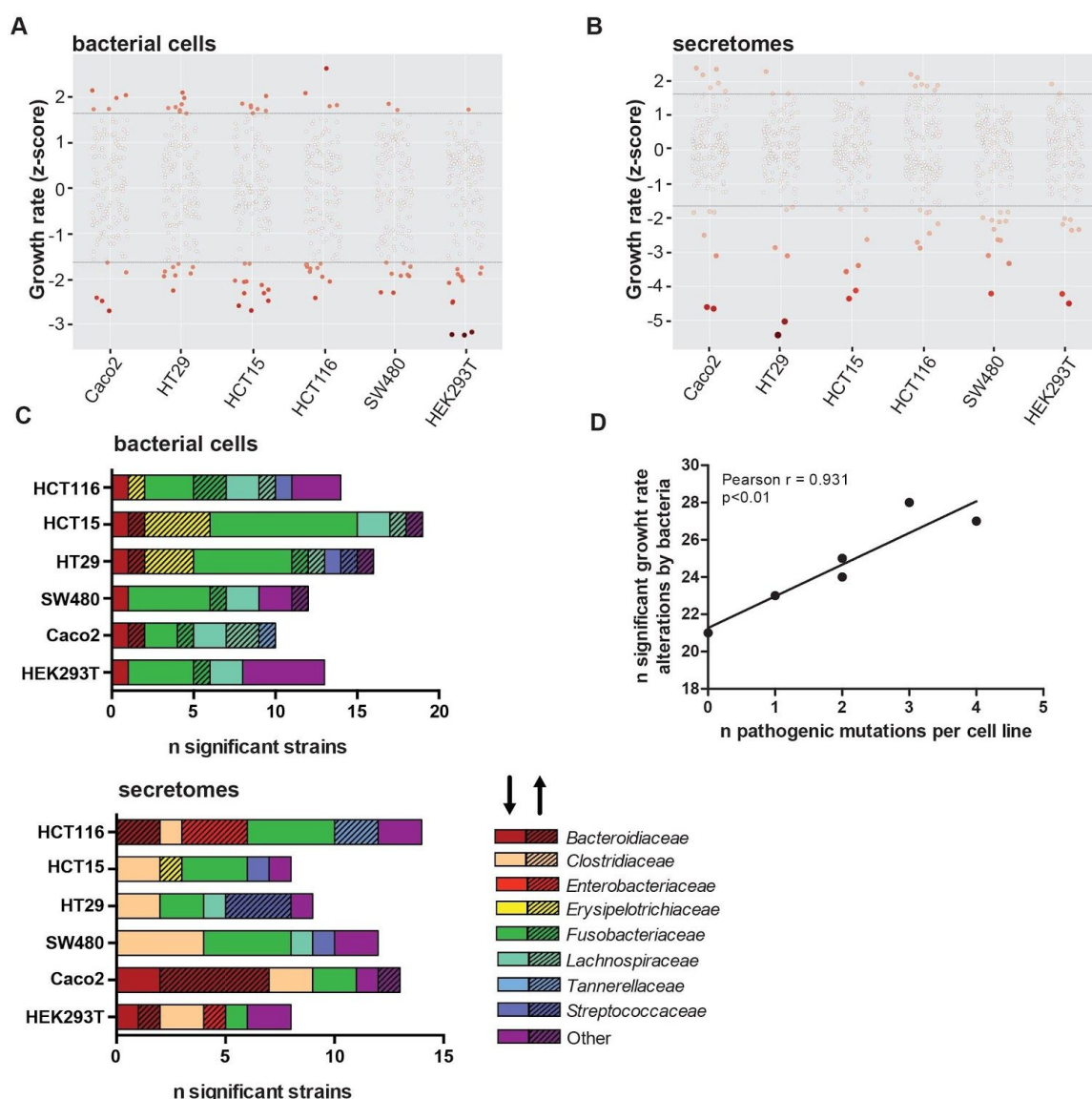


FIGURE 2: Growth rate alterations of cells lines upon incubation with bacterial cells and secretomes. Distribution plots illustrating effects of (A) bacterial cells and (B) secretomes on cell lines. Negative numbers indicate growth inhibition whereas positive numbers show growth enhancement. The color intensity of the circles represents significance of the effect on growth. (C) Overview of the number of bacterial cells and secretomes significantly enhancing or inhibiting cell growth per tested cell line, sorted by bacterial family. The shading of the bar (arrow pointing upwards) highlights enhancing and unshaded bar (arrow pointing downwards) highlights inhibiting strains. (D) Correlation of number of strains significantly altering growth rates to the number of pathogenic mutations present in cell lines. HEK293T, Caco-2, HT29, SW480, HCT116, and HCT15 were shown to possess 0, 1, 2, 2, 3, and 4 pathogenic mutations, respectively.

Bacterial family-level and strain-level effects on CRC cell growth rates

To assess the overall effect of the different bacterial secretomes and cells on our six cell lines, we projected the growth rate scores into a two-dimensional t-SNE plot. Figure 3 shows this lower dimensional space overlayed with family specific colors and a shade corresponding to the average growth effect. We observed a clear clustering of bacterial families, i.e. cells or secretomes from the same families tend to have similar effects on the different cell lines (see also Figure 1, Table 1). For bacterial cells, the most striking effect was observed for *Fusobacteriaceae* that generally inhibited growth of the cancer cells. Most *Bacteroidaceae*, *Enterobacteriaceae*, and *Erysipelotrichaceae* secretomes enhanced cell growth, although not always significantly (Figure 1). Contrastingly, *Clostridiaceae* secretomes generally inhibited growth rates. The effect of bacterial cells and secretomes was significantly clustered for five and three bacterial families, respectively (Supplementary Table S7).

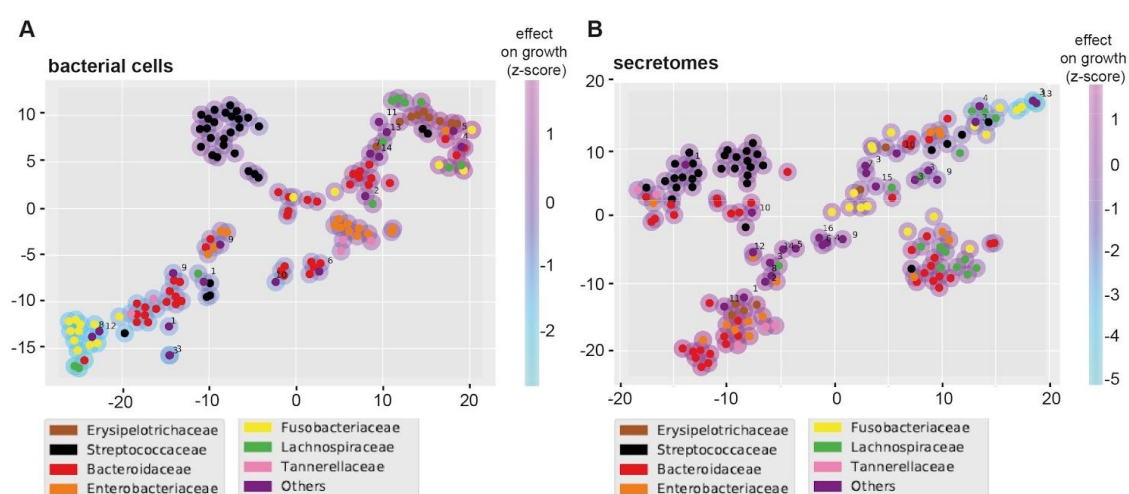


FIGURE 3. t-SNE plots summarizing the overall growth effects of bacterial cells (A) and secretomes (B) on six human cell lines. Coloured circles correspond to strains belonging to particular bacterial families. Magenta and light blue shading around the

circles indicate enhancing and inhibiting effect of strains, respectively. Families labelled as “Others” contains the following strains for bacterial cells (A): *Lactobacillaceae* (1), *Peptostreptococcaceae* (2), *Desulfovibrionaceae* (3), *Eubacteriaceae* (4), *Bifidobacteriaceae* (5), *Enterococcaceae* (6), *Veillonellaceae* (7), *Synergistaceae* (8), *Burkholderiaceae* (9), *Pseudomonadaceae* (10), *Propionibacteriaceae* (11), *Ruminococcaceae* (12), *Akkermansiaceae* (13), *Acidaminococcaceae* (14). And the following strains for secretomes (B): *Lactobacillaceae* (1), *Eubacteriaceae* (2), *Clostridiaceae* (3), *Peptostreptococcaceae* (4), *Bifidobacteriaceae* (5), *Enterococcaceae* (6), *Veillonellaceae* (7), *Synergistaceae* (8), *Burkholderiaceae* (9), *Desulfovibrionaceae* (10), *Propionibacteriaceae* (11), *Ruminococcaceae* (12), *Pseudomonadaceae* (13), *Akkermansiaceae* (14), *Acidaminococcaceae* (15), *Bacillaceae* (16).

In the *Bacteroidaceae* family (n=41 strains tested), secretomes and bacterial cells of seven and one strains significantly enhanced cell growth, respectively. The effects were most prominently observed in Caco-2 cells, while the growth of non-cancerous cell line HEK293T was only significantly enhanced by the secretome of *Bacteroides* sp. 4_1_36 (Figure 2C & Table 1). Only three *Enterobacteriaceae* secretomes (n=15) significantly enhanced growth of HEK293T cells (*Escherichia coli* 4_1_47FAA) and HCT116 (*Escherichia coli* 4_1_47FAA and D9, and *Klebsiella* sp. 1_1_55) while no effects were observed for bacterial cells.

Growth inhibiting effects were mainly observed within the family *Fusobacteriaceae* (Figure 1, Table 1). From the 12 out of 16 significant *Fusobacteriaceae* (81.3%) cells, two enhanced and ten inhibited cellular growth. *Fusobacterium necrophorum* subsp. *funduliforme* 1_1_36S cells enhanced growth in HCT116, SW480, and HEK293T cells. Strikingly, while *Fusobacterium nucleatum* subsp. *animalis* 11_3_2 cells enhanced growth of Caco-2 and HCT116, its secretome inhibited growth in those same cell lines. Especially the cell line HCT15 was sensitive for *Fusobacteriaceae* growth inhibition where 11 out of 16 strains significantly reduced growth rates.

Alternatively, HEK293T and Caco-2 were less sensitive to *Fusobacteriaceae* with only four out of 16 strains inhibiting cell growth. Notably, the effect of *Fusobacteriaceae* secretomes on cell growth may be cancer specific, since most secretomes that inhibited cancer cell growth did not inhibit growth of HEK293T cells.

Families with fewer than 5 strains tested

Among strains from families with less than five tested strains (n=18), *Eubacterium* sp. 3_1_31 and *Propionibacterium* sp. 5_U_42AFAA cells increased cell growth rates in SW480 and HCT15 cells, respectively (Table 1). Interestingly, *Pseudomonas* sp. 2_1_26 secretomes significantly inhibited the growth rates of all cell lines while the cells specifically inhibited SW480. *Pediococcus acidilactici* 7_4 and *Ruminococcaceae* bacterium D16 cells selectively inhibited the non-cancerous cell line, HEK293T, while *Synergistes* sp. 3_1_syn1 also inhibited HCT116. Aerobically cultured *Ralstonia* sp. 5_2_56FAA secretomes inhibited 2 cell lines, SW480 and HEK293T. For *Desulfovibrio* sp. 3_1_syn3, the secretome increased Caco-2 growth while the bacterial cells increased HT29 growth. Contrastingly, these same bacterial cells decreased growth of HCT116 and HEK293T. Similarly, *Desulfovibrio* sp. 6_1_46AFAA cells decreased the growth rates of HCT116, SW480 and HEK293T cells.

Strain-specific effects that contrast their family

While strains from the same bacterial families tend to have similar effects on the growth rates of cell lines (Supplementary Table S7), large variations were observed within certain families. For instance, within the *Clostridiaceae* family, the secretome

of *Clostridium septicum* (Mace 1889) Ford 1927 strongly inhibited growth of all tested cell lines, while the *Clostridium* sp. D5 secretome enhanced growth, although the significance threshold was not reached (Figure 1 and Supplementary Table S4). Similarly, *Bacteroides* sp. 2_1_22 cells strongly inhibited the growth rates of all cell lines while *B. fragilis* K570 cells enhanced growth in most cell lines (Figure 1 and Supplementary Table S3). A large growth rate variation was also observed in cell lines exposed to *Lachnospiraceae* cells (n=11). For this family, the cells of *L. bacterium* 3_1_46FAA and *L. bacterium* 8_1_57FAA significantly inhibited the growth rates of all cell lines, while most of the other strains showed weak or low inhibition.

The observed variations in growth effect within bacterial families might either be explained by the phylogenetic distances between the strains or by characteristics with a non-phylogenetic distribution, such as accessory functions. To evaluate this, we measured the distances on a phylogenomic tree and compared them with the differences in growth rate effects over the cell lines. For most bacterial families, there is no association between the growth rate effects and phylogenetic distances (Supplementary Table S8, Supplementary Figure S4), suggesting that these effects may be associated with accessory functions that are independently gained or lost in different lineages. For *Erysipelotrichaceae* secretomes and cells, *Fusobacteriaceae* cells, and *Lachnospiraceae* secretomes, we found that the phylogenetic distance was significantly correlated with the growth rate effects, suggesting that these effects may be associated to variations in universally shared genes or to accessory functions with phylogenetically consistent dynamics.

The presence of virulence genes is associated with growth rate inhibition

To explain the complex, sometimes strain-dependent patterns of growth enhancement or inhibition, we analyzed the genome sequences of 144/157 tested gut bacteria. First, we checked whether 35 known bacterial family-specific virulence genes were present within the genomes of the tested strains (Supplementary Table S9), because some of the encoded virulence factors have been linked to cell proliferation changes. Seven toxin genes were found, including TcdA (68); FadA (31); colibactin present on the pks-island (69, 70); Shiga toxin ShEt1; *Shigella* enterotoxin Stx2A; effector protein Map secreted by T3SS of *Citrobacter rodentium* and *Escherichia coli* (71, 72); and BFT (38).

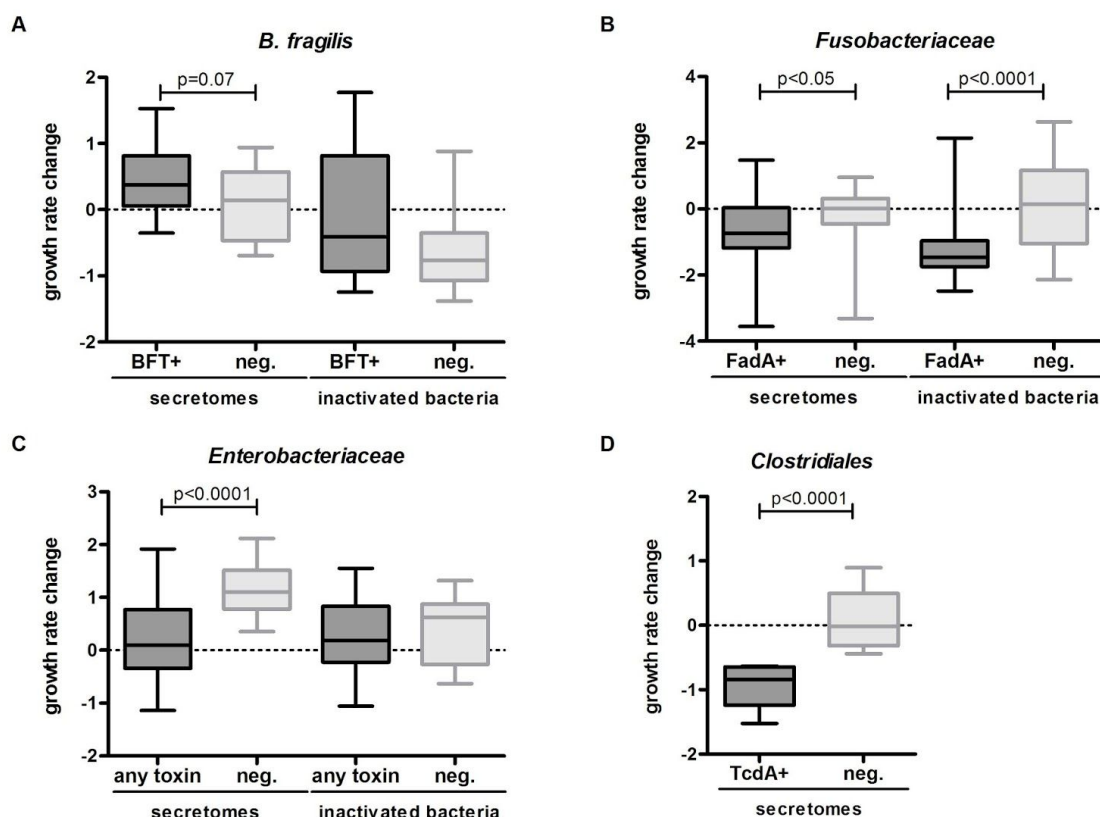


FIGURE 4. Influence of strains with and without encoded virulence factors on cellular growth rates. *B. fragilis* (A), *Fusobacteriaceae* (B), *Enterobacteriaceae* (C) and

Clostridiaceae (D) encoding the virulence factors *bft*, *fadA*, any toxin (*Map*, *pks*, *ShEt1*, *Stx2A*), and *TcdA*, respectively, were compared to strains without these encoded virulence factors (Mann-Whitney U test). A trend towards cell growth enhancement was observed for *B. fragilis* *bft*⁺ secretomes ($p=0.07$) (A), while significant inhibition of cell growth was observed for *fadA*⁺ *Fusobacteriaceae* cells ($p<0.0001$), and secretomes ($p<0.05$) (B), for *Enterobacteriaceae* secretomes encoding toxins ($p<0.0001$) (C), and *TcdA*⁺ *Clostridiales* secretomes ($p<0.0001$) (D).

As shown in Figure 4, strains containing virulence genes tend to change growth rates, relative to related strains without those virulence genes. For example, the secretomes of *Clostridiales* strains significantly inhibited growth rate if their genomes contained *TcdA* (Figure 4A, $p<0.0001$). Similarly, *Fusobacteria* strains encoding the membrane protein *fadA*, that might be responsible for growth rate changes of epithelial cells (31), inhibited growth rates significantly (Figure 4B, $p<0.0001$ and $p<0.05$ for bacterial cells and secretomes respectively). Within the *Enterobacteriaceae* family, multiple secreted toxins were identified in the genomes, including colibactin, *ShEt1*, *Stx2A*, and *Map*. Secretomes of *Enterobacteriaceae* possessing any of these toxins inhibited cell growth relative to strains without these toxins (Figure 4C, $p<0.0001$). No differences were observed between bacterial cells of *Enterobacteriaceae* with or without the toxin genes. The secretomes of three *B. fragilis* strains encoding the secreted enterotoxin *bft* enhanced the growth rates of CRC cells, while the five *B. fragilis* strains without the toxin did not, although this trend was not significant (Figure 4A, $p=0.075$). The trend was not observed for bacterial cells, where only *B. fragilis* K570 significantly enhanced growth rates (Table 1).

Functional categories associated with differential effects within families

Beside the toxin genes described above, other genes might also play a role in the observed effects. Thus, we next performed an unbiased comparative genome analysis where we associated all annotated bacterial genes to the effect of the strain on cell growth. We next grouped the genes by functional category and assessed whether genes within a category were significantly associated with cell growth alterations. Based on the PATRIC (42) annotations we evaluated genes in two hierarchical levels of functions, namely ‘Subsystems’ and ‘Superclass’. All functional categories found to be significantly associated with cell growth alterations are listed in Supplementary Table S10.

The “Membrane transport” superclass was significantly associated with inhibiting *Enterobacteriaceae* cells and secretomes, and with enhancing *Fusobacteriaceae* secretomes. Other enriched superclasses included: “Cell envelope”, “Metabolism”, “Cellular processes”, “Protein processing”, “Energy”, and “Stress response, defense and virulence” (Supplementary Table S10). Subsystems including “Cobalamin synthesis”, “Ethanolamine utilization”, and the “Dpp dipeptide ABC transport system” were consistently found to be associated with growth enhancement or inhibition in multiple bacterial families and in multiple cell lines (Supplementary Table S10). The significant effects of other subsystems including “Vir-like type 4 secretion system”, “Glutamate fermentation”, “Flagellum”, “Branched-chain amino acid biosynthesis”, and others were associated with specific bacterial families. We expect that these statistical associations will provide valuable leads for future experiments.

DISCUSSION

Over 150 human gut bacteria belonging to taxonomic groups that have previously been associated with CRC were tested for their effects on cell growth of five CRC cell lines (HT29, Caco-2, HCT116, SW480 and HCT15) with different mutation landscapes representing commonly mutated genes in CRC, and one non-cancerous kidney cell line (HEK293T). Our results show that cell growth enhancing and inhibiting effects of gut bacteria depend both on the mutational landscape of the cancer cells and on the identity and functional content of the bacteria, including secreted or cell wall attached factors. CRC is a heterogeneous disease, as is reflected in the five different CRC cell lines with mutations in key CRC related genes (*KRAS*, *APC*, *BRAF*, *TP53*, *CTNNB1* and *PIK3CA*). As expected, the growth rate of non-cancerous HEK293T kidney cells was affected by the lowest number of gut bacterial strains, with only small differences.

Closely related bacteria may have distinct effects on cell growth

A striking observation was that the effects of bacterial cells and secretomes were strongly associated to bacterial families, although exceptions to this general pattern were observed. Previous studies have found that *Fusobacteria*, *Streptococcus*, *Peptostreptococcus*, *Ruminococcus* and *Escherichia/Shigella* tend to be enriched in tumors, while *Bacteroides*, *Pseudomonas*, *Lachnospira* and *Anaerostipes* are depleted (5, 7, 9, 22-24, 28, 31, 41, 73-76). Regardless of the enrichment or depletion on CRC tumors *in vivo*, our *in vitro* results indicate that closely related bacteria may have distinct effects on cancer cell growth. For example, we observed that different *Fusobacteria* strains, which were all cultured in the same media under

the same conditions, may have opposing effects on cancer cell growth, while these bacteria are consistently enriched in patients (24, 28, 77). This suggests that specific bacterial factors play a role in CRC.

***Fusobacteriaceae*: enhancing or inhibiting growth?**

Previous studies indicated that *Fusobacteriaceae* enhanced growth of HCT116, SW480, and HT29 cells (31, 76). *F. nucleatum* ATCC25586 was shown to enhance CRC cell growth via interaction with Toll like receptors TLR4, TLR2, and myeloid differentiation primary response protein 88 (MYD88) (76), and the *F. nucleatum* strain Fn12230 was previously shown to enhance cell growth through the cell-wall attached adhesin FadA (31). Our results showed that most *Fusobacteriaceae* significantly inhibited cellular growth, including *Fusobacterium nucleatum* ATCC25586, contrasting previous observations (76, 78), and that the presence of the *FadA* gene was significantly linked to growth inhibition by cells and secretomes (Table 1). Notably, the secretomes showed less pronounced inhibition than bacterial cells. While FadA is membrane-bound, secretomes likely include outer membrane vesicles (OMVs) that are 40-110 nm in size and express FadA (32, 79). To rule out the possibility that these contrasting results were due to differences in methods, we compared our high-throughput MTT-based assay, used in this study, with the cell counting assay, that was employed in the referred studies, on 6 cell lines, using 6 different secretomes, and found a high correlation (Pearson's $r=0.813$, Supplementary Figure S5). These results confirm that the observed inhibitory effects by *Fusobacteriaceae* strains do not depend on the applied experimental techniques, but may partly be due to use of different *Fusobacteriaceae* strains (Fn12230,

ATCC25586, ATCC23726) isolated from extra-intestinal sites(80). Specifically HCT15 cell growth was significantly inhibited by 11/16 *Fusobacteriaceae* strains (nine cells and three secretomes). HCT15 cells contain a missense mutation in MYD88 (p.Arg264Ter) resulting in a MYD88 deficiency, and may thus explain the insensitivity of this cell line to *F. nucleatum* subsp. *animalis* 11_3_2 and *F. necrophorum* subsp. *funduliforme* 1_1_36S, the two *Fusobacteriaceae* strains that promoted growth of the other CRC cell lines, but not of HCT15.

Virulence factors are associated to cell growth inhibition

The growth-inhibiting properties of *Clostridiaceae* secretomes may result from toxins encoded by this family. We observed that the presence of the *TcdA* gene in *Clostridiaceae* was significantly associated with cell growth inhibition. *Clostridium septicum* (Mace 1889) Ford 1927 secretomes inhibited cell growth in all of our cell lines. This strain produces multiple exotoxins (alpha toxin, lethal toxin and hemolytic toxin) and has been associated to CRC (14, 15).

Enterobacteriaceae strains encoding the toxins colibactin, *Stx2A*, *ShEt1*, and *Map* inhibited cell growth relative to non-toxigenic *Enterobacteriaceae* strains. Colibactin (present in four of our *Escherichia* strains) is a genotoxic compound that alkylates DNA and generates DNA double strand breaks (41, 74). The DNA damaging effect of colibactin may not directly affect cell growth in our experimental setup, although colibactin may induce cell cycle arrest via SUMOylation of TP53 causing inactivation (69, 70). Cell cycle arrest would stall cell growth, which can only happen in TP53 wildtype cell lines with active TP53 protein. Indeed, the only cell lines that were

relatively inhibited by strains encoding colibactin were the wildtype *TP53* cell lines HEK293T and HCT116.

An important virulence factor of *B. fragilis* is BFT (81). While in previous research BFT was shown to enhance cell growth of HT29/c1 cells via β -catenin nuclear signalling (38), enterotoxigenic *B. fragilis* secretomes (VPI13784 (*bft1*), 86-5443-2-2 (*bft2*), and K570 (*bft3*)) only marginally enhanced CRC cell growth in our assay compared to the other *B. fragilis* secretomes in our screen. The mild effects as observed may depend on the level of toxin production and secretion under our experimental conditions. Interestingly, enterotoxigenic *B. fragilis* str. Korea 570 cells significantly enhanced growth, which might be independent of BFT and related to other cell-wall attached factors.

***Streptococcus bovis* strains specifically enhance growth of HT29 cells**

Streptococcus bovis infections have been linked to colorectal neoplasia (43, 82, 83). Our results demonstrate that secretomes of *Streptococcus bovis* strains that are closely related to known *S. gallolyticus* and *S. pasteurianus* strains (Supplementary Figure S3), selectively enhance growth of HT29 cells. This is in line with a previous study showing cell growth enhancing effects in HT29 and HCT116 cells that was mediated through β -catenin, while no effect was observed in SW480 and HEK293T cells (84). An intact β -catenin pathway may therefore be required to observe the specific effect of *S. gallolyticus* on cell growth as is the case in HT29 cells (85), which may thus be sensitive to the effects of *S. gallolyticus* in our assay. HCT116 cells have a mutation in *CTNNB1* (*p.Ser45del*) that interferes with β -catenin degradation, which

may explain its insensitivity to *S. gallolyticus*. Alternatively, mutations in the *APC*-gene in the other CRC-cells (86) may interfere with β -catenin signalling depending on the specific mutation.

Bacterial functions associated with cell growth alterations

Several functional categories were significantly associated with CRC cell growth. Most of these functions were identified in specific bacterial families and consistently inhibited or enhanced cell growth in different cell lines. These functions may reflect novel pathways of bacterial interference with CRC cell growth that, to our knowledge, have not been previously identified. Most functions are related to cell metabolism, secretion, and transport systems. For example, secretomes of *Enterobacteriaceae* that encode the “Vir-like type 4 secretion system” inhibited growth of all cell lines. Similarly, the gene superclass “Membrane transport” was mostly associated to secretomes that inhibited cell growth (Supplementary Table S10). Molecules that are secreted by these bacterial transport systems may be responsible for the inhibiting effect. For example, the Vir-like type 4 secretion system allows bacteria to secrete proteinaceous effectors that kill competitors (87). Here, we report an important first step in understanding the cell growth enhancing or inhibiting effects of human gut bacteria by identifying putative transport systems for effector molecules.

While the growth effects of secretomes were mostly associated with membrane transport functions, effects on CRC cell growth by bacterial cells were associated with metabolic pathways (Supplementary Table S10). It is possible that these associations may be attributed to metabolic enzymes that may still be, although the

bacterial cells were inactivated. In other ecosystems, metabolic enzymes of dead bacteria have been shown to remain active for up to 96 hours (88). Our experiment was performed within 72 hours. The synthesis of cobalamin (vitamin B12), which is important for human cell proliferation *in vitro* (89) and a common addition to cell culturing media, was significantly associated with the cell growth enhancing effect of *Bacteroidaceae* and *Enterobacteriaceae* cells. Several possible scenarios can be envisioned to explain this observation. First, it remains to be tested whether vitamin B12 was retained in the bacterial fraction after washing, stimulating human cell growth on those cells. Second, different human gut-associated *Bacteroides* strains contain surface-exposed lipoproteins with high affinity for cobalamin (90). Such molecules may remove cobalamin directly from the media, making it unavailable to the human cells and impeding their growth.

The “Ethanolamine utilization” pathway was another metabolic process that we found to be associated to the inhibiting effect of *Fusobacteriaceae* cells on the growth rate of CRC cell lines. Ethanolamine (EA) is the basal component of phosphatidylethanolamine, a major phospholipid in animal cell membranes and is utilized by bacteria including *Fusobacteria* as a carbon source in the gut (91-93). EA sensing regulators have been proposed to regulate virulence in *Enterobacteriaceae* (93, 94). It remains to be tested if the EA in human cell membranes triggers virulence factors in *Fusobacteria* that encode EA utilization genes, or perhaps if inactivated *Fusobacteria* cells retain the capacity to digest and kill human cells by the activity of EA utilization enzymes.

Overall, the statistical associations found in this exploratory analysis provide valuable clues about the possible functions and mechanisms that drive the interactions of bacteria with human cells in the gut. Future experiments are needed to confirm whether these factors are causal and to further clarify the molecular mechanisms involved.

Outlook

Our broad screen revealed many significant associations between gut bacteria, their encoded functions, and growth enhancement or inhibition of human CRC cell lines. Many growth rate effects remain elusive and need to be further examined. Moreover, it will be important to investigate the growth rate effects of living bacterial communities or mock communities, which are thought to synergize in affecting tumorigenesis (53), but fall outside the scope of our present study. Bacterial effects should be examined in more natural environments that mimic the conditions in the human gut, *e.g.* in co-culture with mucus, immune cells, and/or within organoid cultures (95). Our study forms an important baseline for such further research by identifying important traits in individual bacterial strains that are associated to enhancing or inhibiting cancer cell growth, as well as important host factors that determine sensitivity to those bacterial traits.

CONCLUSIONS

Above, we presented the results of the first large-scale analysis of the effects of gut bacteria on CRC cell growth. Our results with bacterial cells and secretomes reflect the complexity of the microbe-host interactions in the human gut. First, bacterial

families tend to have consistent effects on cell growth, although these effects are not universal. This may partially be explained by the presence of virulence genes in some strains. Second, there are cell line dependent effects in CRC cells due to their mutational landscape heterogeneity. Notably, these cell lines have acquired several different cancer hallmarks, yet their growth can still be influenced by specific bacteria. Our results suggest that the response of CRC cells to gut bacteria may differ between patients due to differences in their gut bacteria, although the relevance of our *in vitro* results for patients remains to be studied. Cell growth enhancing and inhibiting bacterial traits could be important for determining risk for cancer or its progression, and these consequences could potentially be counteracted by microbiome modulation. Currently, microbiome medicine applications have already been adapted to some other diseases. For instance, *Akkermansia muciniphila* was demonstrated to improve diabetes type 2 and obesity in mice (17, 18). Resistant life-threatening *Clostridium difficile* infections and ulcerative colitis were successfully treated with faecal microbiota transplants (FMT) (19, 20). Our study highlights the complex processes at play at the gut-microbiome interface and contributes to a better understanding of the role of different bacterial strains in altering colonic epithelial cell proliferation.

Acknowledgements

We thank Shaoguang Wu and Cynthia Sears from Johns Hopkins Medical Institutions for providing different gut bacterial strains (see Methods).

Funding

This work was supported by the Dutch Cancer Society (KWF; KUN 2015-7739). RT was supported by RIMLS grant 014-058. DRG was supported by CNPQ/BRASIL. BED was supported by the Netherlands Organization for Scientific Research (NWO) Vidi grant 864.14.004. AB was supported by NWO veni grant 016.166.089.

Supplementary Figure captions

S1. Average growth of human cell lines exposed to bacterial cells and secretomes. Colored lines and error bars show the average and standard deviation of MTT measurements for 6 human cell lines exposed to cells and secretomes of 145 and 154 bacteria, respectively. Measurements were recorded at the incubation times of 0, 24, 48, and 72h. The dark lines show the average of the cell line without bacterial products (negative controls).

S2. Reproducibility of four experimental replicates. Scatter plots of the pairwise combinations of four experimental replicates of MTT measurements at incubation times of 0, 24, 48, and 72h. Individual plots exhibit replicates of one cell line exposed to the cells or secretomes of, respectively 145 and 154 bacterial strains. Lines show the best fit to a linear model. The specific linear regression coefficients, intercepts, R^2 , and p-values are shown on the top of each plot.

S3. Cell growth rate alterations ordered by phylogenomic distances. Heatmaps show the growth rate alterations of six cell lines incubated with the cells and secretomes of strains from seven bacterial families. Rows of the heatmap are ranked according to the tips of the phylogenomic trees shown on the left.

S4. *Streptococcus* phylogenomic tree. Genome-based phylogenetic reconstruction of 238 *Streptococcus* genomes confirms that the genome sequences of the *S. bovis* strains reported in this study are closely related to previously sequenced genomes of *S. gallolyticus* and *S. pasteurianus*. The taxa names of strains used in our study are highlighted red. Monophyletic branches containing strains from a single species are collapsed and highlighted with blue triangles.

S5. Linear relation between cell counts and MTT measurements.

Cell growth was recorded by two different methods (MTT assay and cell counting) and plotted on a linear x-y graph. Both methods were significantly correlated ($p < 0.0001$, Pearson $r = 0.813$).

Supplementary Table captions

S1. Bacterial strains used in this study.

S2. Cancer mutational profile of six human cell lines used in this study.

S3. Growth rate scores, z-scores, and p-values measured from human cells incubated with bacterial cells.

S4. Growth rate scores, z-scores, and p-values measured from human cells incubated with bacterial secretomes.

S5. Literature summary of microbial virulence factors potentially associated to cancer.

S6. Correlation between growth rate scores of cells and secretomes.

S7. Statistical significance analysis of family-specific clustering of the growth rate scores.

S8. Correlation between the pairwise phylogenetic distance between bacterial strains used in this study and the pairwise Euclidean distance of the growth rate scores.

S9. Distribution of genes coding for virulence factors in the genomes of the bacteria used in this study. The TcdA toxin was present in bacteria of the *Clostridiales* order while other toxins were present within bacterial families.

S10. Functional genomic terms significantly associated to growth rate scores within bacterial families.

REFERENCES

1. R. Sender, S. Fuchs, R. Milo, Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS biology* **14**, e1002533-e1002533 (2016).
2. M. Rajilić-Stojanović, W. M. de Vos, The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS microbiology reviews* **38**, 996-1047 (2014).
3. J. Qin *et al.*, A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **464**, 59-65 (2010).
4. M. Arnold *et al.*, Global patterns and trends in colorectal cancer incidence and mortality. *Gut* **66**, 683-691 (2017).
5. R. Gao *et al.*, Mucosa-associated microbiota signature in colorectal cancer. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* **36**, 2073-2083 (2017).
6. H. Tjalsma, A. Boleij, J. R. Marchesi, B. E. Dutilh, A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. *Nature reviews. Microbiology* **10**, 575-582 (2012).
7. Z. Gao, B. Guo, R. Gao, Q. Zhu, H. Qin, Microbiota disbiosis is associated with colorectal cancer. *Frontiers in microbiology* **6**, 20 (2015).
8. D. Hanahan, R. A. Weinberg, Hallmarks of cancer: the next generation. *Cell* **144**, 646-674 (2011).
9. J. R. Marchesi *et al.*, Towards the human colorectal cancer microbiome. *PloS one* **6**, e20447-e20447 (2011).
10. J. Wirbel *et al.*, Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. *Nature medicine* **25**, 679-689 (2019).
11. K. Xu, B. Jiang, Analysis of Mucosa-Associated Microbiota in Colorectal Cancer. *Medical science monitor : international medical journal of experimental and clinical research* **23**, 4422-4430 (2017).
12. M. S. Donia, A Toolbox for Microbiome Engineering. *Cell systems* **1**, 21-23 (2015).
13. J. L. Foo, H. Ling, Y. S. Lee, M. W. Chang, Microbiome engineering: Current applications and its future. *Biotechnology journal* **12** (2017).
14. B. Garcia-Jimenez, T. de la Rosa, M. D. Wilkinson, MDPbiome: microbiome engineering through prescriptive perturbations. *Bioinformatics (Oxford, England)* **34**, i838-i847 (2018).
15. J. L. Sonnenburg, Microbiome engineering. *Nature* **518**, S10 (2015).
16. N. Bernardes, R. Seruca, A. M. Chakrabarty, A. M. Fialho, Microbial-based therapy of cancer: current progress and future prospects. *Bioengineered bugs* **1**, 178-190 (2010).
17. S. Song, M. S. Vuai, M. Zhong, The role of bacteria in cancer therapy - enemies in the past, but allies at present. *Infectious agents and cancer* **13**, 9 (2018).
18. K. Lukaszewicz, M. Fol, Microorganisms in the Treatment of Cancer: Advantages and Limitations. *Journal of immunology research* **2018**, 2397808 (2018).
19. N. S. Forbes *et al.*, White paper on microbial anti-cancer therapy and prevention. *Journal for immunotherapy of cancer* **6**, 78 (2018).
20. M. G. Kramer, M. Masner, F. A. Ferreira, R. M. Hoffman, Bacterial Therapy of Cancer: Promises, Limitations, and Insights for Future Directions. *Frontiers in microbiology* **9**, 16 (2018).
21. X. J. Shen *et al.*, Molecular characterization of mucosal adherent bacteria and associations with colorectal adenomas. *Gut microbes* **1**, 138-147 (2010).
22. W. Chen, F. Liu, Z. Ling, X. Tong, C. Xiang, Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. *PloS one* **7**, e39743 (2012).
23. B. Flemer *et al.*, Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut* **66**, 633-643 (2017).
24. G. Zeller *et al.*, Potential of fecal microbiota for early-stage detection of colorectal cancer. *Molecular systems biology* **10**, 766 (2014).
25. T. Wang *et al.*, Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *The ISME journal* **6**, 320-329 (2012).
26. V. L. Hale *et al.*, Synthesis of multi-omic data and community metabolic models reveals insights into the role of hydrogen sulfide in colon cancer. *Methods (San Diego, Calif.)* **149**, 59-68 (2018).
27. A. Boleij *et al.*, The *Bacteroides fragilis* toxin gene is prevalent in the colon mucosa of colorectal cancer patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **60**, 208-215 (2015).
28. A. D. Kostic *et al.*, Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome research* **22**, 292-298 (2012).

29. A. Boleij *et al.*, Bacterial responses to a simulated colon tumor microenvironment. *Molecular & cellular proteomics : MCP* **11**, 851-862 (2012).
30. H. Tjalsma, A. Bolhuis, J. D. Jongbloed, S. Bron, J. M. van Dijk, Signal peptide-dependent protein transport in *Bacillus subtilis*: a genome-based survey of the secretome. *Microbiology and molecular biology reviews : MMBR* **64**, 515-547 (2000).
31. M. R. Rubinstein *et al.*, *Fusobacterium nucleatum* promotes colorectal carcinogenesis by modulating E-cadherin/beta-catenin signaling via its FadA adhesin. *Cell host & microbe* **14**, 195-206 (2013).
32. Y. Fardini *et al.*, *Fusobacterium nucleatum* adhesin FadA binds vascular endothelial cadherin and alters endothelial integrity. *Molecular microbiology* **82**, 1468-1480 (2011).
33. Y. Chen *et al.*, Invasive *Fusobacterium nucleatum* activates beta-catenin signaling in colorectal cancer via a TLR4/P-PAK1 cascade. *Oncotarget* **8**, 31802-31814 (2017).
34. M. S. Donnenberg *et al.*, Role of the *eaeA* gene in experimental enteropathogenic *Escherichia coli* infection. *The Journal of clinical investigation* **92**, 1412-1417 (1993).
35. A. E. Jerse, J. Yu, B. D. Tall, J. B. Kaper, A genetic locus of enteropathogenic *Escherichia coli* necessary for the production of attaching and effacing lesions on tissue culture cells. *Proceedings of the National Academy of Sciences of the United States of America* **87**, 7839-7843 (1990).
36. O. D. Maddocks, A. J. Short, M. S. Donnenberg, S. Bader, D. J. Harrison, Attaching and effacing *Escherichia coli* downregulate DNA mismatch repair protein in vitro and are associated with colorectal adenocarcinomas in humans. *PloS one* **4**, e5517 (2009).
37. K. J. Rhee *et al.*, Induction of persistent colitis by a human commensal, enterotoxigenic *Bacteroides fragilis*, in wild-type C57BL/6 mice. *Infection and immunity* **77**, 1708-1718 (2009).
38. S. Wu, P. J. Morin, D. Maouyo, C. L. Sears, *Bacteroides fragilis* enterotoxin induces c-Myc expression and cellular proliferation. *Gastroenterology* **124**, 392-400 (2003).
39. G. Cuevas-Ramos *et al.*, *Escherichia coli* induces DNA damage in vivo and triggers genomic instability in mammalian cells. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 11537-11542 (2010).
40. J. C. Arthur *et al.*, Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science (New York, N.Y.)* **338**, 120-123 (2012).
41. M. R. Wilson *et al.*, The human gut bacterial genotoxin colibactin alkylates DNA. *Science (New York, N.Y.)* **363** (2019).
42. A. R. Wattam *et al.*, Improvements to PATRIC, the all-bacterial Bioinformatics Database and Analysis Resource Center. *Nucleic acids research* **45**, D535-d542 (2017).
43. A. Boleij, M. M. van Gelder, D. W. Swinkels, H. Tjalsma, Clinical Importance of *Streptococcus gallolyticus* infection among colorectal cancer patients: systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **53**, 870-878 (2011).
44. G. K. Wentling, P. P. Metzger, E. J. Dozois, H. K. Chua, M. Krishna, Unusual bacterial infections and colorectal carcinoma--*Streptococcus bovis* and *Clostridium septicum*: report of three cases. *Diseases of the colon and rectum* **49**, 1223-1227 (2006).
45. R. E. Schaaf *et al.*, *Clostridium septicum* infection associated with colonic carcinoma and hematologic abnormality. *Radiology* **137**, 625-627 (1980).
46. J. S. Sidhu, A. Mandal, J. Virk, V. Gayam, Early Detection of Colon Cancer Following Incidental Finding of *Clostridium septicum* Bacteremia. *Journal of investigative medicine high impact case reports* **7**, 2324709619832050 (2019).
47. Y. Zheng *et al.*, *Clostridium difficile* colonization in preoperative colorectal cancer patients. *Oncotarget* **8**, 11877-11886 (2017).
48. M. H. Fukugaiti *et al.*, High occurrence of *Fusobacterium nucleatum* and *Clostridium difficile* in the intestinal microbiota of colorectal carcinoma patients. *Brazilian journal of microbiology : [publication of the Brazilian Society for Microbiology]* **46**, 1135-1140 (2015).
49. K. Yamazaki *et al.*, The effect of an oral administration of *Lactobacillus casei* strain shirota on azoxymethane-induced colonic aberrant crypt foci and colon cancer in the rat. *Oncology reports* **7**, 977-982 (2000).
50. A. Kato-Kataoka *et al.*, Fermented Milk Containing *Lactobacillus casei* Strain Shirota Preserves the Diversity of the Gut Microbiota and Relieves Abdominal Dysfunction in Healthy Medical Students Exposed to Academic Stress. *Applied and environmental microbiology* **82**, 3649-3658 (2016).

51. T. Morishita, T. Fukada, M. Shirota, T. Yura, Genetic basis of nutritional requirements in *Lactobacillus casei*. *Journal of bacteriology* **120**, 1078-1084 (1974).
52. M. Derrien, E. E. Vaughan, C. M. Plugge, W. M. de Vos, *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *International journal of systematic and evolutionary microbiology* **54**, 1469-1476 (2004).
53. C. M. Dejea *et al.*, Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. *Science (New York, N.Y.)* **359**, 592-597 (2018).
54. T. L. Weir *et al.*, Stool microbiome and metabolome differences between colorectal cancer patients and healthy adults. *PloS one* **8**, e70803 (2013).
55. C. Dingemans *et al.*, *Akkermansia muciniphila* and *Helicobacter typhlonius* modulate intestinal tumor development in mice. *Carcinogenesis* **36**, 1388-1396 (2015).
56. A. Boleij *et al.*, Novel clues on the specific association of *Streptococcus gallolyticus* subsp. *gallolyticus* with colorectal cancer. *The Journal of infectious diseases* **203**, 1101-1109 (2011).
57. M. F. Tripodi *et al.*, *Streptococcus bovis* endocarditis and its association with chronic liver disease: an underestimated risk factor. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **38**, 1394-1400 (2004).
58. M. F. Tripodi, R. Fortunato, R. Utili, M. Triassi, R. Zarrilli, Molecular epidemiology of *Streptococcus bovis* causing endocarditis and bacteraemia in Italian patients. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* **11**, 814-819 (2005).
59. Y. Ogawa *et al.*, The genome of *Erysipelothrix rhusiopathiae*, the causative agent of swine erysipelas, reveals new insights into the evolution of firmicutes and the organism's intracellular adaptations. *Journal of bacteriology* **193**, 2959-2971 (2011).
60. R. Taddese *et al.*, Bacterial Zombies and Ghosts: Production of Inactivated Gram-Positive and Gram-Negative Species with Preserved Cellular Morphology and Cytoplasmic Content. *bioRxiv* 10.1101/458158, 458158 (2018).
61. D. Ahmed *et al.*, Epigenetic and genetic features of 24 colon cancer cell lines. *Oncogenesis* **2**, e71 (2013).
62. A. Eijkelenboom *et al.*, Reliable Next-Generation Sequencing of Formalin-Fixed, Paraffin-Embedded Tissue Using Single Molecule Tags. *The Journal of molecular diagnostics : JMD* **18**, 851-863 (2016).
63. T. Mosmann, Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *Journal of immunological methods* **65**, 55-63 (1983).
64. L. H. van der Maaten, Geoffrey, Visualizing Data using t-SNE. *Journal of Machine Learning Research* **9**, 2579--2605 (2008).
65. J. L. Bentley, Multidimensional binary search trees used for associative searching. *Commun. ACM* **18**, 509-517 (1975).
66. R. K. Aziz *et al.*, The RAST Server: rapid annotations using subsystems technology. *BMC genomics* **9**, 75 (2008).
67. Anonymous, "Poisson Distribution" in Univariate Discrete Distributions. 10.1002/0471715816.ch4, pp. 156-207.
68. Y. Xi, Z. Ma, H. Zhang, M. Yuan, L. Wang, Effects of *Clostridium difficile* toxin A on K562/A02 cell proliferation, apoptosis and multi-drug resistance. *Oncology letters* **15**, 4215-4220 (2018).
69. G. Dalmasso, A. Cougnoux, J. Delmas, A. Darfeuille-Michaud, R. Bonnet, The bacterial genotoxin colibactin promotes colon tumor growth by modifying the tumor microenvironment. *Gut Microbes* **5**, 675-680 (2014).
70. T. Fais, J. Delmas, N. Barnich, R. Bonnet, G. Dalmasso, Colibactin: More Than a New Bacterial Toxin. *Toxins* **10** (2018).
71. P. Dean, B. Kenny, The effector repertoire of enteropathogenic *E. coli*: ganging up on the host cell. *Current opinion in microbiology* **12**, 101-109 (2009).
72. A. P. Singh *et al.*, Enteropathogenic *E. coli* effectors EspF and Map independently disrupt tight junctions through distinct mechanisms involving transcriptional and post-transcriptional regulation. *Scientific reports* **8**, 3719 (2018).
73. T. M. Wassenaar, *E. coli* and colorectal cancer: a complex relationship that deserves a critical mindset. *Critical reviews in microbiology* **44**, 619-632 (2018).
74. N. Bossuet-Greif *et al.*, The Colibactin Genotoxin Generates DNA Interstrand Cross-Links in Infected Cells. *mBio* **9** (2018).

75. J. Ahn *et al.*, Human gut microbiome and risk for colorectal cancer. *Journal of the National Cancer Institute* **105**, 1907-1911 (2013).
76. Y. Yang *et al.*, *Fusobacterium nucleatum* Increases Proliferation of Colorectal Cancer Cells and Tumor Development in Mice by Activating Toll-Like Receptor 4 Signaling to Nuclear Factor-kappaB, and Up-regulating Expression of MicroRNA-21. *Gastroenterology* **152**, 851-866.e824 (2017).
77. M. Castellarin *et al.*, *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma. *Genome research* **22**, 299-306 (2012).
78. C. T. Ma, H. S. Luo, F. Gao, Q. C. Tang, W. Chen, *Fusobacterium nucleatum* promotes the progression of colorectal cancer by interacting with E-cadherin. *Oncology letters* **16**, 2606-2612 (2018).
79. J. Liu *et al.*, Proteomic characterization of outer membrane vesicles from gut mucosa-derived *fusobacterium nucleatum*. *Journal of proteomics* **195**, 125-137 (2019).
80. Y. W. Han *et al.*, Identification and Characterization of a Novel Adhesin Unique to Oral *Fusobacteria*. *Journal of bacteriology* **187**, 5330-5340 (2005).
81. C. L. Sears, The toxins of *Bacteroides fragilis*. *Toxicon* **39**, 1737-1746 (2001).
82. C. Jans, A. Boleij, The Road to Infection: Host-Microbe Interactions Defining the Pathogenicity of *Streptococcus bovis*/*Streptococcus equinus* Complex Members. *Frontiers in microbiology* **9**, 603 (2018).
83. A. Boleij, H. Tjalsma, The itinerary of *Streptococcus gallolyticus* infection in patients with colonic malignant disease. *Lancet Infect Dis* **13**, 719-724 (2013).
84. R. Kumar *et al.*, *Streptococcus gallolyticus* subsp. *gallolyticus* promotes colorectal tumor development. *PLoS Pathog* **13**, e1006440 (2017).
85. J. Yang *et al.*, Adenomatous polyposis coli (APC) differentially regulates beta-catenin phosphorylation and ubiquitination in colon cancer cells. *J Biol Chem* **281**, 17751-17757 (2006).
86. J. G. Tate *et al.*, COSMIC: the Catalogue Of Somatic Mutations In Cancer. *Nucleic acids research* **47**, D941-d947 (2019).
87. G. G. Sgro *et al.*, Bacteria-Killing Type IV Secretion Systems. *Frontiers in microbiology* **10**, 1078 (2019).
88. B. Kiersztyn, W. Siuda, R. J. Chrost, Persistence of bacterial proteolytic enzymes in lake ecosystems. *FEMS Microbiol Ecol* **80**, 124-134 (2012).
89. S. F. Battaglia-Hsu *et al.*, Vitamin B12 deficiency reduces proliferation and promotes differentiation of neuroblastoma cells and up-regulates PP2A, proNGF, and TACE. *Proceedings of the National Academy of Sciences of the United States of America* **106**, 21930-21935 (2009).
90. A. G. Wexler *et al.*, Human gut *Bacteroides* capture vitamin B12 via cell surface-exposed lipoproteins. *Elife* **7** (2018).
91. D. Patel, S. N. Witt, Ethanolamine and Phosphatidylethanolamine: Partners in Health and Disease. *Oxid Med Cell Longev* **2017**, 4829180 (2017).
92. O. Tsoy, D. Ravcheev, A. Mushegian, Comparative genomics of ethanolamine utilization. *Journal of bacteriology* **191**, 7157-7164 (2009).
93. K. G. Kaval, D. A. Garsin, Ethanolamine Utilization in Bacteria. *mBio* **9** (2018).
94. M. M. Kendall, C. C. Gruber, C.T. Parker, V. Sperandio, Ethanolamine controls expression of genes encoding components involved in interkingdom signaling and virulence in enterohemorrhagic *Escherichia coli* O157:H7. *mBio* **3** (2012).
95. M. van de Wetering *et al.*, Prospective derivation of a living organoid biobank of colorectal cancer patients. *Cell* **161**, 933-945 (2015).

Table 1: Secretomes and bacteria significantly enhancing or reducing cell growth rate (z-scores).

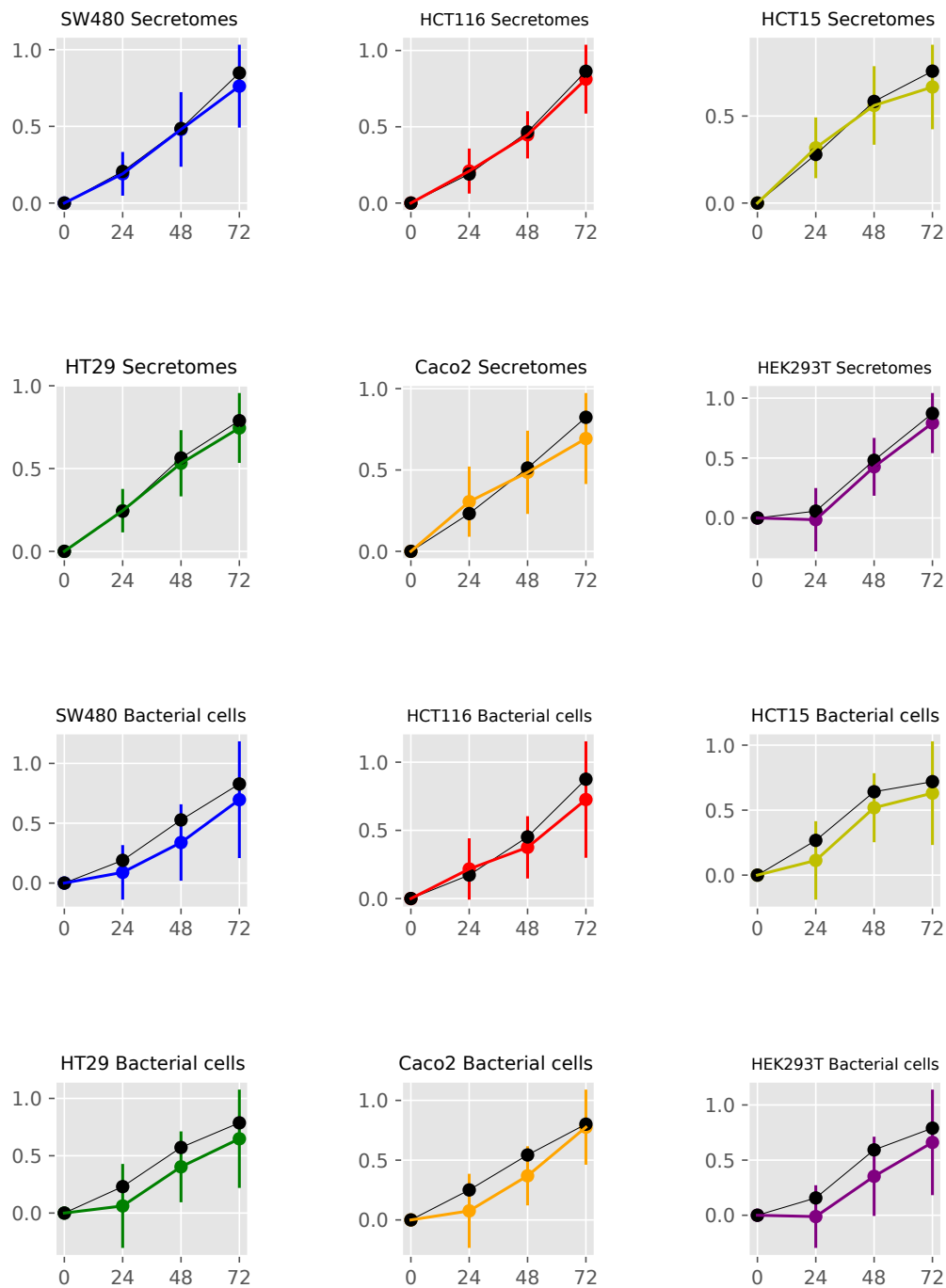
Family	Bacteria	Caco-2	HT29	HCT15	SW480	HCT116	HEK293 T
<i>Bacteroidaceae</i>	<i>B. dorei</i> 5_1_36/D4	0.89	0.82	1.36	0.90	1.87	1.38
	<i>B. eggerthii</i> 1_2_48FAA	1.82	0.59	1.51	1.16	1.21	1.48
	<i>B. fragilis</i> K570 clinda R (ETBF)	1.74	1.71	1.77	0.71	1.15	0.36
	<i>B. massiliensis</i> 3972 T(B)2	-0.44	-1.63	-0.83	-0.51	-1.45	-2.01
	<i>B. ovatus</i> 3_8_47FAA	1.96	0.17	1.17	1.27	1.24	1.42
	<i>Bacteroides</i> sp. 1_1_6	2.36	-0.21	0.63	0.86	1.27	0.93
	<i>Bacteroides</i> sp. 2_1_16	1.15	0.51	0.98	0.53	1.87	1.17
	<i>Bacteroides</i> sp. 2_1_22	-1.83	-0.73	-0.05	-0.49	0.82	-0.08
	<i>Bacteroides</i> sp. 2_1_22	-2.49	-2.26	-2.31	-1.64	-2.42	-1.78
	<i>Bacteroides</i> sp. 4_1_36	2.39	0.67	1.34	1.58	1.50	1.93
	<i>Bacteroides</i> sp. 9_1_42FAA	1.71	-0.06	0.71	1.09	1.46	0.87
	<i>Bacteroides</i> sp. D2	-1.82	-0.64	-0.04	-0.17	0.45	0.04
<i>Clostridiaceae</i>	<i>C. septicum</i> (Mace 1889) Ford 1927	-4.64	-5.02	-4.11	-2.63	-1.84	-4.49
<i>Enterobacteriaceae</i>	<i>E. coli</i> 4_1_47FAA	1.63	1.05	1.26	1.17	2.12	1.65
	<i>E. coli</i> D9	0.48	0.64	1.12	0.88	1.75	1.28
	<i>Klebsiella</i> sp. 1_1_55	0.77	1.15	1.19	0.57	1.92	0.70
<i>Erysipelotrichaceae</i>	<i>Coprobacillus</i> sp. 29_1	-0.06	1.32	1.94	1.03	0.81	0.91
	<i>Coprobacillus</i> sp. 29_1	0.40	1.84	1.64	1.15	0.72	0.21
	<i>Coprobacillus</i> sp. 8_2_54BFAA	0.68	1.78	1.59	1.15	0.82	0.46
	<i>Coprobacillus</i> sp. D7	1.02	1.64	1.74	1.18	0.80	0.58
	<i>Erysipelotrichaceae</i> bacterium 2_2_44A	1.07	1.26	1.70	0.95	1.82	0.68
	<i>Erysipelotrichaceae</i> bacterium 21_3	1.19	1.51	1.85	1.13	1.47	1.10
<i>Fusobacteriaceae</i>	<i>F. gonidiaformans</i> 3-1-5R	-0.43	-1.52	-2.62	-3.32	-2.16	-1.16
	<i>F. necrophorum</i> subsp. <i>funduliforme</i> 1_1_36S	1.18	1.98	1.12	1.71	2.63	1.72
	<i>F. nucleatum</i> subsp. <i>animalis</i> 11_3_2	-2.50	-2.86	-3.56	-3.09	-2.70	-0.77
	<i>F. nucleatum</i> subsp. <i>animalis</i> 11_3_2	2.15	0.48	1.11	0.96	2.09	1.20
	<i>F. nucleatum</i> subsp. <i>animalis</i> 21_1A	-1.45	-1.74	-2.31	-1.33	-1.47	-1.03
	<i>F. nucleatum</i> subsp. <i>animalis</i> 3_1_33	-0.66	-1.74	-2.07	-1.24	-1.60	-1.25
	<i>F. nucleatum</i> subsp. <i>animalis</i> 7_1	0.14	-0.72	-1.49	-1.83	-1.81	0.10
	<i>F. nucleatum</i> subsp. <i>animalis</i> 7_1	-1.86	-1.40	-2.48	-1.73	-1.30	-1.75
	<i>F. nucleatum</i> subsp. <i>nucleatum</i> ATCC 25586	-1.64	-1.67	-1.67	-1.89	-1.67	-2.04
	<i>F. nucleatum</i> subsp. <i>polymorphum</i> ATCC 10953	-1.51	-1.39	-1.33	-1.94	-1.60	-1.88
	<i>F. nucleatum</i> subsp. <i>vincentii</i> 3_1_27	-0.48	-1.88	-2.13	-1.65	-1.56	-1.20
	<i>F. nucleatum</i> subsp. <i>vincentii</i> 3_1_36A2	-0.95	-1.62	-2.24	-1.72	-1.17	-1.26
	<i>F. nucleatum</i> subsp. <i>vincentii</i> 4_1_13	-0.97	-1.92	-2.06	-1.52	-1.76	-1.45
	<i>F. periodonticum</i> 1_1_41FAA	-0.83	-1.94	-2.04	-1.27	-1.69	-1.48
	<i>F. periodonticum</i> 2_1_31	-3.10	-3.10	-3.38	-2.64	-2.44	-2.35
	<i>F. periodonticum</i> 2_1_31	-1.08	-1.32	-1.66	-0.86	-0.97	-1.90
<i>Lachnospiraceae</i>	<i>Anaerostipes</i> sp. 3_2_56FAA	-0.51	-1.67	-1.39	-2.08	-1.54	-1.47
	<i>C. symbiosum</i> WAL-14163	-1.01	-1.27	-1.75	-1.82	-0.70	-2.33
	<i>C. symbiosum</i> WAL-14673	-1.80	-1.20	-1.56	-2.32	-1.14	-1.14
	<i>Lachnospiraceae</i> bacterium 1_1_57FAA	2.04	0.78	0.80	1.62	0.60	0.81

	<i>Lachnospiraceae</i> bacterium 3_1_46FAA	-2.41	-1.37	-2.59	-2.30	-1.84	-3.22
	<i>Lachnospiraceae</i> bacterium 4_1_37FAA	1.98	0.93	1.19	1.46	1.80	1.23
	<i>Lachnospiraceae</i> bacterium 5_1_63FAA	0.50	1.68	1.81	1.04	0.09	1.04
	<i>Lachnospiraceae</i> bacterium 8_1_57FAA	-2.70	-1.52	-2.70	-2.30	-1.95	-3.24
<i>Tannerellaceae</i>	<i>Parabacteroides</i> sp. 2_1_7	0.06	0.17	0.56	0.88	1.89	0.73
	<i>Parabacteroides</i> sp. 2_1_7	1.73	-0.64	0.92	-0.04	0.32	0.41
	<i>Parabacteroides</i> sp. D13	0.86	0.56	1.04	1.22	2.21	1.10
<i>Streptococcaceae</i>	<i>S. bovis</i> 1212	0.23	1.64	0.40	0.62	-0.66	-0.41
	<i>S. bovis</i> 1417	0.49	1.65	0.39	0.67	-0.51	-0.02
	<i>S. bovis</i> 1459	0.63	2.10	0.84	1.13	0.94	0.53
	<i>S. bovis</i> 207	0.35	2.29	0.45	0.81	-0.59	-0.42
	<i>S. salivarius</i> NTB2	-0.98	-0.89	-1.73	-1.98	-1.52	-0.86
	<i>S. sp.</i> 2_1_36FAA	-1.57	-1.84	-0.52	-0.51	-1.73	-1.54
Other	<i>C. difficile</i> (Prévot 1938) Lawson et al. 2016	0.13	-1.75	-1.26	-2.10	-1.22	-2.04
	<i>Desulfovibrio</i> sp. 3_1_syn3	2.20	0.17	0.41	0.99	-0.37	-0.17
	<i>Desulfovibrio</i> sp. 3_1_syn3	-0.77	1.76	-0.40	-1.47	-1.77	-2.52
	<i>Desulfovibrio</i> sp. 6_1_46FAA	0.90	0.06	-0.87	-0.55	-1.75	-1.35
	<i>Desulfovibrio</i> sp. 6_1_46FAA	-0.78	1.17	-0.69	-1.93	-2.06	-3.17
	<i>Eubacterium</i> sp. 3_1_31	1.25	1.02	1.24	1.85	0.96	1.43
	<i>P. acidilactici</i> 7_4	-1.58	-0.82	0.71	0.33	-1.39	-1.95
	<i>Propionibacterium</i> sp. 5_U_42FAA	0.20	0.20	2.02	0.96	-0.31	-1.33
	<i>Pseudomonas</i> sp. 2_1_26	-4.60	-5.41	-4.35	-4.20	-2.87	-4.21
	<i>Pseudomonas</i> sp. 2_1_26	-0.02	-1.26	-0.72	-1.91	-1.45	0.35
	<i>Ralstonia</i> sp. 5_2_56FAA	-1.12	-0.28	0.99	-2.05	-0.36	-2.18
	<i>Ruminococcaceae</i> bacterium D16	-1.14	-1.53	-1.34	-1.23	-1.22	-2.50
	<i>Synergistes</i> sp. 3_1_syn1	-1.40	-1.60	-1.57	-1.34	-1.68	-2.09

Secretomes are highlighted in grey, green represents significant enhancement ($p < 0.05$) in cell growth rate and red represents significant reduction ($p < 0.05$) in cell growth rate.

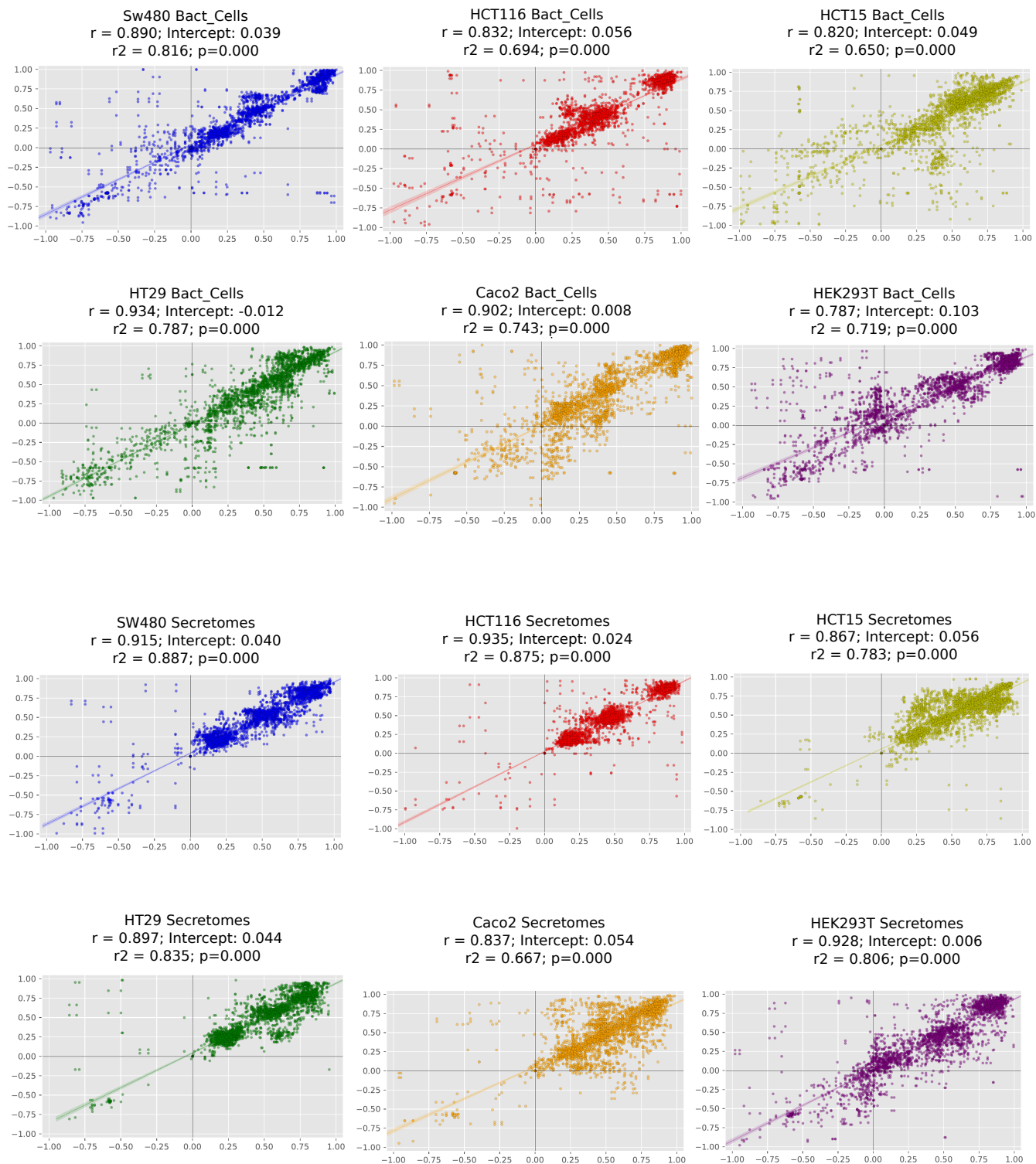
Supplementary Figure S1

Average growth of human cell lines

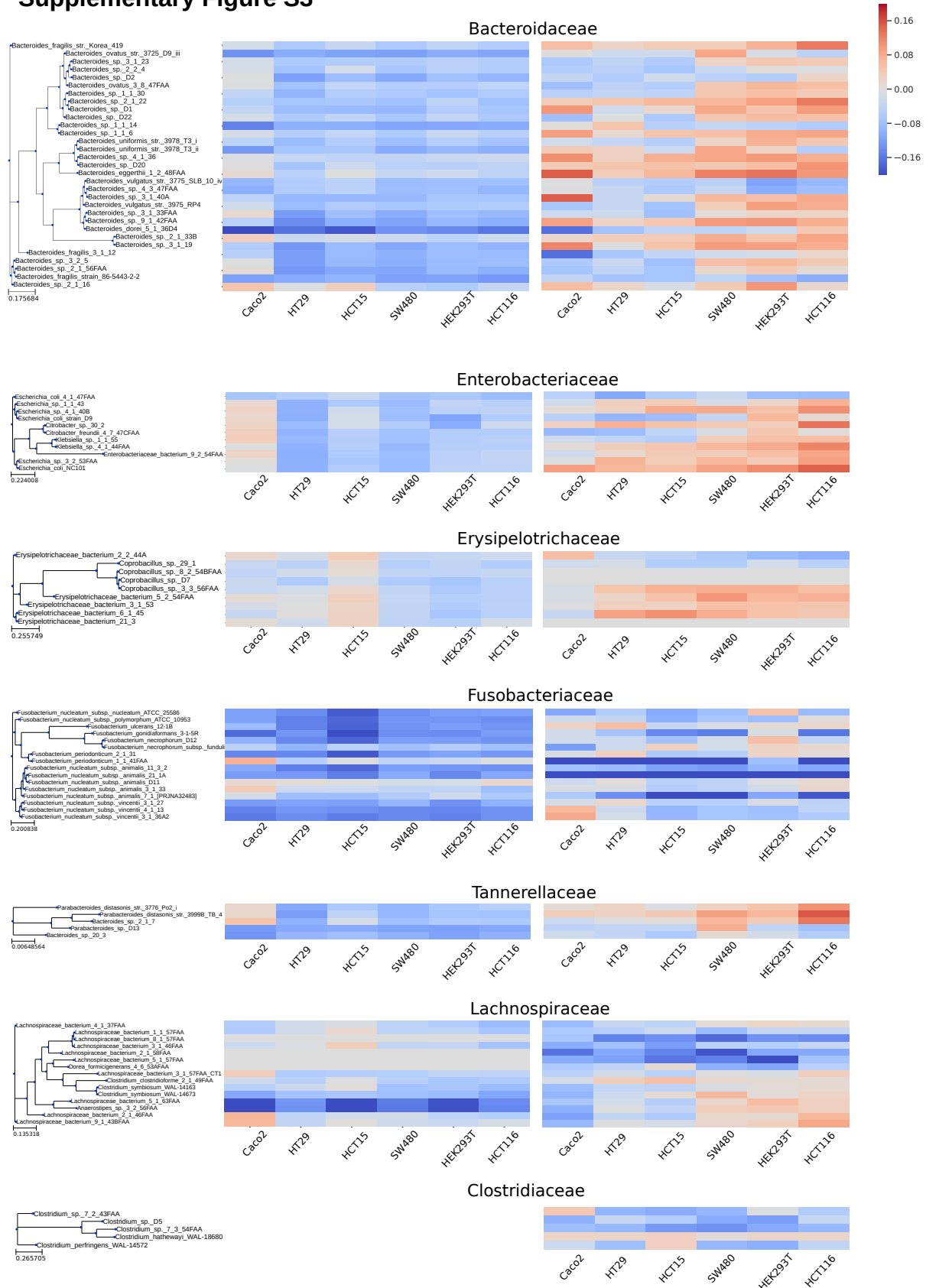


Supplementary Figure S2

Reproducibility of experimental replicates



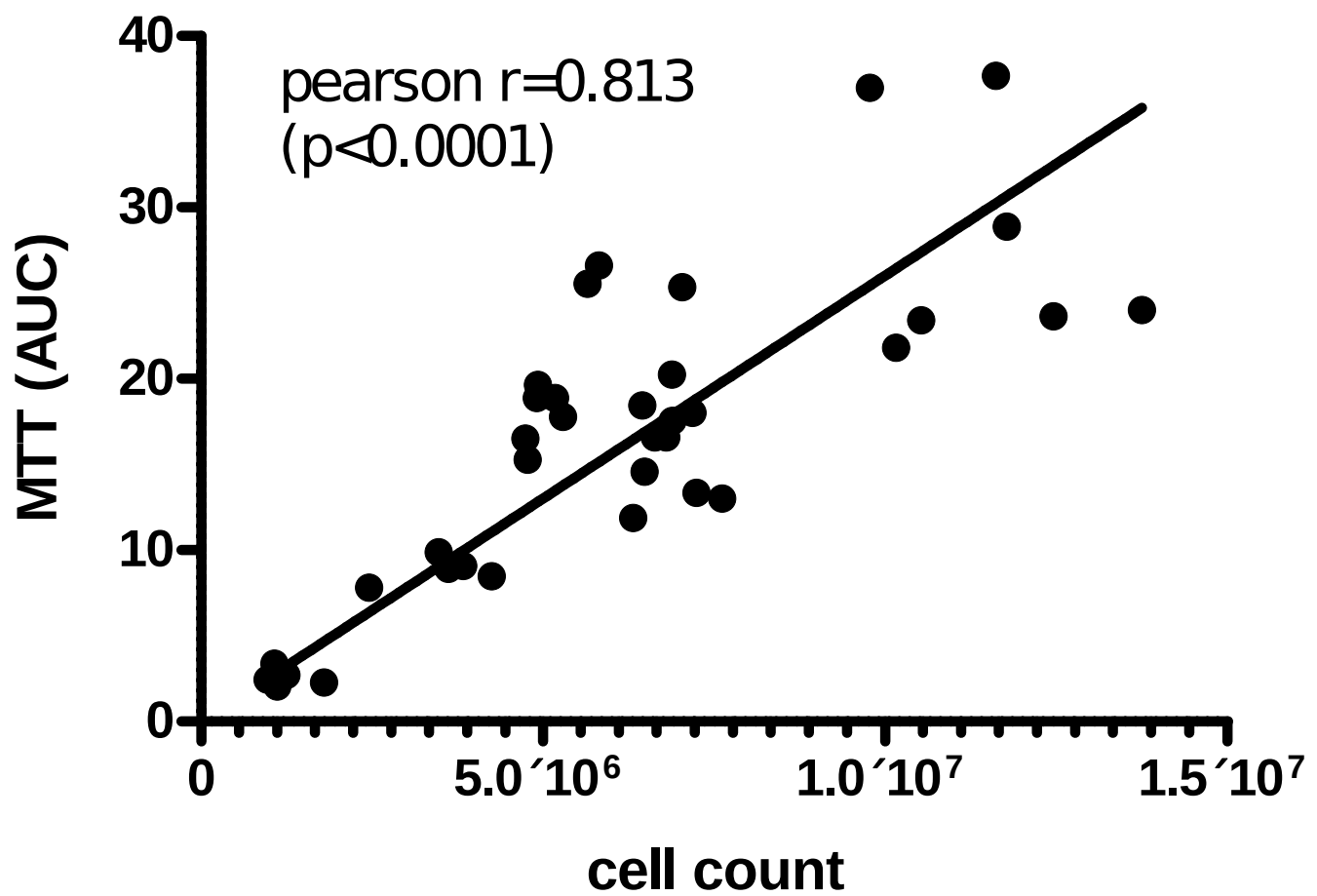
Supplementary Figure S3



Supplementary Figure S4



Supplementary Figure S5



Supplementary Table S1

Bacterial strain	Phylum	Family	Genome ID	Known Toxins	NCBI Taxon ID	Genome Status	GenBank Accessions	RefSeq Accessions	Contigs	Genome Length	GC Content	Isolation Source	Collection	Isolation Country	Host Name	Host Gender	Host Age	Host Health	Body Sample Site	Spoolation	Temperature	Growth condition	Medium
Citrobacter freundii 4_7_47CFAA	Proteobacteria	Enterobacteriaceae	742730.3	Map	742730 WGS	ADL000000000	-	-	36	5120174	52.1	isolated from an intestinal	University of Guelph, Canada	United States	Human, Homo sapiens	female	23	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Citrobacter sp. 30_2	Proteobacteria	Enterobacteriaceae	469595.3	Map	469595 WGS	ACDJ000000000	NZ_ACDJ000000000	18	525150	51.9	biopsy specimen	University of Guelph, Canada											
Bacteroides fragilis 86-5443-2-2 (ETBF)	Bacteroidetes	Bacteroidaceae	817.96	BFT	817 WGS	LDJ500000000	-	-	156	5128250	43.3	Stool sample	JHMI, USA										
Bacteroides fragilis K570 clinda R (ETBF)	Bacteroidetes	Bacteroidaceae	-	BFT	-	-	-	-	-	-	-	-	JHMI, USA										
Bacteroides fragilis VPI clinda R (ETBF)	Bacteroidetes	Bacteroidaceae	-	BFT	-	-	-	-	-	-	-	-	JHMI, USA	United States	Human, Homo sapiens	male	60	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Fusobacterium nucleatum DSM 15643 (ATCC 25586)	Fusobacteria	Fusobacteriaceae	190304.8	FadA	190304 Complete	AE009951	NC_003454	1	2174500	27.2	healthy biopsy tissue from a	University of Guelph, Canada											
Fusobacterium nucleatum DSM 20482 (ATCC 10953)	Fusobacteria	Fusobacteriaceae	393480.8	FadA	393480 WGS	AAR000000000	NZ_AARG000000000	2	2441632	26.8	healthy biopsy tissue from a	University of Guelph, Canada											
Fusobacterium nucleatum subsp. animalis 11_3_2	Fusobacteria	Fusobacteriaceae	457403.8	FadA	457403 WGS	ACU000000000	NZ_ACU000000000	81	2702139	26.9	60 year old male	University of Guelph, Canada											
Fusobacterium nucleatum subsp. animalis 21_1A	Fusobacteria	Fusobacteriaceae	469601.8	FadA	469601 WGS	ADEE000000000	NZ_ADEE000000000	49	2128810	26.8	40 year old female, inflamed biopsy tissue from a	University of Guelph, Canada	United States	Human, Homo sapiens	female	49	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Fusobacterium nucleatum subsp. animalis 3_1_33	Fusobacteria	Fusobacteriaceae	469603.3	FadA	469603 WGS	ACQE000000000	NZ_ACQE000000000	40	2307769	26.9	Crohn's disease	University of Guelph, Canada											
Fusobacterium nucleatum subsp. animalis 7_1	Fusobacteria	Fusobacteriaceae	457405.3	FadA	457405 WGS	ACDF000000000	NZ_ACDF000000000	18	2510873	26.8	healthy biopsy tissue from a 45 year old male patient	University of Guelph, Canada											
Fusobacterium nucleatum subsp. animalis D11	Fusobacteria	Fusobacteriaceae	556264.3	FadA	556264 WGS	ACDS000000000	NZ_ACDJ000000000	76	2446817	26.9	Crohn's disease	University of Guelph, Canada											
Fusobacterium nucleatum subsp. vincentii 4_1_13	Fusobacteria	Fusobacteriaceae	469606.3	FadA	469606 WGS	ACDE000000000	NZ_ACDE000000000	12	2268505	26.9	59 year old female	University of Guelph, Canada	United States	Human, Homo sapiens	female	59	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Fusobacterium periodonticum 1_1_41FAA	Fusobacteria	Fusobacteriaceae	469621.8	FadA	469621 WGS	ADGG000000000	-	80	2454647	27.9	inflamed biopsy tissue from a 25 year old female patient	University of Guelph, Canada											
Fusobacterium periodonticum 2_1_31	Fusobacteria	Fusobacteriaceae	469599.3	FadA	469599 WGS	ACDC000000000	NZ_ACDJ000000000	35	2532453	28.0	Crohn's disease	University of Guelph, Canada											
Fusobacterium sp. 3_1_36A2	Fusobacteria	Fusobacteriaceae	469604.7	FadA	469604 WGS	CP003700.1	NC_022196.1	51	2236033	26.9	healthy biopsy tissue from a 40 year old female patient	University of Guelph, Canada											
Klebsiella sp. 1_1_55	Proteobacteria	Enterobacteriaceae	469608.3	Map	469608 WGS	ACKA000000000	NZ_ACKA000000000	19	5459739	57.5	50 year old female	University of Guelph, Canada	South Korea	Human, Homo sapiens	female	40	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Klebsiella sp. 4_1_44FAA	Proteobacteria	Enterobacteriaceae	665944.3	Map	665944 WGS	ACW000000000	-	195	5478883	57.1	50 year old female	University of Guelph, Canada											
Escherichia coli DH5 alpha plks	Proteobacteria	Enterobacteriaceae	668369.7	pkA	668369 WGS	JRYM000000000	-	89	4507030	50.7	common laboratory strain	JHMI, USA											
Escherichia coli NC101	Proteobacteria	Enterobacteriaceae	733642.3	pkA, ShE11	733642 WGS	AEFA000000000	NZ_AEFA000000000	27	5021144	50.6	feces	JHMI, USA											
Escherichia coli Nissle 1917	Proteobacteria	Enterobacteriaceae	316435.10	pkA, ShE11	316435 Complete	CP007799	NZ_CP007799.1	1	5441200	50.6	inflamed biopsy tissue from a 52 year old male patient with Crohn's disease	Radboudumc, Netherlands	United States	Human, Homo sapiens	male	52	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Escherichia sp. 3_2_53FAA	Proteobacteria	Enterobacteriaceae	469598.5	pkA, Sh2A	469598 WGS	ACAC000000000	NZ_AACAC000000000	56	5175730	50.5	inflamed biopsy tissue from a 38 year old female with Crohn's disease	University of Guelph, Canada											
Escherichia coli NC101 delta pks	Proteobacteria	Enterobacteriaceae	-	ShE11	-	-	-	-	-	-	-	-											JHMI, USA
Escherichia sp. 4_1_40B	Proteobacteria	Enterobacteriaceae	457401.3	ShE11, Sh2A	457401 WGS	ACDM000000000	NZ_ACDM000000000	33	4934999	50.5	ulcerative colitis	University of Guelph, Canada											
Clostridium clostridioforme 2_1_49FAA	Firmicutes	Lachnospiraceae	742735.4	TcdA	742735 WGS	ADL100000000	-	148	5455952	48.9	50.5 ulcerative colitis	University of Guelph, Canada	United States	Human, Homo sapiens	female	38	ulcerative colitis	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Clostridium hathewayi WAL-18680	Firmicutes	Clostridiaceae	742737.3	TcdA	742737 WGS	ADL100000000	-	142	5654180	50.0	50.5 ulcerative colitis	University of Guelph, Canada											
Clostridium perfringens WAL-14572	Firmicutes	Clostridiaceae	742739.3	TcdA	742739 WGS	ADL100000000	-	35	3462156	28.1	healthy biopsy tissue from a 19 year old female patient	University of Guelph, Canada											
Clostridium sp. 7_3_54FAA	Firmicutes	Clostridiaceae	665940.3	TcdA	665940 WGS	ACW000000000	-	172	5432458	48.1	45 year old female patient	University of Guelph, Canada											
Clostridium symbiosum WAL-14163	Firmicutes	Lachnospiraceae	742740.3	TcdA	742740 WGS	ADL000000000	NZ_ADL000000000	52	5352498	47.4	50.7 common laboratory strain	University of Guelph, Canada	United States	Human, Homo sapiens	male	55	Crohn's disease	Gastrointestinal tract	Yes	37 °C	Anaerobic	RCM	
Clostridium symbiosum WAL-14673	Firmicutes	Lachnospiraceae	742741.3	TcdA	742741 WGS	ADLR000000000	NZ_ADLR000000000	55	4916964	47.6	the human gastrointestinal	University of Guelph, Canada											
Acidaminococcus sp. D21	Firmicutes	Acidaminococcaceae	563191.3	WGS	563191 WGS	ACGB000000000	NZ_ACGB000000000	79	2238973	50.2	the human gastrointestinal	University of Guelph, Canada											
Akkermansia muciniphila	Verrucomicrobia	Akkermansiaceae	-	-	-	-	-	-	-	-	-	-											JHMI, USA
Bacillus smithii 7_3_47FAA	Firmicutes	Bacillaceae	665952.3	-	665952 WGS	ACWF000000000	-	175	3224201	40.7	inflamed biopsy tissue from a 40.7 patient with Crohn's disease	University of Guelph, Canada	United States	Human, Homo sapiens			Crohn's disease	Gastrointestinal tract	Yes	50 °C	Anaerobic	NB	
Bacteroides fragilis 3_1_36D4	Bacteroidetes	Bacteroidaceae	556260.3	-	556260 WGS	ACDI000000000	NZ_ACDI000000000	42	5530727	41.7	Crohn's disease	University of Guelph, Canada											
Bacteroides fragilis 3_1_12	Bacteroidetes	Bacteroidaceae	665953.3	-	665953 WGS	ACWG000000000	NZ_ACWG000000000	41	4586481	44.5	symptoms	University of Guelph, Canada											
Bacteroides fragilis 9343 delta cap	Bacteroidetes	Bacteroidaceae	457424.5	-	457424 WGS	ABZX000000000	NZ_ABZX000000000	33	5530115	43.6	52 year old female	University of Guelph, Canada											
Bacteroides fragilis 9343 delta cap delta pilus 77	Bacteroidetes	Bacteroidaceae	-	-	-	-	-	-	-	-	-	-	JHMI, USA	United States	Human, Homo sapiens	male	25	irritable bowel syndrome	Gastrointestinal tract; Terminal ileum	No	37 °C	Anaerobic	BHI-S
Bacteroides fragilis 9343 delta tsr 15 M4	Bacteroidetes	Bacteroidaceae	-	-	-	-	-	-	-	-	-	-	JHMI, USA										
Bacteroides fragilis NCTC 9343 (NTBF)	Bacteroidetes	Bacteroidaceae	272559.47	-	272559 WGS	OCGB010000000	-	3523	4438570	50.9	44.5 symptoms	University of Guelph, Canada											
Bacteroides massiliensis 3972 T1(B)2	Bacteroidetes	Bacteroidaceae	-	-	-	-	-	-	-	-	-	-	JHMI, USA										
Bacteroides ovatus 3_8_47FAA	Bacteroidetes	Bacteroidaceae	665954.3	-	665954 WGS	ACWH000000000	NZ_ACWH000000000	42	6545234	42.4	50 year old female patient	University of Guelph, Canada	United States	Human, Homo sapiens	female	25	Crohn's disease	Gastrointestinal tract; Sigmoid colon	No	37 °C	Anaerobic	BHI-S	
Bacteroides ovatus 3729 DIII	Bacteroidetes	Bacteroidaceae	133947.3	-	133947 WGS	JNH000000000	-	556	6980703	42.4	tissue	JHMI, USA											
Bacteroides ovatus 547R17	Bacteroidetes	Bacteroidaceae	-	-	-	-	-	-	-	-	-	-											JHMI, USA
Bacteroides sp. 1_1_14	Bacteroidetes	Bacteroidaceae	469585.3	-	469585 WGS	ACRP000000000	NZ_ACRP000000000	57	6446424	42.9	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 1_1_30	Bacteroidetes	Bacteroidaceae	457387.3	-	457387 WGS	ADCL000000000	NZ_ADCL000000000	171	6441725	42.2	the human gastrointestinal	University of Guelph, Canada	United States	Human, Homo sapiens	male	40	microscopic colitis	Gastrointestinal tract; Transverse colon	No	37 °C	Anaerobic	BHI-S	
Bacteroides sp. 1_1_6	Bacteroidetes	Bacteroidaceae	469586.3	-	469586 WGS	ACIC000000000	NZ_ACDI000000000	71	6855195	43.1	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 2_1_16	Bacteroidetes	Bacteroidaceae	469587.3	-	469587 WGS	ACPP000000000	NZ_ACP000000000	18	5236303	43.2	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 2_1_22	Bacteroidetes	Bacteroidaceae	469588.3	-	469588 WGS	ACPD000000000	NZ_ACPQ000000000	36	6003748	41.9	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 2_1_33B	Bacteroidetes	Bacteroidaceae	469589.3	-	469589 WGS	ACPR000000000	NZ_ACP000000000	24	4927045	44.9	the human gastrointestinal	University of Guelph, Canada	United States	Human, Homo sapiens	female	54	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Bacteroides sp. 2_1_56FAA	Bacteroidetes	Bacteroidaceae	665938.3	-	665938 WGS	NZ_ACDI000000000	-	96	5632316	43.5	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 2_2_4	Bacteroidetes	Bacteroidaceae	469590.5	-	469590 WGS	ABZ200000000	NZ_ABZ200000000	64	7101224	42.1	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 3_1_19	Bacteroidetes	Bacteroidaceae	469592.4	-	469592 WGS	ADJC000000000	NZ_ACDJ000000000	20	5501116	44.8	tissue	University of Guelph, Canada											
Bacteroides sp. 3_1_23	Bacteroidetes	Bacteroidaceae	457390.3	-	457390 WGS	ACRS000000000	-	36	6205278	41.5	gastrointestinal tract	University of Guelph, Canada	United States	Human, Homo sapiens	female	59	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Bacteroides sp. 3_1_53FAA	Bacteroidetes	Bacteroidaceae	457391.3	-	457391 WGS	ACPS000000000	NZ_ACP000000000	35	5419714	42.0	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 3_1_40A	Bacteroidetes	Bacteroidaceae	469593.3	-	469593 WGS	ACRT000000000	NZ_ACDI000000000	73	5505782	42.1	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 3_2_5	Bacteroidetes	Bacteroidaceae	457392.3	-	457392 WGS	ACIB000000000	NZ_ACDI000000000	48	5157255	43.2	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 4_1_36	Bacteroidetes	Bacteroidaceae	457393.3	-	457393 WGS	ACTC000000000	NZ_ACDI000000000	38	4638757	45.8	the human gastrointestinal	University of Guelph, Canada	United States	Human, Homo sapiens	male	45	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Bacteroides sp. 4_3_47FAA	Bacteroidetes	Bacteroidaceae	457394.3	-	457394 WGS	ACDR000000000	NZ_ACDI000000000	88	5452289	42.7	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. 9_1_42FAA	Bacteroidetes	Bacteroidaceae	457395.6	-	457395 WGS	ACAA000000000	NZ_ACDI000000000	50	5622644	42.3	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. D1	Bacteroidetes	Bacteroidaceae	556258.5	-	556258 WGS	ACAB000000000	NZ_ACDI000000000	58	5986762	41.9	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. D2	Bacteroidetes	Bacteroidaceae	556259.3	-	556259 WGS	ACGA000000000	NZ_ACDI000000000	20	6943133	41.7	the human gastrointestinal	University of Guelph, Canada	United States	Human, Homo sapiens	female	54	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Bacteroides sp. D20	Bacteroidetes	Bacteroidaceae	585543.3	-	585543 WGS	ACPT000000000	NZ_ACDI000000000	15	4487454	46.4	the human gastrointestinal	University of Guelph, Canada											
Bacteroides sp. D22	Bacteroidetes	Bacteroidaceae	585544.3	-	585544 WGS	ADCK000000000	NZ_ACDI000000000	94	6344045	41.6	the human gastrointestinal	University of Guelph, Canada											
Bacteroides stercoris 3972 D14 (B)	Bacteroidetes	Bacteroidaceae	-	-	-	-	-	-	-	-	-	-											JHMI, USA
Bacteroides thetaiotaomicron VPI5482	Bacteroidetes	Bacteroidaceae	226186.12	-	226186 Complete	AE015928.VI171001	-	2	6203399	42.9	the feces of a healthy adult	JHMI, USA	United States	Human, Homo sapiens	male	59	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Bacteroides uniformis 3978 T31	Bacteroidetes	Bacteroidaceae	133948.3	-	133948 WGS	JHHC000000000	-	47	5047633	46.4	tissue	JHMI, USA											
Bacteroides uniformis 3978 T31	Bacteroidetes	Bacteroidaceae	133949.3	-	133949 WGS	JHHC000000000	-	185	4073214	46.3	tissue	JHMI, USA											
Bacteroides vulgatus 3775 S1(B)10lv	Bacteroidetes	Bacteroidaceae	133950.3	-	133950 WGS	JHHC000000000	-	134	5443924	42.3	tissue	JHMI, USA											
Bacteroides vulgatus 3975 RP4	Bacteroidetes	Bacteroidaceae	133952.3	-	133952 WGS	JHHC000000000	-	184	4896967	42.2	tissue	JHMI, USA	United States	Human, Homo sapiens	male	59	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S	
Bacteroides stercoris 4009 NB117	Bacteroidetes	Bacteroidaceae	-	-	-	-	-	-	-	-	-	-											JHMI, USA
Actinobacterium sp. 12_1_47BFAA	Actinobacteria	Bifidobacteriaceae	468594.3	-	468594 WGS	ADCM000000000	NZ_ACDN000000000	61	2405960	60.0													

Desulfovibrio sp. 3_1_syn3	Proteobacteria	Desulfovibrionaceae	457398.5	457398 WGS	ADDR000000000	NZ_ADDR000000000	58	3725567	59.1 60 year old female	University of Guelph, Canada	Human, Homo sapiens	female	60	Gastrointestinal tract	No	37 °C	Anaerobic	Desulfo medium (ATCC Medium: 2755 Desulfovibrio Medium)	
Desulfovibrio sp. 6_1_46FAAA	Proteobacteria	Desulfovibrionaceae	665942.3	665942 WGS	ACWM000000000	-	97	3826115	61.1	University of Guelph, Canada					No	37 °C	Anaerobic	Desulfo medium (ATCC Medium: 2755 Desulfovibrio Medium)	
Enterobacteriaceae bacterium 9_2_54FAA	Proteobacteria	Enterobacteriaceae	469613.3	469613 WGS	ADCU000000000	NZ_ADCU000000000	38	4679347	47.9 Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	male	74	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Escherichia coli 4_1_4773FAA	Proteobacteria	Enterobacteriaceae	1127356.4	1127356 WGS	ACTG000000000	NZ_CP010152.1.NZ_CP010153.1.NZ_CP010154.1.NZ_CP010155.1.NZ_CP010156.1	109	5256230	50.6	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Escherichia coli D9	Proteobacteria	Enterobacteriaceae	56,213,757	562 Complete	CP010152.CP010153.CP010154.CP010155.CP010156					University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Escherichia coli PL1	Proteobacteria	Enterobacteriaceae								JHMI, USA					No	37 °C	Anaerobic	BHI-S	
Escherichia sp. 1_1_43	Proteobacteria	Enterobacteriaceae	457400.3	457400 WGS	ACID000000000	NZ_ACID000000000	43	2235585	51.1 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	59	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Enterococcus saccharolyticus 30_1	Firmicutes	Enterococcaceae	742813.4	742813 WGS	ADLV000000000	-	61	3119200	40.7	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Coprobacillus sp. 29_1_D6	Firmicutes	Erysipelotrichaceae	469596.3	469596 WGS	ADKX000000000	NZ_ADKX000000000	38	3857363	31.1	University of Guelph, Canada	Human, Homo sapiens				No	37 °C	Anaerobic	BHI-S	
Coprobacillus sp. 3_3_56FAA	Firmicutes	Erysipelotrichaceae	665941.3	665941 WGS	ACWL000000000	-	106	3952410	31.3	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Coprobacillus sp. 8_2_54BFAA	Firmicutes	Erysipelotrichaceae	469597.4	469597 WGS	ACTG000000000	-	21	3785849	31.8	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Coprobacillus sp. D7	Firmicutes	Erysipelotrichaceae	556270.3	556270 WGS	ACDT000000000	NZ_ACDT000000000	95	3561737	31.4 Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	59	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Erysipelotrichaceae bacterium 2_2_44A	Firmicutes	Erysipelotrichaceae	457422.3	457422 WGS	ADCR200000000	-	89	4966377	43.34	University of Guelph, Canada					No	37 °C	Anaerobic	BHI w/ 0.1% Tween 80, pH 8.0	
Erysipelotrichaceae bacterium 21_3	Firmicutes	Erysipelotrichaceae	658657.3	658657 WGS	ACTI000000000	-	37	4403767	43.7	University of Guelph, Canada					No	37 °C	Anaerobic	BHI w/ 0.1% Tween 80, pH 8.0	
Erysipelotrichaceae bacterium 3_1_53	Firmicutes	Erysipelotrichaceae	658659.3	658659 WGS			85	4486197		University of Guelph, Canada	Human, Homo sapiens				No	37 °C	Anaerobic	BHI w/ 0.1% Tween 80, pH 8.0	
Erysipelotrichaceae bacterium 5_2_54FAA	Firmicutes	Erysipelotrichaceae	552396.3	552396 WGS			48	3193878		University of Guelph, Canada	Human, Homo sapiens				No	37 °C	Anaerobic	BHI w/ 0.1% Tween 80, pH 8.0	
Erysipelotrichaceae bacterium 6_1_45	Firmicutes	Erysipelotrichaceae	469614 WGS	469614 WGS	ACTK000000000	-	91	4835437	44.0	University of Guelph, Canada					No	37 °C	Anaerobic	BHI w/ 0.1% Tween 80, pH 8.0	
Eubacterium sp. 3_1_31	Firmicutes	Eubacteriaceae	457402.3	457402 WGS	ACTL000000000	-	45	3065786	37.9 fecal sample	University of Guelph, Canada	Human, Homo sapiens				No	37 °C	Anaerobic	BHI-S	
Fusobacterium gonidiformans 3-1-5R	Fusobacteria	Fusobacteriaceae	469605.7	469605 WGS	ACDD000000000	-	99	1848430	32.3	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Fusobacterium necrophorum D12	Fusobacteria	Fusobacteriaceae	556263 WGS	556263 WGS	ACDO000000000	-	118	1950825	35.2	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Fusobacterium necrophorum subsp. funduliforme 1_1_36S	Fusobacteria	Fusobacteriaceae	742814 WGS	742814 WGS	ADLZ000000000	NZ_CP007064.1.NZ_CP007065.1.NZ_CP007066.1	39	2300242	34.6	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Fusobacterium nucleatum subsp. vincentii 3_1_27	Fusobacteria	Fusobacteriaceae	469602.7	469602 WGS	CP007064.1.CP007065.1.NZ_CP007066.1	-	77	2197574	27.0	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Fusobacterium ulcerans 12-1B	Fusobacteria	Fusobacteriaceae	457404.5	457404 WGS	AGWJ000000000	-	38	3677742	30.3	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Anaerostipes sp. 3_2_56FAA	Firmicutes	Lachnospiraceae	665937.3	665937 WGS	ACWB000000000	NZ_ACWB000000000	13	3286322	44.0 Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	29	Crohn's disease	Gastrointestinal tract	Yes	37 °C	Anaerobic	RCM
Dorea formicigenerans 4_6_53AFAA	Firmicutes	Lachnospiraceae	742765.5	742765 WGS	ADLU000000000	-	143	3825700	40.3	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Lachnospiraceae bacterium 1_1_57FAA	Firmicutes	Lachnospiraceae	658081.3	658081 WGS	ACTM000000000	NZ_ACTM000000000	92	2910479	41.9 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	22	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lachnospiraceae bacterium 2_1_46FAA	Firmicutes	Lachnospiraceae	742723.3	742723 WGS	ADLB000000000	NZ_ADLB000000000	46	2204631	39.8	University of Guelph, Canada	Human, Homo sapiens				No	37 °C	Anaerobic	BHI-S	
Lachnospiraceae bacterium 2_1_58FAA	Firmicutes	Lachnospiraceae	658082.3	658082 WGS	ACTO000000000	-	90	3437939	42.4 feces	University of Guelph, Canada	Human, Homo sapiens				No	37 °C	Anaerobic	BHI-S	
Lachnospiraceae bacterium 3_1_46FAA	Firmicutes	Lachnospiraceae	665950.3	665950 WGS	ACWP000000000	NZ_ACWP000000000	80	3092386	42.0 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	46	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lachnospiraceae bacterium 3_1_57FAA_CT1	Firmicutes	Lachnospiraceae	658086.3	658086 WGS	ACTP000000000	NZ_ACTP000000000	145	7693209	46.8 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	22	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lachnospiraceae bacterium 5_1_57FAA	Firmicutes	Lachnospiraceae	658085.3	658085 WGS	ACTR000000000	NZ_ACTR000000000	64	3336973	46.3 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	22	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lachnospiraceae bacterium 5_1_63FAA	Firmicutes	Lachnospiraceae	658089.3	658089 WGS	ACTS000000000	NZ_ACTS000000000	48	3041190	37.1 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	51	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lachnospiraceae bacterium 6_1_37FAA	Firmicutes	Lachnospiraceae	552395.3	552395 WGS	ADCR000000000	NZ_ADCR000000000	15	3067358	40.9 human fecal sample	University of Guelph, Canada	Human, Homo sapiens	female	71	Crohn's disease colitis	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lachnospiraceae bacterium 8_1_57FAA	Firmicutes	Lachnospiraceae	665951.3	665951 WGS	ACWQ000000000	NZ_ACWQ000000000	51	2927350	41.6 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	22	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lachnospiraceae bacterium 9_1_43BFAA	Firmicutes	Lachnospiraceae	658088.3	658088 WGS	ACTX000000000	NZ_ACTX000000000	26	2840852	41.4 with Crohn's disease	University of Guelph, Canada	Human, Homo sapiens	female	59	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Lactobacillus casei Shirota	Firmicutes	Lactobacillaceae								Radboudumc, Netherlands					No	37 °C	Anaerobic	BHI-S	
Pedococcus acididactyl 7_4	Firmicutes	Lactobacillaceae	563194.3	563194 WGS	ACXB000000000	NZ_ACXB000000000	9	2017888	42.0 tract	University of Guelph, Canada	Human, Homo sapiens	male	45	Crohn's disease	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Peptostreptococcus stomatis DSM17678	Firmicutes	Peptostreptococcaceae	595115.3	595115 WGS	ADCG000000000	NZ_ADCG000000000	74	1989044	36.7 the human oral cavity	DSMZ	Human, Homo sapiens			Oral	No	37 °C	Anaerobic	BHI-S	
Propionibacterium sp. 5_U_42AFAA	Actinobacteria	Propionibacteriaceae	450748.3	450748 WGS	ACJE000000000	-	14	2530254	60.1	University of Guelph, Canada					No	37 °C	Anaerobic	BHI-S	
Pseudomonas sp. 2_1_26	Proteobacteria	Pseudomonadaceae	665948.3	665948 WGS	ACWU000000000	-	293	6282392	66.4 gastrointestinal tract	University of Guelph, Canada	Human, Homo sapiens				No	37 °C	Aerobic	NB	
Ruminococcaceae bacterium D16	Firmicutes	Ruminococcaceae	552398.3	552398 WGS	ADDX000000000	NZ_ADDX000000000	104	3210947	56.8 57 year old male	University of Guelph, Canada	Human, Homo sapiens	male	57		Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Streptococcus agalactiae ATCC 13813	Firmicutes	Streptococcaceae	888745.3	888745 WGS	AEQO000000000	-	134	2114958	35.3 oral cavity	ATCC	Human, Homo sapiens			Oral	No	37 °C	Anaerobic	BHI-S	
Streptococcus bovis 1067	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1212	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1293	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1294	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1361	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1364	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1365	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1417	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1445	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 1459	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 207	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis 992	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis NCTC8133	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Italy, Napoli	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis NTB22	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Nijmegen	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus bovis NTB7	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Nijmegen	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus 9L-1503 1121 L	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Weert	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus NTB1	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Nijmegen	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus NTB11	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Amsterdam	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus NTB12	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Nijmegen	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus NTB4	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Nijmegen	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus subsp. macedonicus NTB3	Firmicutes	Streptococcaceae	this study						Blood	Radboudumc, Netherlands	Netherlands, Nijmegen	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus UCN34	Firmicutes	Streptococcaceae	637909.5	637909 Complete	FN597254	NC_013798	1	2350911	37.6 colon cancer, blood	Radboudumc, Netherlands	France, Institut Pasteur	Human, Homo sapiens			Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus gallolyticus UCN50	Firmicutes	Streptococcaceae								Radboudumc, Netherlands	France, Institut Pasteur				Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus macedonicus 19A5	Firmicutes	Streptococcaceae	59310.16	59310 WGS	PEBN010000000	-	98	2249955	37.3 Asiago cheese	Radboudumc, Netherlands	Italy, Thiene				Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus macedonicus 33H0	Firmicutes	Streptococcaceae	59310.8	59310 WGS	JNCV000000000	-	76	2223217	37.4 curd of Morlazzo cheese	Radboudumc, Netherlands	Italy, Thiene				Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus macedonicus 85P	Firmicutes	Streptococcaceae	this study						Spressa cheese	Radboudumc, Netherlands	Italy, Thiene				Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus macedonicus ACA-DC 205	Firmicutes	Streptococcaceae	this study						Greek Kasseri cheese	Radboudumc, Netherlands	Greece, Athens				Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus macedonicus CIP105685T	Firmicutes	Streptococcaceae	this study							Radboudumc, Netherlands	France, Institut Pasteur				Blood	No	37 °C	Anaerobic	BHI-S
Streptococcus salivarius NTB2	Firmicutes	Streptococcaceae	this study																

Synergistes sp. 3_1_syn1	Synergistetes	Synergistaceae	457415.3	457415 WGS	ACUH000000000	-	65	3281561	56.1	University of Guelph, Canada					No	37 °C	Anaerobic	Synergistes medium		
Parabacteroides distasonis 39998 T(B)4	Bacteroidetes	Tannerellaceae	1339344.3	1339344 WGS	JNHP000000000	-	180	5315679	44.9 tissue	JHMI, USA	United States	Human, Homo sapiens	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S			
Parabacteroides distasonis 3776 Po2 I	Bacteroidetes	Tannerellaceae	1339341.3	1339341 WGS	JNHL000000000	-	172	5288232	44.9 tissue	JHMI, USA	United States	Human, Homo sapiens	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S			
Parabacteroides sp. 2_1_7									inflamed biopsy tissue from a 37 year old female patient											
	Bacteroidetes	Tannerellaceae	457388.5	457388 WGS	ABZY000000000	NZ_ABZY000000000	38	5180144	45.1 with ulcerative colitis	University of Guelph, Canada		Human, Homo sapiens	female	37	ulcerative colitis	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
Parabacteroides sp. 20_3	Bacteroidetes	Tannerellaceae	469591.4	469591 WGS	ACRQ000000000	NZ_ACRQ000000000	61	5749901	45.0 tract	University of Guelph, Canada		Human, Homo sapiens	female	49		Gastrointestinal tract; Colon	No	37 °C	Anaerobic	BHI-S
									inflamed biopsy tissue from a 27 year old male patient with ulcerative colitis											
Parabacteroides sp. D13	Bacteroidetes	Tannerellaceae	563193.3	563193 WGS	ACPW000000000	NZ_ACPW000000000	22	5370710	45.2 ulcerative colitis	University of Guelph, Canada		Human, Homo sapiens	male	27	ulcerative colitis	Gastrointestinal tract	No	37 °C	Anaerobic	BHI-S
									healthy biopsy tissue from a 25 year old male patient with											
Veillonella sp. 3_1_44	Firmicutes	Veillonellaceae	457416.3	457416 WGS	ADCV000000000	NZ_ADCV000000000	16	2163458	38.6 Crohn's disease	University of Guelph, Canada		Human, Homo sapiens	male	25	Crohn's disease	Gastrointestinal tract; Descending colon	No	37 °C	Anaerobic	RCM+ (ATCC 1252)

Supplementary Table S2: smMIP mutation analysis

			Mutations confirmed from Ahmed et al.(2013)							From Ahmed et al. (2013) ^b		additional variants detected with smMIP panel															
Cel Lines	gender	MSI/MSS ^a	KRAS	%	BRAF	%	PIK3CA	%	PTEN	TP53	CTNNB1	%	CXCR4	%	EGFR	%	HRAS	%	MYD88	%	PDGFRA	%	SF3B1	%			
<u>HCT116</u>	<u>F</u>	<u>MSI</u>	c.38G>A (p.Gly13Asp)	51	--	--	c.3140A>G (p.His1047Arg)	51	--	--	c.133_135delTCT (p.Ser45del)	54	c.1002C>A p.=	58%	c.2361G>A p.=	100	--	--	c.510G>A (p.Met170Ile)	50	c.1701A>G p.=	100	c.2631T>C p.=	52			
<u>CACO-2</u>	<u>F</u>	<u>MSS</u>	--	--	--	--	--	--	--	c.610G>T (p.Glu204*)	--	--	--	--	c.2361G>A p.=	49	c.81T>C p.=	100	--	--	c.1701A>G p.=	100	c.2631T>C p.=	21			
<u>HCT15</u>	<u>M</u>	<u>MSI</u>	c.38G>A (p.Gly13Asp)	51	--	--	c.1633G>A (p.Glu545Lys) & c.1645G>A (p.Asp549Asn)	52	--	c.722C>T (p.Ser241Phe)	--	--	--	--	c.2361G>A p.=	51	c.81T>C p.=	46	c.790C>T (p.Arg264Ter)	49	c.1701A>G p.=	100	c.2631T>C p.=	52			
<u>HT29</u>	<u>F</u>	<u>MSS</u>	--	--	c.1799T>A (p.Val600Glu)	24	--	--	--	c.818G>A (p.Arg273His)	--	--	--	--	c.2361G>A p.=	68	c.81T>C p.=	81	--	--	c.1701A>G p.=	100	c.2631T>C p.=	100			
<u>SW480</u>	<u>F</u>	<u>MSS</u>	c.35G>T (p.Gly12Val)	100	--	--	--	--	--	c.818G>A (p.Arg273His) & c.925C>T (p.Pro309Ser)	--	--	--	--	c.2361G>A p.=	100	c.81T>C p.=	100	--	--	c.1701A>G p.= c.2472C>T p.=	100	c.2631T>C p.=	34			
<u>HEK293T</u>	<u>F</u>	<u>MSS</u>	--	--	--	--	--	--	ND	ND	--	--	--	--	c.2361G>A p.=	100	--	--	--	--	c.1701A>G p.=	100	c.2631T>C p.=	100			

green cells represent pathogenic mutations, ND = not done, ^aMSI (based on BAT25, NR21, NR22, NR24, NR27), ^bnot tested with smMIP panel
no variants detected in *CHEK2*, *ERBB2*, *EZH2*, *GNA11*, *GNAQ*, *GNAS*, *H3F3A*, *H3F3B*, *IDH1*, *IDH2*, *JAK2*, *MPL*, and *NRAS*

Supplementary Table S3: Growth rate change of cell lines by bacterial cells

Bacteria	growth rates							growth rates (z-scores)						
	Accession	HT29	HCT15	SW620	HEK293T	HCT116	Average	Accession	HT29-p	HCT15-z	SW620-z	HEK293T-z	HCT116-z	Average
Acidimicrobium sp. D21	0.00099094	0.006082	0.0145893	0.0054031	0.0093159	0.0779483	0.0474111	0.0202199	0.0267908	0.0678472	0.2814403	0.1336922	0.0772522	0.405741
Akkermansia muciniphila	0.00118895	0.0491758	0.0254187	0.0486173	0.0404504	0.0512841	0.0437230	0.0328776	0.0721126	0.0610586	0.7589771	0.2617931	0.6651085	0.0973662
Bacteroides dorsalis 8_1_36/DA	0.0502408	0.0687988	0.00417147	0.075207	0.00494717	0.0762565	0.0626265	0.0454413	0.0898724	0.0358911	0.0025323	0.0876139	0.0161004	0.16687162
Bacteroides eggerthii 1_2_48FA	0.0320405	0.0349286	0.0141995	0.0393534	0.0393534	0.0254378	0.0268766	0.0530916	0.0300534	0.0619686	0.0001698	0.0030806	0.0030806	0.0030806
Bacteroides fragilis 3_1_12	0.00515316	0.1165573	0.0823052	0.0823052	0.0753603	0.0090983	0.0866377	0.1132056	0.0369816	0.0455577	0.0032019	0.0281746	0.4455577	0.3275533
Bacteroides fragilis 86-5443-2 (ETBF)	0.1326289	0.1046532	0.1120566	0.1124431	0.1420235	0.1016812	0.1135673	0.2442504	0.7007426	0.0076081	0.1933783	0.0363725	0.0895791	0.9889959
Bacteroides fragilis 9343 delta cap	0.1326289	0.1046532	0.1120566	0.1124431	0.1420235	0.1016812	0.1135673	0.2442504	0.7007426	0.0076081	0.1933783	0.0363725	0.0895791	0.9889959
Bacteroides fragilis 9343 delta cap plus 77	0.1272445	0.0995728	0.1039285	0.1236083	0.075207	0.1133841	0.1123842	0.1861232	0.6895838	0.0540478	0.3260374	0.0289472	0.0795827	0.9624193
Bacteroides fragilis 9343 delta tra 15 MA	0.117543	0.0279718	0.0745701	0.0730381	0.0595595	0.0869270	0.0696279	0.0922481	0.1732454	0.0381633	0.0386718	0.0696279	0.0696279	0.0696279
Bacteroides fragilis K570 clinda R (ETBF)	0.0514474	0.1067358	0.0335163	0.0534712	0.0091738	0.0534712	0.0162623	0.7354254	0.7118523	0.3791363	0.7065370	0.3060035	0.1468904	0.2621930
Bacteroides fragilis NCTC 9343 (NTBF)	0.1092448	0.0837818	0.08173436	0.1146824	0.0599044	0.1024659	0.0903615	0.0781427	0.2782471	0.3426701	0.1205416	0.3138403	0.7592344	0.6192495
Bacteroides fragilis VPI clinda R (ETBF)	0.0816292	0.0308037	0.00800445	0.1130677	0.0187197	0.1054414	0.0536354	0.4915139	0.3338471	0.3480785	0.0892622	0.2385716	0.8540548	0.5562407
Bacteroides massiliensis 3972 T162	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794	0.03783794
Bacteroides ovatus 3_8_47FA	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131	0.0105131
Bacteroides ovatus 3725 D9	0.1168791	0.0302821	0.09286217	0.1113333	0.1284032	0.1269408	0.0828351	0.0863233	0.03028217	0.5475071	0.1688489	0.1032754	0.46448	0.3071905
Bacteroides ovatus 547R17	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07516261	0.0845894	0.02799351	0.10297351	0.0488187	0.6142548	0.5796181	0.2261328	0.9452032	0.4969559	0.7858847	0.6081249
Bacteroides sp. 1_1_30	0.01935281	0.00505791	0.07											

Supplementary Table S4: Growth rate change of cell lines by bacterial secretions

[illegible]

Supplementary Table S5: Screened microbial virulence factors in genomes

Genera	Species	virulence factors	Genbank ID	Pubmed ID	Reference
<i>Citrobacter</i>	<i>C. freundii</i>	slt-licA	X67514.1	8423084	Schmidt, H. et al. (1993) Infect. Immun. 61, 534–43.
		slt-licB	X67515.1	8423084	Schmidt, H. et al. (1993) Infect. Immun. 61, 534–43.
	<i>C. rodentium</i>	Map	FN543502.1	16759225	Ma, C. et al. (2006) Cell. Microbiol. 8, 1669–86.
<i>Shigella</i>	<i>S. flexneri</i>	ShET2 enterotoxin	NC_002698.1	11292750	Venkatesan, M. et al. (2001) Infect. Immun. 69, 3271–85.
		VirG	NC_002698.1	11292750	Venkatesan, M. et al. (2001) Infect. Immun. 69, 3271–85.
		ShET1 enterotoxin	DM147453.1	23768555	Dutilh, B. E., Backus, L., van Hijum, S. A. F. T., and Tjalsma, H. (2013) Best Pract. Res. Clin. Gastroenterol. 27, 85–99.
	<i>S. dysenteriae</i>	stxA stxB	M19437.1	2830229	Strockbine, N. A., Jackson, M. P., Sung, L. M., Holmes, R. K., and O'Brien, A. D. (1988) J. Bacteriol. 170, 1116–22.
		tox1	AB035142.1	23768555	Dutilh, B. E. et al. (2013) Best Pract. Res. Clin. Gastroenterol. 27, 85–99.
		tox2	AB035143.1	23768555	Dutilh, B. E. et al. (2013) Best Pract. Res. Clin. Gastroenterol. 27, 85–99.
<i>Salmonella</i>	<i>S. enterica</i>	enterotoxin stn	JX293348.1	23768555	Dutilh, B. E. et al. (2013) Best Pract. Res. Clin. Gastroenterol. 27, 85–99.
	<i>S. typhimurium</i>	typhoid toxin	DQ823381.1	23842500	Song, J. et al. (2013) Nature 499, 350–4.
<i>Escherichia</i>	<i>E. coli</i>	Colibactin	AM229678.1	16902142	Nougayrède, J.-P. et al. (2006) Science 313, 848–51.
		cdt-III	U89305.1	9220015	Pérès, S. Y. et al. (1997) Mol. Microbiol. 24, 1095–107.
		CNF1 cytotoxin	NC_007946.1	16585510	Chen, S. L. et al. (2006) Proc. Natl. Acad. Sci. U. S. A. 103, 5977–82.
		CIF	AY128544.1	14651638	Marchès, O. et al. (2003) Mol. Microbiol. 50, 1553–67.
		Intimin	M58154.1	2172966	Jerse, A. E. et al. (1990) Proc. Natl. Acad. Sci. U. S. A. 87, 7839–43.
		enteroaggregative heat-stable enterotoxin 1 aStA	L11241.1	8385356	Savarino, S. J. et al. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 3093–7.
		heat-labile enterotoxin LT1	A16419.1	15364995	Reischl, U. et al. (2004) J. Clin. Microbiol. 42, 4092–100.
		pTC plasmid toxin	AJ555214.1	23768555	Dutilh, B. E. et al. (2013) Best Pract. Res. Clin. Gastroenterol. 27, 85–99.
		heat-labile enterotoxin LT87	X83966.1	23768555	Dutilh, B. E. et al. (2013) Best Pract. Res. Clin. Gastroenterol. 27, 85–99.
		heat-stable ST	AY342058.1	15364995	Reischl, U. et al. (2004) J. Clin. Microbiol. 42, 4092–100.
		subA subB	FJ664545.1	19940059	Tozzoli, R. et al. (2010) J. Clin. Microbiol. 48, 178–83.
<i>Bacteroides</i>	<i>B. fragilis</i>	bft1	AB026625.1	10655354	Scotto d'Abusco, A. S. et al. (2000) J. Clin. Microbiol. 38, 607–12.
		bft2	AB026626.1	10655354	Scotto d'Abusco, A. S. et al. (2000) J. Clin. Microbiol. 38, 607–12.
		bft3	AB026624.1	10655354	Scotto d'Abusco, A. S. et al. (2000) J. Clin. Microbiol. 38, 607–12.
		bft Korea	AF081785.2	10655354	Scotto d'Abusco, A. S. et al. (2000) J. Clin. Microbiol. 38, 607–12.
<i>Clostridium</i>	<i>C. difficile</i>	tcDA	AY238985.1	14550648	Letourneur, O. et al. (2003) Protein Expr. Purif. 31, 276–85.
		tcDB	AY238986.1	14550648	Letourneur, O. et al. (2003) Protein Expr. Purif. 31, 276–85.
	<i>C. perfringens</i>	enterotoxin cpe	U11259.1	7960138	Ladero, V. et al. (2013) Genome Announc. 1.
	<i>C. botulinum</i>	BtA (C2-toxin)	AJ224480.1	11741886	Barth, H. et al. (2002) J. Biol. Chem. 277, 5074–81.
	<i>C. septicum</i>	α-toxin	AY589051.1	16102005	Kennedy, C. L. et al. (2005) Mol. Microbiol. 57, 1357–66.
<i>Fusobacterium</i>	<i>F. nucleatum</i>	FadA	AY850357.1	16030227	Han, Y. W. et al. (2005) J. Bacteriol. 187, 5330–40.
<i>Enterococcus</i>	<i>E. faecalis</i>	Cytolysin	L37110.1	23628786	Van Tyne, D. et al. (2013) Toxins (Basel). 5, 895–911.
	<i>E. faecium</i>	Enterotoxin	NZ_LKPH01000073	24316578	Tatusova, T. et al. (2014) Nucleic Acids Res. 42, D553–9.
	<i>E. durans</i>	labile enterotoxin output A	NZ_AOSM0100009	23682153	Ladero, V. et al. (2013) Genome Announc. 1.

Supplementary Table S6: correlation of growth rates between bacterial cells and secretomes

Bacterial family	Cell line	R2	P-value	Benjamini-Hochberg adjusted P-value
<i>Bacteroidaceae</i>	HEK293T	0,36991	2,00E-05	0,00048
	HCT15	0,07469	0,08383	0,30953
	Caco2	0,04151	0,20137	0,43935
	HCT116	0,38997	1,00E-05	0,00048
	SW480	0,10675	0,03707	0,19771
	HT29	0,21012	0,00258	0,03096
<i>Enterobacteriaceae</i>	HEK293T	0,05259	0,41099	0,58022
	HCT15	0,00013	0,96774	0,98833
	Caco2	0,15732	0,14326	0,38203
	HCT116	0,74442	3,00E-05	0,00048
	SW480	0,00024	0,95618	0,99775
	HT29	0,191	0,10333	0,35427
<i>Erysipelotrichaceae</i>	HEK293T	0,80678	0,01501	0,1441
	HCT15	6,00E-05	0,98846	0,98846
	Caco2	0,65394	0,05141	0,22433
	HCT116	0,29054	0,26978	0,46248
	SW480	0,35235	0,21419	0,42838
	HT29	0,29737	0,26311	0,46775
<i>Fusobacteriaceae</i>	HEK293T	0,00822	0,73838	0,86444
	HCT15	0,00477	0,7994	0,9136
	Caco2	0,13257	0,16562	0,41841
	HCT116	0,03511	0,48709	0,6319
	SW480	0,05401	0,38639	0,59828
	HT29	0,01296	0,67465	0,80958
<i>Lachnospiraceae</i>	HEK293T	0,48532	0,01722	0,13776
	HCT15	0,00069	0,93869	1,00127
	Caco2	0,00094	0,92878	1,01321
	HCT116	0,06767	0,43981	0,58641
	SW480	0,12644	0,28318	0,46871
	HT29	0,22901	0,13647	0,38533
<i>Streptococcaceae</i>	HEK293T	0,02475	0,398	0,57891
	HCT15	0,16228	0,02464	0,16896
	Caco2	0,02491	0,39643	0,59465
	HCT116	0,02307	0,41466	0,56868
	SW480	0,08477	0,11204	0,33612
	HT29	0,11354	0,06379	0,25516
<i>Tannerellaceae</i>	HEK293T	0,83684	0,02947	0,17682
	HCT15	0,48796	0,18945	0,43303
	Caco2	0,34303	0,29944	0,4791
	HCT116	0,76745	0,0514	0,24672
	SW480	0,00314	0,92867	1,03665
	HT29	0,43883	0,22312	0,41191
others	HEK293T	0,02778	0,52259	0,66011
	HCT15	0,10305	0,20899	0,43615
	Caco2	0,02479	0,54619	0,67223
	HCT116	0,11267	0,18778	0,45067
	SW480	0,16597	0,10457	0,33462
	HT29	0,09869	0,21945	0,42134

Supplementary Table S7: Significance of family-specific clustering

Bacterial family	Bacterial Secretomes		Bacterial Cells	
	clustering p-value	B-H adjusted p-value	clustering p-value	B-H adjusted p-value
<i>Bacteroidaceae</i>	0,047	9,40E-02	3,03E-06	1,06E-05
<i>Clostridiaceae</i>	0,806	1	NA	NA
<i>Enterobacteriaceae</i>	0,178	2,85E-01	1,62E-05	2,84E-05
<i>Erysipelotrichaceae</i>	0,941	1	0,006	8,40E-03
<i>Fusobacteriaceae</i>	0,009	2,40E-02	8,40E-06	1,96E-05
<i>Lachnospiraceae</i>	0,003	1,20E-02	0,104	1,21E-01
<i>Streptococcaceae</i>	3,24E-27	2,59E-26	5,35E-25	3,75E-24
<i>Tannerellaceae</i>	1	1	0,883	8,83E-01

Reported p-values are derived from Fischer's exact test evaluating the likelihood that the strains from a family are nearest neighbors, compared to a random sampling with replacement of the same size. P-values reported are the harmonic mean of 103 iterations. For this calculation, only strains from families with more than four representatives were considered.

Supplementary Table S8: correlation between phylogenetic distance and pairwise eucladian distance of growth rate changes

Bacterial family	Bacterial cells		Bacterial secretomes	
	Pearson R	P-value	Pearson R	P-value
<i>Bacteroidaceae</i>	-0,05729	0,0808	-0,05117	0,1189
<i>Clostridiaceae</i>			0,03481	0,8842
<i>Enterobacteriaceae</i>	-0,05052	0,6002	0,10128	0,2924
<i>Erysipelotrichaceae</i>	0,53025	0,0026	0,96029	0,0000
<i>Fusobacteriaceae</i>	0,44857	0,0000	-0,02809	0,6650
<i>Lachnospiraceae</i>	-0,03352	0,7281	0,39881	0,0000
<i>Tannerellaceae</i>	-0,18133	0,4442	-0,17130	0,4702

Correlation between the pairwise phylogenetic distance and and the pairwise euclidean distance of the effects of bacterial cells and secretomes on the growth rate of of six cell lines

Supplementary Table S9: Distribution of toxins in bacterial genomes

Bacterial strain	Bacterial family	Gene
Bacteroides fragilis K570 clinda R (ETBF)	Bacteroidaceae	BFT
Bacteroides fragilis VPI clinda R (ETBF)	Bacteroidaceae	BFT
Bacteroides fragilis 86-5443-2-2 (ETBF)	Bacteroidaceae	BFT
Bacteroides fragilis 9343 delta cap	Bacteroidaceae	
Bacteroides fragilis 3_1_12	Bacteroidaceae	
Bacteroides fragilis 9343 delta cap delta pilus 77	Bacteroidaceae	
Bacteroides fragilis 9343 delta tsr 15 M4	Bacteroidaceae	
Bacteroides fragilis NCTC 9343 (NTBF)	Bacteroidaceae	
Citrobacter freundii 4_7_47CFAA	Enterobacteriaceae	Map
Citrobacter sp. 30_2	Enterobacteriaceae	Map
Klebsiella sp. 1_1_55	Enterobacteriaceae	Map
Klebsiella sp. 4_1_44FAA	Enterobacteriaceae	Map
Escherichia coli DH5 alpha pks	Enterobacteriaceae	pks
Escherichia coli NC101	Enterobacteriaceae	pks, ShEt1
Escherichia coli Nissle 1917	Enterobacteriaceae	pks, ShEt1
Escherichia sp. 3_2_53FAA	Enterobacteriaceae	pks, Stx2A
Escherichia coli NC101 delta pks	Enterobacteriaceae	ShEt1
Escherichia sp. 4_1_40B	Enterobacteriaceae	ShEt1, Stx2A
Enterobacteriaceae bacterium 9_2_54FAA	Enterobacteriaceae	
Escherichia coli 4_1_47FAA	Enterobacteriaceae	
Escherichia coli D9	Enterobacteriaceae	
Escherichia sp. 1_1_43	Enterobacteriaceae	
Fusobacterium nucleatum subsp. animalis 11_3_2	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. animalis 21_1A	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. animalis 3_1_33	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. animalis 7_1	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. animalis D11	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. Nucleatum ATCC 25586	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. Polymorphum ATCC 10953	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. vincentii 3_1_36A2	Fusobacteriaceae	FadA
Fusobacterium nucleatum subsp. vincentii 4_1_13	Fusobacteriaceae	FadA
Fusobacterium periodonticum 1_1_41FAA	Fusobacteriaceae	FadA
Fusobacterium periodonticum 2_1_31	Fusobacteriaceae	FadA
Fusobacterium gonidiaformans 3-1-5R	Fusobacteriaceae	
Fusobacterium necrophorum D12	Fusobacteriaceae	
Fusobacterium necrophorum subsp. funduliforme 1_1_36S	Fusobacteriaceae	
Fusobacterium nucleatum subsp. vincentii 3_1_27	Fusobacteriaceae	
Fusobacterium ulcerans 12-1B	Fusobacteriaceae	
Clostridium hathewayi WAL-18680	Clostridiales	TcdA
Clostridium sp. 7_3_54FAA	Clostridiales	TcdA
Clostridium clostridioforme 2_1_49FAA	Clostridiales	TcdA
Clostridium perfringens WAL-14572	Clostridiales	TcdA
Clostridium symbiosum WAL-14163	Clostridiales	TcdA
Clostridium symbiosum WAL-14673	Clostridiales	TcdA
Clostridium sp. 7_2_43FAA	Clostridiales	
Clostridium sp. D5	Clostridiales	

Supplementary Table S10: Functional genomic terms significantly associated to growth rate scores within bacterial families

functional term	level	cell	effect	experiment type	family	Adjusted p-values
<i>Multi-subunit cation antiporter</i>	Subsystem	HCT116	enhancing	secretomes	Clostridiaceae	0,015602743
<i>Flagellum</i>	Subsystem	HEK293T	inhibiting	cells	Enterobacteriaceae	0,016628384
<i>Flagellum</i>	Subsystem	Caco2	enhancing	cells	Enterobacteriaceae	0,029933622
<i>Flagellum</i>	Subsystem	HCT15	enhancing	cells	Enterobacteriaceae	1,30E-05
<i>Cell Envelope</i>	SuperClass	HCT116	inhibiting	secretomes	Bacteroidaceae	0,005184393
<i>Cell Envelope</i>	SuperClass	Caco2	enhancing	cells	Bacteroidaceae	0,018445869
<i>Cell Envelope</i>	SuperClass	Caco2	enhancing	cells	Enterobacteriaceae	0,002175021
<i>Cell Envelope</i>	SuperClass	SW480	enhancing	cells	Enterobacteriaceae	0,033695227
<i>Cell Envelope</i>	SuperClass	HCT15	enhancing	cells	Enterobacteriaceae	0,002765181
<i>Glycerol fermentation to 1,3-propanediol</i>	Subsystem	SW480	enhancing	cells	Enterobacteriaceae	0,016986143
<i>Phenylacetyl-CoA catabolic pathway (core)</i>	Subsystem	SW480	enhancing	cells	Enterobacteriaceae	0,000430919
<i>Phenylacetyl-CoA catabolic pathway (core)</i>	Subsystem	Caco2	enhancing	cells	Enterobacteriaceae	0,029933622
<i>L-fucose dissimilation cluster</i>	Subsystem	HEK293T	enhancing	secretomes	Clostridiaceae	0,015596175
<i>Autoinducer 2 (AI-2) transport and processing (IsrACDBFGE operon)</i>	Subsystem	Caco2	enhancing	secretomes	Enterobacteriaceae	1,37E-07
<i>Cobalamin synthesis</i>	Subsystem	HCT15	enhancing	secretomes	Bacteroidaceae	0,00327217
<i>Cobalamin synthesis</i>	Subsystem	HT29	enhancing	cells	Bacteroidaceae	0,024730743
<i>Cobalamin synthesis</i>	Subsystem	SW480	enhancing	cells	Bacteroidaceae	0,004290681
<i>Cobalamin synthesis</i>	Subsystem	HCT15	enhancing	cells	Bacteroidaceae	0,004322283
<i>Cobalamin synthesis</i>	Subsystem	HEK293T	enhancing	cells	Bacteroidaceae	0,006420869
<i>Cobalamin synthesis</i>	Subsystem	HCT116	enhancing	cells	Bacteroidaceae	0,000885398
<i>Cobalamin synthesis</i>	Subsystem	SW480	enhancing	cells	Enterobacteriaceae	0,006127826
<i>Cobalamin synthesis</i>	Subsystem	Caco2	enhancing	cells	Enterobacteriaceae	0,029933622
<i>Metabolism</i>	SuperClass	SW480	inhibiting	secretomes	Enterobacteriaceae	0,039429132
<i>Metabolism</i>	SuperClass	Caco2	enhancing	cells	Enterobacteriaceae	0,00083275
<i>Metabolism</i>	SuperClass	SW480	inhibiting	cells	Enterobacteriaceae	0,036397619
<i>Metabolism</i>	SuperClass	HT29	inhibiting	cells	Enterobacteriaceae	0,02019638
<i>Metabolism</i>	SuperClass	SW480	enhancing	cells	Enterobacteriaceae	0,000130798
<i>Metabolism</i>	SuperClass	HCT15	enhancing	cells	Enterobacteriaceae	0,002765181
<i>Ethanolamine utilization</i>	Subsystem	HT29	inhibiting	secretomes	Clostridiaceae	5,04E-05
<i>Ethanolamine utilization</i>	Subsystem	HT29	inhibiting	cells	Fusobacteriaceae	0,024990067
<i>Ethanolamine utilization</i>	Subsystem	HCT15	inhibiting	cells	Fusobacteriaceae	0,022004459
<i>Ethanolamine utilization</i>	Subsystem	SW480	inhibiting	cells	Fusobacteriaceae	0,042265856
<i>Ethanolamine utilization</i>	Subsystem	HCT116	inhibiting	cells	Fusobacteriaceae	0,02504088
<i>Histidine Degradation</i>	Subsystem	SW480	enhancing	cells	Enterobacteriaceae	0,045251785
<i>Membrane Transport</i>	SuperClass	Caco2	inhibiting	secretomes	Enterobacteriaceae	0,007575454
<i>Membrane Transport</i>	SuperClass	HEK293T	enhancing	secretomes	Enterobacteriaceae	0,03671857
<i>Membrane Transport</i>	SuperClass	HEK293T	inhibiting	secretomes	Enterobacteriaceae	0,03739392
<i>Membrane Transport</i>	SuperClass	HCT15	inhibiting	secretomes	Enterobacteriaceae	0,020242991
<i>Membrane Transport</i>	SuperClass	HCT116	inhibiting	secretomes	Enterobacteriaceae	0,027083664
<i>Membrane Transport</i>	SuperClass	SW480	inhibiting	secretomes	Enterobacteriaceae	6,35E-05
<i>Membrane Transport</i>	SuperClass	HT29	inhibiting	secretomes	Enterobacteriaceae	0,030080704
<i>Membrane Transport</i>	SuperClass	SW480	inhibiting	cells	Enterobacteriaceae	1,06E-05
<i>Membrane Transport</i>	SuperClass	HT29	inhibiting	cells	Enterobacteriaceae	2,27E-05
<i>Membrane Transport</i>	SuperClass	SW480	enhancing	cells	Enterobacteriaceae	0,001357179
<i>Membrane Transport</i>	SuperClass	HCT116	inhibiting	cells	Enterobacteriaceae	0,033516935
<i>Membrane Transport</i>	Products	HEK293T	enhancing	secretomes	Fusobacteriaceae	0,014422697
<i>Membrane Transport</i>	SuperClass	HEK293T	enhancing	secretomes	Fusobacteriaceae	0,017505156
<i>Hyaluronate utilization</i>	Subsystem	HCT15	enhancing	secretomes	Lachnospiraceae	0,033361224
<i>D-threonate, L-threonate and D-erythronate utilization</i>	Subsystem	HEK293T	inhibiting	secretomes	Enterobacteriaceae	0,010116446
<i>Urea carboxylase and Allophanate hydrolase cluster</i>	Subsystem	SW480	enhancing	secretomes	Enterobacteriaceae	0,000222083
<i>Urea carboxylase and Allophanate hydrolase cluster</i>	Subsystem	HT29	enhancing	cells	Enterobacteriaceae	2,43E-05
<i>Urea carboxylase and Allophanate hydrolase cluster</i>	Subsystem	SW480	enhancing	cells	Enterobacteriaceae	0,016986143
<i>Homoprotocatechuate degradative cluster</i>	Subsystem	Caco2	enhancing	secretomes	Enterobacteriaceae	9,80E-08
<i>Urease subunits</i>	Subsystem	SW480	enhancing	cells	Enterobacteriaceae	0,003243115
<i>Dpp dipeptide ABC transport system</i>	Subsystem	SW480	enhancing	secretomes	Enterobacteriaceae	4,15E-05
<i>Dpp dipeptide ABC transport system</i>	Subsystem	HEK293T	enhancing	secretomes	Enterobacteriaceae	5,23E-06
<i>Dpp dipeptide ABC transport system</i>	Subsystem	HEK293T	enhancing	cells	Enterobacteriaceae	3,17E-06
<i>Dpp dipeptide ABC transport system</i>	Subsystem	HCT15	inhibiting	cells	Enterobacteriaceae	8,04E-06
<i>Dpp dipeptide ABC transport system</i>	Subsystem	HEK293T	enhancing	secretomes	Fusobacteriaceae	0,020180097
<i>Riboflavin, FMN and FAD metabolism with fusion events</i>	Subsystem	HT29	inhibiting	secretomes	Clostridiaceae	0,022400659
<i>Riboflavin, FMN and FAD metabolism with fusion events</i>	Subsystem	Caco2	inhibiting	cells	Erysipelotrichaceae	0,028588475
<i>Arsenic resistance</i>	Subsystem	HCT15	enhancing	secretomes	Bacteroidaceae	0,026841657
<i>Cellular Processes</i>	SuperClass	Caco2	enhancing	secretomes	Enterobacteriaceae	0,00481013
<i>Cellular Processes</i>	SuperClass	Caco2	enhancing	cells	Enterobacteriaceae	0,000932912
<i>Cellular Processes</i>	SuperClass	HEK293T	inhibiting	cells	Enterobacteriaceae	0,009543743
<i>Cellular Processes</i>	SuperClass	SW480	enhancing	cells	Enterobacteriaceae	0,008160047
<i>Cellular Processes</i>	SuperClass	HCT15	enhancing	cells	Enterobacteriaceae	0,016574654
<i>Type 4 secretion and conjugative transfer</i>	Subsystem	SW480	inhibiting	cells	Enterobacteriaceae	0
<i>Type 4 secretion and conjugative transfer</i>	Subsystem	HT29	inhibiting	cells	Enterobacteriaceae	0
<i>Tricarballylate Utilization</i>	Subsystem	SW480	enhancing	secretomes	Enterobacteriaceae	0,025496186
<i>Tricarballylate Utilization</i>	Subsystem	HT29	enhancing	cells	Enterobacteriaceae	0,012769654
<i>Protein Processing</i>	SuperClass	SW480	inhibiting	cells	Lachnospiraceae	0,008353249

Protein Processing	Products	HT29	enhancing	cells	Lachnospiraceae	0,047863977
Protein Processing	Products	SW480	inhibiting	cells	Lachnospiraceae	0,00672378
Energy	SuperClass	HCT15	enhancing	secretomes	Bacteroidaceae	0,042758192
Energy	SuperClass	HEK293T	enhancing	cells	Bacteroidaceae	0,044418417
Energy	SuperClass	HEK293T	inhibiting	cells	Enterobacteriaceae	0,016889509
Energy	SuperClass	HCT15	enhancing	cells	Enterobacteriaceae	0,032209953
Stress Response, Defense, Virulence	SuperClass	HCT15	enhancing	secretomes	Bacteroidaceae	0,023574463
Stress Response, Defense, Virulence	SuperClass	SW480	enhancing	secretomes	Bacteroidaceae	0,014792296
Listeria Pathogenicity Island LIPI-1 extended	Subsystem	SW480	enhancing	secretomes	Bacteroidaceae	0,045449008
Miscellaneous	SuperClass	HCT15	enhancing	secretomes	Bacteroidaceae	0,042758192
Miscellaneous	SuperClass	HEK293T	inhibiting	secretomes	Bacteroidaceae	0,013348729
Miscellaneous	SuperClass	HEK293T	enhancing	secretomes	Bacteroidaceae	0,043760887
Miscellaneous	SuperClass	SW480	enhancing	secretomes	Bacteroidaceae	0,02678131
Branched-Chain Amino Acid Biosynthesis	Subsystem	HEK293T	inhibiting	secretomes	Fusobacteriaceae	0,00125237
Branched-Chain Amino Acid Biosynthesis	Subsystem	SW480	inhibiting	secretomes	Fusobacteriaceae	0,001667137
Histidine Biosynthesis	Subsystem	HCT116	enhancing	secretomes	Clostridiaceae	0,007312145
Glutamate fermentation	Subsystem	SW480	enhancing	secretomes	Enterobacteriaceae	0,001367254
Glutamate fermentation	Subsystem	HEK293T	enhancing	secretomes	Enterobacteriaceae	0,000995688
Glutamate fermentation	Subsystem	HEK293T	enhancing	cells	Enterobacteriaceae	0,000664067
Glutamate fermentation	Subsystem	HCT15	inhibiting	cells	Enterobacteriaceae	0,000376733
Inositol catabolism	Subsystem	HEK293T	enhancing	secretomes	Clostridiaceae	0,002311461
Vir-like type 4 secretion system	Subsystem	Caco2	inhibiting	secretomes	Enterobacteriaceae	9,44E-05
Vir-like type 4 secretion system	Subsystem	HCT15	inhibiting	secretomes	Enterobacteriaceae	4,66E-06
Vir-like type 4 secretion system	Subsystem	SW480	inhibiting	secretomes	Enterobacteriaceae	0,006015428
Vir-like type 4 secretion system	Subsystem	HCT116	inhibiting	secretomes	Enterobacteriaceae	1,14E-05
Vir-like type 4 secretion system	Subsystem	HT29	inhibiting	secretomes	Enterobacteriaceae	3,86E-06
Vir-like type 4 secretion system	Subsystem	HCT116	inhibiting	cells	Enterobacteriaceae	1,03E-05
High affinity phosphate transporter and control of PHO regulon	Subsystem	SW480	enhancing	secretomes	Fusobacteriaceae	0,001624476
High affinity phosphate transporter and control of PHO regulon	Subsystem	Caco2	enhancing	secretomes	Fusobacteriaceae	0,000751743
Tryptophan synthesis	Subsystem	HCT15	inhibiting	cells	Lachnospiraceae	0,022298862
Na-driven 2-hydroxyglutarate pathway	Subsystem	Caco2	inhibiting	secretomes	Lachnospiraceae	0,037556695