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- 1 Phages enter the fight against colorectal cancer
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24 Summary

Intestinal microbiota undergo significant changes in colorectal cancer (CRC). Zheng *et al.*(Nature Biomed Eng. 2019) observe detrimental overpopulation of *Fusobacterium nucleatum* (*F. nucleatum*) in mice and patients, suppressing the beneficial butyrateproducing *Clostridium butyricum*. Phage-guided irinotecan-loaded dextran nanoparticles
promote release of bacterial-derived butyrate, while *F. nucleatum* and CRC cells are
eliminated. These findings describe a possible novel therapeutic strategy for CRC.

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32 Keywords

33 Bacteriophage; colorectal cancer; chemotherapy; microbiota

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Colorectal cancer (CRC) is one of the three leading causes of cancer-related deaths 35 worldwide. This multi-factorial and multi-stage disease impacts the life of millions of 36 newly-diagnosed patients annually. Due to disease recurrence and metastasis, clinical 37 management of CRC patients is associated with high healthcare costs. Currently, novel 38 therapeutic strategies are urgently needed. A recently reported alternative approach has 39 40 been to treat patients with bacteriophage (phage) for different pathological conditions. These bacteria-killing viruses can be classified as lytic or temperate units, as they either 41 42 undergo lytic or lysogenic cycles, respectively. Although both events lead to bacterial 43 destruction, lysogenic events require that viral and bacterial genomes integrate and replicate during the virus's dormant phase [1-4]. 44

45 Recently, Zheng *et al.* [1] identified that CRC patients and Apc^{Min/+} mice exhibit a
 46 significant increase of *Fusobacterium nucleatum* (*F. nucleatum*), which is typically found

in oral and nasal cavities. As an alien bacterial species to the intestines, F. nucleatum 47 produces immune blocking agents and competes with the beneficial butyrate-producing 48 Clostridium butyricum (C. butyricum) units, thus promoting CRC development and 49 enhancing chemotherapy resistance. In human saliva, the authors isolated a temperate 50 phage capable of specialized and targeted killing of *F. nucleatum* without impacting the 51 52 C. butyricum population. From this, the authors went on to treat piglets with phage-guided dextran nanoparticles. Their experiments reveal that in response to this therapeutic 53 strategy, minimal changes occur in vital metabolic or immunological functions. They 54 further developed a phage-guided biotic-abiotic hybrid nanosystem that could increase 55 the chemotherapeutic potency of irinotecan against CRC cells whilst also selectively 56 killing the *F. nucleatum* population and allowing the butyrate-producing bacteria to expand 57 in numbers at the same time. Phages have a long history of usage with varying success 58 (Figure 1). Careful consideration should thus be given to this exciting discovery, as this 59 new therapeutic strategy of administering phage-guided irinotecan-loaded dextran 60 nanoparticles may impact CRC treatment in coming years. 61

It should be appreciated that the composition of the intestinal phage population 62 63 has been reported to be altered at different stages of CRC development. Parabacteroides 64 phage YZ-2015b units undergo an exponential increase from early to late CRC stages 65 [5]. In keeping with this idea, adherent invasive *Escherichia coli* promotes tumor growth 66 in APC^{Min/+} mice, while phage treatment has been found capable of increasing survival and reducing tumor growth in these bacteria-infected mice. However, elimination of 67 cancer-causing bacteria via phages appears to worsen inflammatory bowel disease, as 68 69 they alter the intestinal immunity. Studies have found lower phage levels in responsive

rather than non-responsive ulcerative colitis patients who received fecal microbiota 70 transplantation since phages increase the release of interferon y (IFN-y) in this non-71 responders group [2]. Another study further reveals that colitis changes the intestinal 72 phage population toward a stochastic state of dysbiosis in mice and humans [3]. 73 Moreover, intestinal inflammation has been shown to promote bacterial pathogenic 74 75 evolution through a disease-driven transfer of temperate phages, as it supports the expression of phage promoter Tum, free phage production and transfer, and bacterial 76 SOS response [4]. Collectively, these findings should focus our attention on the fact that 77 phage therapy may lead to unforeseeable side effects in humans. 78

Treating humans with bioengineered phages has, however, been proven a 79 promising therapeutic strategy in cases where traditional approaches have failed. 80 Successfully, Spencer and colleagues applied a three-phage cocktail in a teenager 81 patient who underwent bilateral lung transplantation but had a drug-resistant bacterial 82 83 infection. Following 121 days of phage treatment, this patient exhibited a favorable clinical improvement, including enhanced liver function and significant resolution of infection sites 84 [6]. Another exciting investigation involved the use of engineered virus-like particles with 85 86 multiple IgG-binding ZZ domains from Q β phage capsids. This molecular strategy enabled the specific elimination of human pluripotent stem cells by 5-fluorocytosine 87 88 without impacting on the non-target differentiated cellular population [7].

Although the idea of Zhang and colleagues to block CRC development by enhancing bacteria-producing butyrate through bioengineering-related methods is indeed remarkable and mechanistically attractive [1], there is a wealth of evidence countenancing caution to be considered. For instance, dextran has been chemically bound to 2-

nitroimidazole (NI). NI can be metabolized into bioreductive species that block DNA 93 synthesis and damage several intracellular targets in both eukaryotic and prokaryotic 94 cells, leading to nonselective cell death. Compounds of this class have indeed been 95 suggested to act as radiosensitisers [8]. This illustrates the carcinogenic potential that this 96 class of compounds have been reported to possess [9]. On the other hand, Park et al. 97 98 report that Gram-positive commensal bacteria control the intestinal epithelial cell turnover by releasing short-chain fatty acids [10]. Stappenbeck and colleagues then revealed that 99 while the short-chain fatty acid butyrate is essential to colonocytes' metabolism, it inhibits 100 101 forkhead box o3 (FOXO3) transcriptional activity impairing proliferation in the colonic stem cell niche [11]. However, Merchant and colleagues indicated that in Apc mutant stem 102 cells, in which β -catenin signaling is high, butyrate-dependent regulation through zinc 103 finger DNA-binding protein 89 (ZBP-89) promotes the development of early CRC stages 104 [12]. These facts should stimulate a thoughtful debate on the diverse effects of butyrate 105 on stem cells in physiological or malignant colon conditions, as it could significantly impact 106 cancer relapse and the patient's overall survival. 107

We believe that the findings of Zheng *et al.* embrace a promising and feasible therapeutic strategy for CRC patients, as it provides a significant advancement in therapies that strengthens the body's anticancer mechanisms with chemotherapy. Further development should shed light on how this type of treatment reinvigorates the anti-tumor immunity and impacts the behavior of cancer stem cells in CRC cases.

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143 Figure legend

Figure 1 – A century of phage research and therapy. Following the discovery of phages 144 at the beginning of the 20th century, this class of bacteria-killing viruses was successfully 145 146 applied in the treatment of a broad range of bacterial infections. However, unfortunate events impaired the evolution of such therapies in Western countries for more than a half-147 century. The urgent emerging need for treatments for extensively drug-resistant or totally 148 drug-resistant bacteria has led the scientific community to revisit the potential application 149 of phages in treating a wide range of conditions. This has been expanded to include 150 151 cancer.