International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Bugs as Drugs - Trends in Biotechnology

Mahesh Shanmugasundaram*[1], Rakesh Kumar Sharma[2]

*[1]Corresponding author-Freeze Drying and Animal Products Technology, Defence Food Research Laboratory, Siddarthanagar, Mysuru-570011. India
Email: sundaram[at]dfrl.drdo.in
Phone: 0821-2579010, Fax-0821-2473468
[2]Vice Chancellor, Saveetha Institute of Medical and Technical Sciences, Saveetha Nagar, Thandalam, Chennai-602105, India

Abstract: ***The gut microbiota has more than 1000 types of bacteria in it. The metabolites like the short chain fatty acids synthesized by the gut bacteria plays a role in proper functioning of the different organs and inhibit pathogen colonization. Changes in the gut microbiota are linked to several non-communicable diseases including diabetes, obesity, cancer, nervous system disorders etc. The current trend is to use Bugs as Drugs which involves treatment of some of the diseases by microbes. Bacteriophages are used as a cure against cancer by vaccination and tailoring its specific delivery. Bacteria are used to fight cancer by its interaction and modulating its response on inherent cancer mechanisms. Anaerobic and some facultative anaerobes are involved in control and elimination of cancer. Bacteria can be genetically modified by attenuation and effective targeting. Bacteriophages are also useful in the treatment of bacterial infections. Probiotics can be engineered to kill pathogens, and facilitate re-colonization of the resident beneficial microflora. Replacing the malfunctioned intestinal microbiota with a consortium of bacteria derived from the intestine has a bright future for therapy.***

Keywords: Gut Microbiota; Bacteriophages; Cancer; Bacteria; Food; Drug Metabolites

1. Introduction

The human microbiota is a mixed community of prokaryotes like bacteria, viruses, archaea, and eukaryotic like yeast. The collection of these microbes and their genes is called the human microbiome. The adult human gut contains nearly 100 trillion microbial cells and more than 1,000 bacterial species. Gram positive *Firmicutes* and the Gram-negative *Bacteroidetes* dominate the intestinal flora.

The interpersonal variability's of the human microbiome are affected by the different factors exposed since early in life. Microbes produce short-chain fatty acids (SCFAs), vitamins, amino acids and other important biomolecules. The gut microbiota ferments dietary plant polysaccharides or fibers, indigestible oligosaccharides, non-digested proteins, and intestinal mucin by *Clostridial* clusters IV, XIVa, *Lactobacillus*, and *Actinobacteria* (*Bifidobacterium* spp.) in order to produce SCFAs (acetate, propionate, and butyrate). They act as an energy source and help in maintaining intestinal homeostasis.

Butyrate-producing bacteria *Clostridium* sps, *Roseburia* spp., *Butyricicoccus* and *Lactobacillus* and *Bifidobacterium* group of bacteria benefit the host by preventing inflammation, tumor formation, and pathogen exclusion. Several diseases, like diabetes, obesity are linked to the changes in microbiome development [1,2]. The gastrointestinal tract is sensitive to stress and stress mediators, which might be linked to irritable bowel [2]. The gut microbiota has a negative side effect by promoting atherosclerosis through metabolism of dietary carnitine and phosphatidyl-choline. Choline forms trimethylamine that promotes atherosclerosis [3].

Widespread antibiotic uses, has degraded microbiota diversity and thereby susceptibility to diseases such as *Clostridium difficile* infection[4]. Probiotic therapies were generally limited to a single or few strains of healthy bacteria. This is being replaced by a consortia of microbial communities derived directly from the human gastrointestinal tract. This involves replacing a malfunctioning gut environment with a fully developed and healthy ecosystem of 'native' intestinal bacteria [5]. The review highlights some of the recent trends in the use of bugs as drugs in the fight against diseases.

2. Bacteriophages against Cancer

Oncolytic virus will infect cancer cells and multiply within the cells and release more virions which would kill the surrrounding cells. (Fig-1). Bacteriophages (phages), viruses that infect bacterial cells, can be genetically engineered to stimulate anti-cancer immune response as well as to inject cytotoxic agents to cancer cells. Imlygic is a Herpes simplex virus oncolytic agent and is used for the treatment of melanoma in patients with inoperable tumor [6].

1. **Vaccination**- Phages can be genetically modified to express several types of tumor-specific antigens along with native phage components and induce robust antitumor immune responses. Phages can be used as adjuvants to amplify innate and adaptive immune responses. There are two major types of phage-based, antitumor vaccines. In the first one, the fusion protein of phage and disease antigens are displayed on antigen presenting cells which activates the CD4 and CD8 response. In the second stategy DNA-based vaccines are engineered to include disease antigens encoded within the phage genome and regulated under a eukaryotic promoter. When antigen producing cells (APCs) engulf these DNA molecules, the APC cells express the disease antigen, inducing T-cell responses.

2. **Specific Delivery**- Bacteriophages have to be engineered for its entry into tumor cells and delivery of antitumor agents. For the purpose of targeting a tumor by a phage, first a tumor specific antigen is identified to serve as a receptor eg, a receptor that brings essential nutrients into tumor cells and these phage display ligands dock on the receptor. Alternatively, phage that target tumor cells can be generated by exposing phage with variable tail domains to tissue culture or whole animals, and then

isolating phage that are found within tumor cells. Toxic chemotherapy agents can be linked to phage surfaces for delivery specifically targeted at malignant tumors, and, thus, avoiding their toxic side effects. Phage can be genetically modified to inject genes encoding proteins with antitumor effects into tumor cells. These proteins may include inhibitors of cell growth and proliferation and other metabolic functions[7].

3. Bacteria versus Cancer

Dr. William Coley (1862– 1936) developed a mixture of bacterialspecies with *Streptococcus pyogenes* OK-432 and administered them to a patient with non operative bone sarcoma. The results were extremely promising because remarkable tumor regression was observed. Since then there has been a continuous development in the fight against cancer.

a) Mechanisms of Antitumor Activity

Mechanisms of bacterial antitumor activity vary depending on the bacterial species and strain being used, but generally fall under three themes:

i) ***Direct cytotoxic effects on tumor cells.*** ii)***Indirect killing through attack of vasculature*** iii)***Indirect killing through immune activation***

I) Direct cytotoxic effects on tumor cells

Most bacteria used to treat cancers are pathogens, each one carrying its own variety of virulence mechanisms capable of infecting and potentially killing host cells. These virulence mechanisms are unleashed against the tumor when bacteria contact tumor tissues often causing tumor cell lysis[7]. *Pseudomonas* exotoxin A inhibit protein synthesis by catalytically ribosylate EF-2. Binding of toxins to cell-binding proteins e.g monoclonal antibodies or growth factors, cause regression in growth of cancer by targetting them into the specific sites on cancers. For example transferrin-Diphtheria toxin(DT), DT- epidermal growth factor (EGF) in brain tumor and metastatic carcinomas and IL4-PE against human gliboblastoma tumor [8].

II) **Indirect Killing through Attack of Vasculature-**

To meet their own high metabolic demands, tumors require new blood vessels to supply nutrients and oxygen. Bacterial vectors like *Clostridium* and *Salmonella* will destroy blood vessels in tumors by apoptosis of vascular endothelial cells of cancerin the host and thus treating cancer indirectly by interfering with vasculogenesis.

III) Indirect Killing through Immune Activation

Infecting tumors with bacteria can attract immune cells, including macrophages, neutrophils, and white blood cells to such sites. In the case of infected tumors, non-specific inflammatory responses can damage and destroy tumor cells and the vasculature.

Intracellular pathogens such as *Listeria* and *Salmonella* as well as extracellular pathogens such as *Clostridium novyi* can elicit T-cell responses directed specifically against infected tumor cells. Tumor-specific T-cells attack the primary tumor and patrol for any fresh incidences for malignancy. However, memory T-cells continue to patrol long after the initial treatment. Bacterial antigens such as Lipopolysaccharide (LPS) induce tumor necrosis factor(TNF-α) which is also attributable to its antitumor effects [7].

Listeria monocytogenes expressing nucleoprotein from influenza virus has shown potential to attenuate the growth of microscopic tumors[8]. *Mycobacterium bovis* is an etiological agent of bovine tuberculosis. The use of BCG was accompanied with the cancer regression; the vaccine was approved as the complementary treatment of bladder cancer. BCG's mechanism of action is based on stimulating the patient's immune system. It appears that IFN-γ and effector cells, that is, CD4+ and CD8+ lymphocytes, play an extremely important role in the recognition of tumor antigens. Treatment of this type of cancer with the *M. bovis* BCG strain requires the intravesical infusion of the microbial suspension using urethral catheters [9] (Table 1).

b) Basic Targeting Mechanisms

Therapeutic bacteria are developed specially to target tumors. The inner core of a tumor is hypoxic and is starved of oxygen. The anaerobic inner environment is ideal for the survival of some obligate bacteria. Attenuated and even avirulent bacteria can survive within the immune privileged tumor site to escape immune attack. Myeloid – derived suppressor cells (MDSCs) can deliver bacteria to tumor tissue. *Listeria* and *Salmomella* infect MDSC. Once inside them, these bacteria are protected from extracellular responses which could otherwise eliminate them before they reach the tumor. When MDSC home to attack and infiltrate tumor tissue, bacteria escape to infect the tumor.

c) Immune Stimulation by Genetic Engineering

Bacteria can be engineered to produce cytokines that attracts immune cells, stimulate immune responses of Th1/Th2 type. Indolamine 2,3-dioxygenase (IDO) is a mediator of immune suppression and is overexpressed by tumors and correlates with disease progression. Bacteria can be used to deliver IDO-silencing shRNA to tumors, preventing overexpression of this compound. The bacterial vector might serve as an additional role by attracting and activating antitumor immune cells. Tumor specific antigens can be expressed by bacterial vaccines stimulating adaptive immune response with the potential to eradicate tumors[7]. Genetically engineered attenuated *Salmonella typhimurium* expressing murine cytokines (IL-2) suppress the growth of tumor[8].

d) Safety with Genetic Engineering

1.1). *Attenuation*

Attenuation must strike a balance between safety and efficacy. Bacteria must have some virulence to attack the tumor or induce antitumor immune response. Therapeutic bacteria will not harm the patient or cause invasive disease.

The pathogen may be stripped of some virulence factors that injure host cells, such as toxins or bacterial secretion systems which facilitate movement of bacterial proteins, yet some others may be retained within bacteria because they act against tumors. For example, *C. novyi* must be stripped of α-toxin for safety, but its PLC toxin is retained for efficacy. Auxotrophy- mutants such as those from *Salmonella* which cannot synthesize essential amino acids or nucleic acid components can survive only in necrotic tumor cells where nutrients are available.

The lipopolysaccharides (LPS) on the outer surface of *Salmonella* can induce release of TNF-α in recipient individuals, resulting in potentially deadly toxic shock. *Salmonella-msbB* mutants do not produce the inflammatory form of these lipids. Macrophages, which release TNF α when they bind ordinary LPS, do not recognize the LPS produced by *Salmonella msb* mutants [7].

1.2) *Effective Targeting*

Macrophages engulf microbes and shield them from immune responses or other environmental conditions, they appear to be a good choice for transporting therapeutic bacteria to tumor tissues. Hypoxia-inducible promoter (HIP-1)can limit toxic gene expression in bacteria until after they infiltrate tumors. Shiga toxin 2 expression can be controlled in *Salmonella* by a promoter that is tumor-specific. It is responsive to acidic pH, which is characteristic of the tumor microenvironment. Passaging microbial strains through tumor-bearing animals leads to selection of strains that are safer and more effective than in the parent microbe [7].

IV) Encounter with bacteria which are best suited for cancer therapy

The obligate anaerobes are safer because they cannot survive in oxygenated healthy tissue. In contrast, facultative anaerobes can infect hypoxic as well as oxygenated tissues, treating both necrotic and viable areas of tumor. *Clostridium novyi* and *Salmonella enterica* serovar *Typhimuriu*m are obligate anaerobes and facultative anaerobes that have a potential to be used in anticancer therapies as they grow under oxygen unavailability (hypoxia). Further, because obligate anaerobes apparently need to be injected intratumorally their use in treating patients with disseminated metastases is limited.

1.1) Obligate Anaerobes-

Clostridium is a genus of obligate anaerobes with antitumor activities when its alpha/lethal toxin are removed,. The spores from *C. novyi* are being used in clinical trials as a treatment against tumors.The attenuated strain of *Clostridium novyi*-NT has positively undergone phase I and phase II clinical trials, giving extremely promising results for the treatment of leiomyoma. The mechanism of the anticancer activity of *Clostridium* spp. is unknown yet.

1.2) Facultative Anaerobes-

Salmonella typhimurium is an example of a facultative anaerobe with antitumor activity and suited for oral delivery as it is attenuated. *Salmonella* cells infect intestinal epithelial cells, where they induce immune responses and attract immune cells. They also infect macrophage which is used to target tumor tissue. Oral delivery of *Salmonella* might foster contact with macrophages better than intravenous delivery. *Salmonella* infect both intracellularly and extracellularly, delivering direct cytotoxic effects as well as inducing indirect immune responses [10]. *Salmonella* are effective against a broad spectrum of cancers being treated in animal models, including primary and metastatic. The orally delivered A1-R strain of *S. typhimurium* appears to be effective and safe [7].

In the treatment of cancer, the attenuated strain *Salmonella typhimurium* VNP20009 is used for safety reasons and can be used for melanoma treatment. In addition, the VXM01 antitumor vaccine, which is based on the attenuated strain of *Salmonella typhi,* has successfully passed phase I clinical trials. This bacterium has a plasmid encoding expression of VEGFR2 (vascular endothelial growthfactor receptor-2). The vaccine blocks the angiogenesis process. The formulation was tested in individuals with pancreatic cancer [9].

Listeria, another facultative anaerobe being evaluated for its antitumor activity, infects Myeloid-derived suppressor cells (MDSCs), which can be used to deliver these bacteria to tumors. Once within a tumor, *Listeria* cells escape MDSCs to infect the tumor cells, producing reactive oxygen species (ROS) and eliciting immune responses against the tumor cells. The highly antigenic *Listeria* enzyme, listeriolysin O (LLO), shows antitumor activity from this microbe. Chimeric molecules combining listeriolysin O with tumor antigens elicit strong antitumor T-cell responses. This includes lasting memory that protects against tumor regrowth and metastasis[7].

E. coli strain Nissle 1917 (EcN), is a probiotic which is characterized by absence of virulence genes and has minimum side effect when taken orally. It is also serum sensitive caused by EcN's semi-rough lipopolysaccharide. EcN requires less genetic alteration in order to achieve a very high selectivity for tumor colonization in mice. In fact, EcN colonised almost exclusively the tumor tissue as compared to other organs even in immunocompromised animals[10].

V) Bacteriophages for treatment of bacterial infections in food

Lytic phages are much better suited than lysogenic phages for treating human bacterial infections because they specifically kill the host bacteria with simultaneous release of progeny phages that stimulate the innate immune responses to clear remaining pathogenic bacteria. Phage therapy offers many advantages over antibiotics for treating bacterial infections. Lytic phages typically kill bacteria within several minutes bringing quick relief to patients while allowing little time for the bacteria to develop any resistance. Multiple phages and their differential attack mechanisms make it difficult for the bacterial pathogens to evade them. This will ensure elimination of drug-resistant pathogenic bacteria.. Phages replicate at the site of a bacterial infection, rapidly increasing only when they are needed. Phages are very species specific, leaving benign members of the microbiota intact[7] (Fig-1).

Bacteriophage was administered against Salmonella typhimurium infection in chicken. Following multiple administration of phage mixture at pre and post infection at 6 h, 24 h, and 30 h, Salmonella counts fell in cecum. Foods of bovine origin mainly transmit *E. coli* 0157:H7 to humans. When *E .coli* 0157: H7 specific bacteriophages were administered in cattle, fecal shedding of the organism was reduced[11].

Bacteriophages specific for Salmonella when applied on cut melons reduced the count of Salmonella by 3.5-logs when stored at 5◦C and 10◦C [12]. The antibacterial potential of six mycobacteriophages on *Mycobacterium smegmatis* in reconstituted skim milk showed complete elimination of the bacteria over time[13].

Endolysins (lysins) are peptidoglycan-degrading enzymes produced by bacteriophages and when applied exogenously to Gram-positive bacteria, resulted in immediate bacteriolysis[14]. *Lactococcus lactis* was engineered to secrete the anti-*Listeria* endolysin Ply511, which can be useful in controlling the organism in cheese[15]. In the area of *Salmonella* biocontrol, studies were conducted with a purified truncated phage tails pike endoglycosidase (P22sTsp) from the bacteriophage P22 targeting *S. typhimurium* which resulted in significant reduction [16].

In 2007, the FDA approved the use of anti-*E.coli* and anti-*Salmonella* phage-based preparations, produced by OmniLytics Inc., to decontaminate live animals prior to slaughter. In 2013, Salmo FreshTM (IntralytixInc.) received regulatory approval for phage therapy to eliminate *Salmonella* in poultry products and other foods. Elanco Food Solutions together with OmniLytics Inc. produced two phage products to reduce contamination in meats and poultry prior to processing. One is Finalyse that targets E. coli O157:H7 and is used as hide spray on cattle prior to slaughter. Another is Armament, which contains phages that targets Salmonella on poultry [17]. In USA, the FDA approved ListshieldTM, a food additive containing only bacteriophages that could kill *Listeria monocytogenes* in meat and poultry was developed[17]. BioTector, developed in Seoul, South Korea, is the first phage-based product to replace antibiotics in animal feed, controlling Salmonella species responsible for causing fowl typhoid and pullorum disease [11].

VI. Prebiotics and probiotics

Probiotics are ”a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance[18]. Prebiotics are non-digestible foods that stimulate growth or activity of beneficial bacteriaeg.fructo-polysaccharides, inulin-like fructans. These reach the colon intact, where they undergo fermentation [19].

Saccharomyces boulardii, Lactobacillus acidophilus and *bulgaricus, Enterococcus faecium SF68, Bifidobacterium longum*, and *Lactobacillus GG* are involved in preventing bacteria -associated diarrhea. In irritable bowel syndrome (IBS) *Bifidobacterium infantis 35624*, appears to improve both pain and global symptoms. *Lactobacillus bulgaricus* may prevent colon cancer by modulating the activity of β-glucuronidase. The strains of *Lactobacillus plantarum, Lactobacillus casei*etc were used in a combined or single treatment for respiratory infections with positive results [19]. (Table -2).

There are increasing cases of development of antibiotic resistance among pathogenic bacteria in the poultry which is removed by probiotics and normal bacteria is restored. *L. salivarius* 3d strain reduced the number of *Salmonella enteritidis* and *Clostridium perfringens* in the group of chickens infected. Certain probiotic bacteria produce potent antimicrobial peptides (bacteriocins) which specifically target the invading pathogen [20].

VII) Gut microbiota and its influence

Diet has an important influence on the commensal microbes. Prebiotics(poly/oligosaccharides) has an influence on the microbiota. Gut microbiota is an important regulator of fat storage in humans. Microbial metabolism of dietary fatty acid has a role in the composition of fatty acids in the adipose tissue which influences the immunoinflammatory response.

There are different interactions which govern the influence of the gut microbiota

1.1) Host– microbe interactions: The specific composition of the gut microbiota has an impact on immunological differentiation. This is shown in the balance of effector and regulatory cell (T H17/ T reg) activity. In any case of imbalance between the mucosal and systemic limbs of the immune system, it can be restored by colonization with commensal bacteria [21].

The intestinal immune responses and commensal bacteria play a role in the control of inflammatory bowel diseases like Crohn's disease and ulcerative colitis (IBD) and probiotics have played a role in homeostasis[22]. The gut microbiota has emerged as an important contributor to the

obesity and the type 2 diabetes mellitus epidemic and is proposed to act by increasing energy harvest from the diet which depends on digesting otherwise indigestible common polysaccharides in our diet and effect of signalling molecules involved in host metabolism [23].

1.2) Dietary–microbe–host interactions: There is enough evidence of the controlling influence of the microbiota on fat storage. The composition of bioactive fatty acids, such as conjugated linoleic acid and eicosapentanoic acid are prominent among them [21]

1.3) Microbe – microbe interactions: The one to one interaction between microbes regulates its population in different locations of the gut. This interactions mediated by signals could contribute to the discovery of novel antibiotics. Bacteriocins are peptide molecule which inhibits the growth of. other bacteria. Lacticin 3147 is a antimicrobial peptide and have been shown to have activity against Clostridiun diffiicile [21].

VIII) Drug metabolism and microbes

There is an effect of metabolic activity of gut microbial communities on antibiotics and botanicals. The human microbiome project is aimed at understanding the composition and functional variation of microbes that affect drug action and its fate in the human gut [24]. Cytosine deaminase have been successfully expressed in *Clostridium. sporogenes* and *Clostridium. acetobutylicum.* which converts 5-fluorocytosine to 5-fluorouracil [8].

The microbiome shows individual variation in the metabolites produced. The effect of the host microbes on natural products with pharmacological activity is different. Interethnic variation of the cardiac drug digoxin to its metabolites is seen more in North Americans (36%) compared with a South Indian population (13.7%). Bacteria from individuals digesting soya isoflavones were fed to mice along with soya isoflavones and they showed active metabolites equol and lignin. When soya isoflavones were given to control germ free rats, they did not secrete any active metabolite [25].

IX) Bugs –some events

Bacterial nanotechnology can be employed to deliver drugs and vaccines. The structures include S layer protein, bacterial ghosts, spores, bacterial outer membrane vesicles. The Bacterial ghost (BG) technology involves cell envelopes derived from Gram-negativebacteria having a preserved cellular morphology. BGs can be used as delivery vehicles for subunit or DNA-vaccines and target the humoral and cellular immune response [26, 27].

Genome-scale metabolic models (GEMs) are models useful in understanding gut microbiota. GEMs have proven to be useful in the design of chemically defined growth media, as has been shown for the lactic acid bacterium *Lactobacillus plantarum* WCFS1 and human pathogen *Staphylococcus aureus* N315 [28].

4. Conclusion

The study of the human microbiome and metabolome far exceeds the complexity of the human genome. There is a greater need for research done on the interactions between persons, microbes and the resultant metabolites. Many of the nascent bacterial delivery platforms have entered human clinical trials. Therapeutic microbes can help to coordinate innate and adaptive responses in eliminating primary tumors and prevent relapses. Studies for oral vaccination, gene delivery using *Clostridial* species, *S. typhimurium*[29] are at the clinical trial level. Discoveries like the bacterial protein Azurin[30] which interferes in the growth of cancer at multiple levels offers a hope for the future. A greater understanding of the science of gut bacteria and its physiology, together with the interactions involved will expand the utility of Bugs as Drugs for sure

References

[1] Souhaila A K, Bernd R & Ibrahim F S, The microbiome and blood pressure: Can microbes regulate our blood pressure?, Frontiers in Pediatrics, 5 (2017)138.
[2] www.singularityhub.com
[3] Jun S & Chang E B, Exploring gut microbes in human health and disease: Pushing the envelope, Genes Dis, 1,2 (2014) 132-139.
[4] www.canada.ca.html.
[5] Petrof E O, Claud E C, Gloor G B & Allen-V E, Microbial ecosystems therapeutics: a new paradigm in medicine?, Beneficial Microbes, 4,1 (2013), 53-65.
[6] https://en.wikipedia.org/wiki/Oncolytic_virus
[7] Fox J, Harnessing the power of microbes as therapeutics: Bugs as Drugs,
[8] A Report on an American Academy of Microbiology Colloquium held in San Diego, CA, April 2014, https://www.ncbi.nlm.nih.gov/books/NBK519801/. https://www.slideshare.net/appurvavaish/bacteria-in-cancer-therapy
[9] Klaudia L & Marek F H, Microorganisms in the treatment of Cancer: Advantages and limitations, Journal of Immunology Research,(2018) 1-8. https://doi.org/10.1155/2018/2397808
[10] Tobias A O, Bacteria as tumor therapeutics?, Bioengineered Bugs, 1,2 (2010) 146-147.
[11] Lorraine E, Jim O'M, Colin H, Paul R P, Olivia M & Aidan C et al, Phage therapy in the food industry, Annual Review of Food Science and Technology, 5 (2014) 327-49.
[12] Leverentz B, Conway W S, Alavidze Z, Janisiewicz W J, Fuchs Y et al, Examination of bacteriophages as a biocontrol method for Salmonella on fresh-cut fruit, J. Food Prot, 64 (2001)1116–21.
[13] Endersen L, Coffey A, Neve H, McAuliffe O, Ross R P et al, Isolation and characterisation of six novel mycobacteriophages and investigation of their antimicrobial potential in milk, Int. Dairy J, 28 (2012) 8–14.
[14] Loessner M J, Bacteriophage endolysins current state of research and applications, Curr.Opin.Microbiol, 8 (2005) 480–87.

[15] Gaeng S, Scherer S, Neve H & Loessner, Gene cloning and expression and secretion of Listeria monocytogenes bacteriophage-lytic enzymes in Lactococcus lactis, Appl. Environ. Microbiol, 66 (2000) 2951–2958.
[16] Waseh S, Hanifi-Moghaddam P, Coleman R, Masotti M, Ryan S et al, Orally administered P22 phage tail spike protein reduces Salmonella colonization in chickens: prospects of a novel therapy against bacterial infections, PLoS ONE, 5 (2010)13904.
[17] http://sitn.hms.harvard.edu/flash/2018/bacteriophage-solution-antibiotics-problem/
[18] Fuller R, Probiotics in man and animals, J. Appl. Bacterio, 66 (1989) 365-378.
[19] http://www.patientcareonline.com/infection/bugs-drugs-prebiotics- and probiotics- gastroenterology
[20] Roy D S, Probiotic therapy - recruiting old friends to fight new foes, Gut Pathogens, 2,1(2010) 5.
[21] Fergus S, Gut Microbes: From Bugs to Drugs, Am J Gastroenterol,105 (2010) 275–279.
[22] Hormannsperger G & Haller D, Molecular crosstalk of probiotic bacteria with the intestinal immune system: clinical relevance in the context of inflammatory bowel disease Int J Med Microbiol,300,1 (2010), 63-73.
[23] Kootte R S, Vrieze A, Holleman F, Dallinga-Thie G M, Zoetendal E G et al, The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus, Diabetes Obes Metab, 14,2 (2012),112-20.
[24] Rama S, Mariam R & Ramy K, Gut Pharmacomicrobiomics : the tip of an iceberg of complex interactions between drugs and gut-associated microbes, Gut Pathogens, 4 (2012) 16. http://www.gutpathogens.com/content/4/1/16.
[25] Wilson I D, Drugs, bugs, and personalized medicine: Pharmacometabonomics enters the ring, PNAS, 106, 34 (2009) 14187–14188.
[26] Farjadian F, Moghoofei M, Mirkiani S, Ghasemi A, Rabiee N et al, Bacterial components as naturally inspired nano-carriers for drug/gene delivery and immunization: Set the bugs to work?, Biotechnol Adv. 36,4(2018), 968-985. https://www.ncbi.nlm.nih.gov/pubmed/29499341
[27] Timo L, Verena J K, Abbas M, Pavol K ,Ulrike B M et al, The bacterial ghost platform system -Production and applications, Bioeng Bugs, 1,5 (2010) 326–336.
[28] Kees C H, van d. A, Ruben G A, van H, Vitor A P, Martins D S, Clara B & Willem M De V, More than just a gut feeling: constraint based genome-scale metabolic models for predicting functions of human intestinal microbes, Microbiome, 5(2017)78.
[29] Kubiak A M & Minton N P, The potential of Clostridial spores as therapeutic delivery vehicles in tumour therapy, Research in Microbiology,166,4 (2015), 244-254.
[30] Nuno B, Raquel S, Ananda, M C. & Arsenio M F, Microbial-based therapy of cancer. Current progress and future prospects, Bioengineered Bugs, 1,3 (2010), 178-190

Table 1: Microorganisms used for Cancer therapy

Microorganism	Strain/antigen	Cancer	Type of treatment	Deployment
Mycobacterium bovis	Atenuated strain Calmette-Guérin	Superficial bladder cancer	Complementary therapy	Commonly used
Streptococcus pyogenes	OK-432	Lymphangioma	Alternative therapy for surgical treatment	Commonly used
Clostridium novyi	Strain NT	Solid tumors	No data	Clinical trials
Salmonella enterica serovar Typhimurium	Strain VNP20009	Melanoma	No data	Clinical trials
Magnetococcus marinus	MC1	Solid tumors and some metabolic tumors	Additional therapy supporting chemotherapy	Experimental research (animal studies)
Reference-(9)				

Table 2: Probiotic organisms used for therapy

Disease	Strain
Hypercholesterolemia	*Enterococcus faecium; Lactobacillus plantarum* PH04
Traveller's diarrhea	*Lactobacillus casei* DN-114 001, *L. plantarum*
Gastroenteritis	*Lactobacillus casei*
Irritable bowel syndrome (IBS)	*Bifidobacterium infantis* 35624
Urogenital tract infection (UTI)	*Lactobacillus rhamnosus* GR-1 *L. reuteri*RC-14
Eczema	*Bifidobacterium bifidum B. lactis Lactococcuslactis*
Immunity	*Lactobacillus plantarum* DSMZ12028

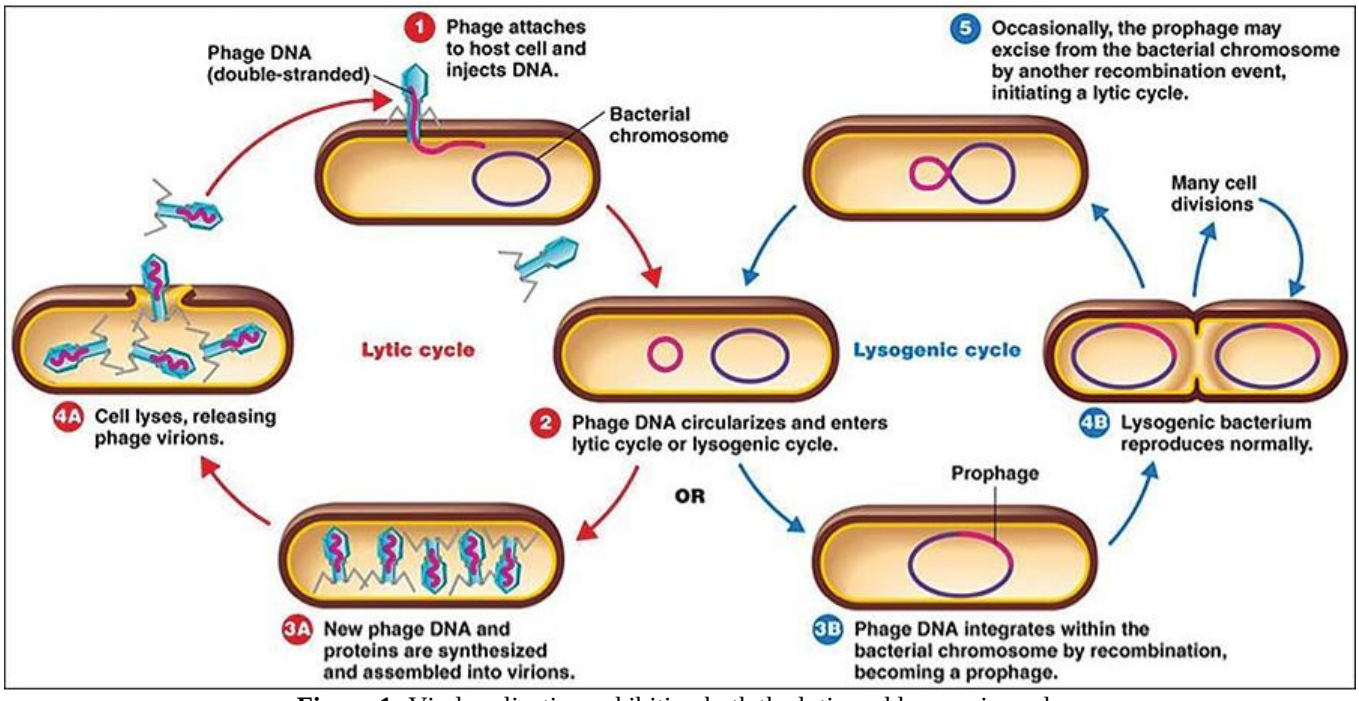

Figure 1: Viral replication exhibiting both the lytic and lysogenic cycle

Acknowledgement

The author would like to thank Dr. Anil Dutt Semwal, Director, Defence Food Research Laboratory for giving the necessary support.