Old Herborn University Seminar Monograph 34: The Biological Empire of the Bacteriophage.
Editors: Peter J. Heidt, John Bienenstock, Colin Hill, and Volker Rusch.
Old Herborn University Foundation, Herborn, Germany: 69-77 (2022).

TRIPARTITE INTERACTIONS BETWEEN BACTERIOPHAGES AND THEIR BACTERIAL AND MAMMALIAN HOSTS

JEREMY J. BARR

School of Biological Sciences, Monash University, Clayton Campus,
25 Rainforest Walk, Clayton, Victoria 3800, Australia

SUMMARY

Bacteriophages are obligate bacterial viruses capable of infecting and replicating only within their bacterial hosts. Yet this classical definition is limiting when we begin to consider bacteriophages within the broader context of their mammalian or eukaryotic hosts. Within this tripartite context bacteriophages may directly interact and influence their bacterial hosts, but they can further bind, enter, and stimulate the mammalian host directly. These interactions are largely unexplored and there exists an enormous potential for discovery of diver mechanisms, feedback loops, and symbioses within these tripartite contexts.

LINEAR RELATIONSHIPS

Picking up any undergraduate microbiology textbook you will find the definition of a 'bacteriophage' something akin to "*a virus capable of infecting and replicating only within bacterial cells*". This description applies when considering the diverse array of interactions that bacteriophages (or simply phages for short) can have with their bacterial hosts. These interactions span the diversity of symbioses including strictly parasitic through to mutualism. While this definition is technically correct, it is limiting when considering bacteriophages in a broader context of tripartite symbioses. In these tripartite systems bacteriophages may indeed directly interact with their bacterial hosts, but they also interact with their mammalian or eukaryotic host through a diverse range of mechanisms (Figure 1). These interactions can include direction binding to eukaryotic cells, in a fashion similar to their bacterial host, yet without the injection of their genetic material (*Lehti* et al., 2017). This was demonstrated by Lehti et al. showing that an *Escherichia coli* infecting bacteriophage that recognised a polysialic acid residue on its bacterial host could also target and bind the same residue on a eukaryotic neuroblastoma cell, triggering receptor mediated endocytosis and internalisation. Phages can also non-specifically adsorb or adhere to eukaryotic cell layers or their secretions (i.e. mucins) and be subsequently internalised through non-specific micropinocytosis events (*Barr* et al., 2013; *Bichet* et al., 2021a; *Nguyen* et al., 2017). Binding or directly adhering to cellular mucins may further elicit intracellular responses (*Barr*, 2017). This was demonstrated by Bloch et al. who characterised the interactions between phages and malignant tumour cells, showing that phages bound externally displayed mucins and inhibited the growth of these tumours (*Bloch*, 1940). Decades later, Dabrowska et al.

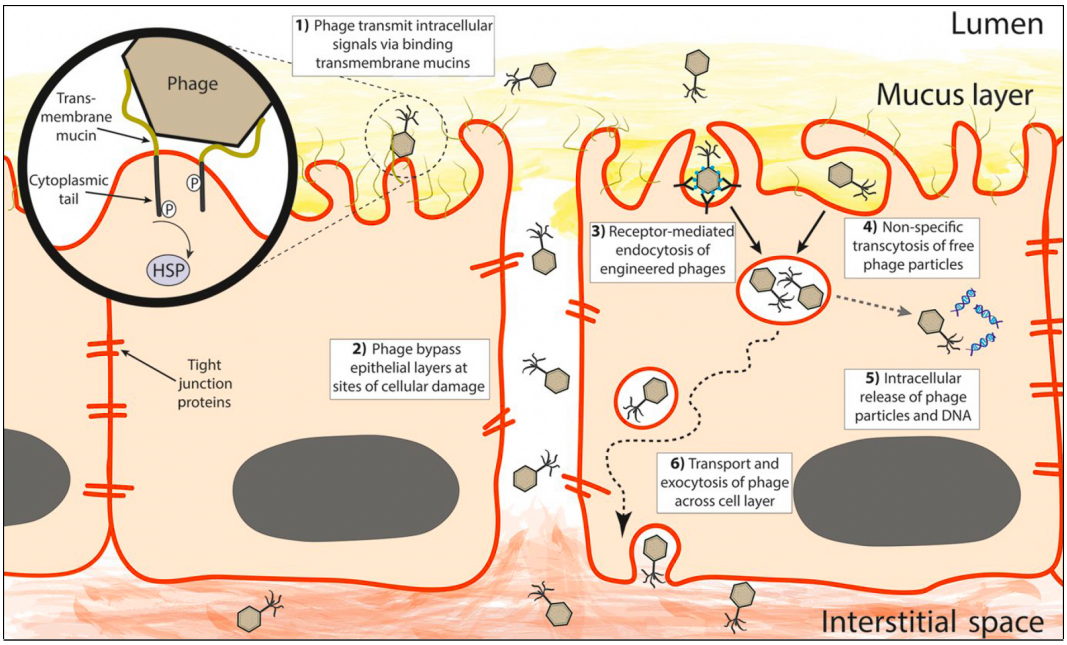

Figure 1: Bacteriophage interaction with the mammalian cell layer depicting the broad mechanism that phages can interact and stimulate the mammalian host directly. (Taken from Barr, 2017).

tested this observation, showing that T4 phages bound the membranes of cancer cells, attenuating tumour growth (*Dabrowska* et al., 2004a,b). Further, phages may indirectly stimulate or inhibit mammalian host cells and tissues through the production of auxiliary metabolic compounds encoded within their genomes and produced during either lytic or lysogenic infections of their bacterial hosts (*Sanchez* et al., 2015; *Thompson* et al., 2011). Indeed, the diversity of auxiliary metabolic genes that phages encode is highly diverse, with the production of these compounds having potentially varied effects. As such, it is important that we consider bacteriophages as not only 'viruses capably of infecting bacterial cells' but also as diverse biological agents capable of interacting with and influencing their broader mammalian hosts.

TRIPARTITE SYMBIOSES

Here I will discuss the concept of tripartite symbioses whereby bacteriophages can both directly and indirectly interact with their bacterial and mammalian hosts. This description is set in place of the previously described linear model, where bacteriophages were limited to only direct interactions with their bacterial hosts and indirect interactions with the mammalian host. Utilising this new tripartite model allows us to consider much broader affects those bacteriophages can have on larger symbiotic systems.

Taking the naturally-occurring phage populations residing within the human body we can consider the diversity of mechanisms by which they may

interact with both bacterial and mammalian hosts. In most cases, the mucosal surface is the first point of contact between the mammalian cell layer and phage populations that naturally reside within and upon it. Once there, bacteriophages can adhere to the mucosal surface (*Barr* et al., 2013; 2015). By adhering, bacteriophages can find and infect the resident bacterial community with greater ease. Once past the mucosa, phages can directly access the cell surface and interact with the underlying cellular epithelium. It has been demonstrated that phages are even capable of crossing this epithelial cell barrier in the gut and gain direct access to the bloodstream (*Górski* et al., 2006; *Nguyen* et al., 2017). This non-specific transcytosis mechanism has been proposed to facilitate 31 billion bacteriophage transcytosis events across the human gut epithelial barrier every day (*Nguyen* et al., 2017). Once within the circulatory system these 'intra-body phages' are able to gain access to all cells, organs and systems of the body (*Barr*, 2017). In fact it has been shown that some of these phages are even capable of crossing the blood-brain barrier – the most stringent biological barrier within the human body that even some small molecules and drugs fail to cross (*Geier* et al., 1973).

This tripartite model of bacteriophage-bacterial-mammalian interactions has led to a wave of research that has highlighted the diverse and surprising ways that bacteriophages can interact with and influence mammalian cells and those of other higher vertebrates. Bacteriophages have been demonstrated to bind cellular receptors on the apical surface of epithelial cell layers, leading to the activation of signal transduction pathways and other cellular functions (*Lehti* et al., 2017; *Singh* and *Hollingsworth*, 2006). These bacteriophage-cellular binding effects have been associated with increased mucus production, activation of anti-inflammatory responses, and even the aforementioned attenuation of tumour growth (*Dabrowska* et al., 2004; *Van Belleghem* et al., 2017). Further evidence suggests that phages are endocytosed by epithelial cells and trafficked throughout the endo-membrane system (*Lehti* et al., 2017; *Nguyen* et al., 2017). Once internalised, phages are encaged within membrane-bound vesicles. Once here, phage proteins and/or nucleic acids may be recognised by either cytostolic or endosomal membrane-bound receptors, triggering a broad host of cellular responses. But from where do these phages originate, and how can they build upon these tripartite models?

THE INTRA-BODY PHAGEOME

In a previous review article, I introduced and discussed the role of the 'intra-body phageome' (*Barr*, 2017). This phageome is proposed to originate from the highly diverse, expansive, and naturally occurring bacteriophage populations that are resident within the human gut. The gut microbiome plays an essential role in modulating our overall health and disease (*Scarpellini* et al., 2015). While the bacterial component of the gut microbiome has received considerable attention, comparatively little research and understanding has been provided to the gut viruses. Consisting overwhelmingly of bacteriophages, the gut virome is noted to contribute increasingly important roles in our overall health and well-being (*Clooney* et al., 2019; *Gregory* et al., 2020; *Liang* et al., 2020; *Sutton* and *Hill*, 2019). Gut bacteriophages can directly predate upon and regulate gut bacterial populations. Further, gut

phages can indirectly influence gut bacterial populations through the opening of niche space, release of diverse metabolites, and in-direct modulation of inter-bacterial species competition (*Hsu* et al., 2019). There have been a number of studies investigating the role of gut bacteriophages in states of dysbiosis. As such it has been found that specific bacteriophage populations have been correlated with a range of inflammatory bowel diseases, such as Crohn's and Ulcerative Colitis (*Norman* et al., 2015; *Clooney* et al., 2019). Conversely, gut bacteriophages have also been linked with a number of beneficial implications, including a reported increase in cognitive function through the modulation of bacterial populations and the secretion of key neuro-transmitters in the gut, which were found to affect short-term memory in flies and mice, while correlations were seen within human cohorts (*Maynernis-Percaxhs* et al., 2022). As such, there is a growing body of evidence suggestion the potential health and disease benefits of these gut bacteriophages.

Importantly, these resident gut bacteriophage populations with their potential health and immune-modulatory affects are also the source for the 'intra-body phageome'. Here, gut bacteriophage populations interact with the epithelial cell layers of the large intestine and subsequently are internalised by non-specific macropinocytosis mechanisms (*Bichet* et al., 2021b; *Nguyen* et al., 2017). This was proposed to facilitate over 31 billion phage uptake and transcytosis events within an adult human every single day (*Nguyen* et al., 2017). Thus, there exists a large potential for resident gut bacteriophages to be continually internalised and trafficked into the 'classically-sterile' regions of the body. This allows for a low-level, constituent resident collection of naturally occurring gut bacteriophages that are interacting with the broader mammalian host cells, organs and systems. This broader tripartite system has incredible potential to modulate the mammalian host in diverse and largely as yet undiscovered ways.

PHAGE UPTAKE, DELIVERY AND ACTIVATION OF THE MAMMALIAN SYSTEM

The broader question when considering tripartite symbioses is 'why do bacteriophages interact with mammalian cells' and 'what potential response could they be mediating?' (Or, if you're proclivity is mammalian-centric, 'why do mammalian cells internalise bacteriophages and for what purpose?'). The answer to this question could be surprising, diverse, and unexpected. In fact, these interactions and their derivative effects may be so unexpected that it would be foolish to predict these entirely. Instead, we should look to the diversity of interactions that the gut bacteria mediate and the process towards their discoveries. Here I will explore two potential mechanisms that bacteriophages can and may directly influence the mammalian host.

The first is through the triggering of pattern recognition receptors (PRRs). As bacteriophages contain either RNA or DNA genomes as part of their life cycle, the nucleic acid sensing of the mammalian cell could be triggered. Once bacteriophage particles are internalised by mammalian cells there exist two main mechanisms through which

their genomes could trigger PRRs (*Tan* et al., 2018). The first is through TLR9 receptors positioned within the endosomal structures. It has been shown that bacteriophage particles are endocytosed and trafficked through the endomembrane system (*Bichet*, et al., 2021a; *Nguyen* et al., 2017). If bacteriophage capsids are damaged or tail fiber structures triggered, then their genomic material could be exposed within the endosomes and lead to the activation of TLR9, whose downstream activation can stimulate Type I IFN response (*Sweere* et al., 2019; *Van Belleghem* et al., 2019). Alternatively, if bacteriophage particles or their genomes escape these endomembrane vesicles, they may gain access to the mammalian cytosol. There the major innate immune sensor for nucleic acids is the cGAS/STING (cyclic GMP-AMO synthase/stimulator of interferon genes) pathway (*Tan* et al., 2018). When dsDNA fragments are detected by cGAS, a molecule of cGAMP will be produced and sent to the STING complex to activate the production of cytokines like INF (*Blasius* and *Beutler*, 2010). These two pathways lead to signalling cascades that culminate in the production of inflammatory cytokines, leading to the induction of an antimicrobial state, activation of adaptive immunity, and eventual clearance of the triggering pathogen.

The second potential mechanism that bacteriophages could influence the mammalian cell is through direct protein-to-protein interactions. This could be initiated through bacteriophage capsid interactions with G-protein coupled receptors at the cell membrane (*Bosch* et al., 2009). Once activated these could lead to protein phosphorylation cascade within the cell that may activate a diverse array of mechanistic responses and modulation of cellular function (*Carraway* et al., 2003; *Lillehoj* et al., 2004). Mechanistically these two responses are diverse in both their activation and downstream signal cascades. Further experimental validation of if and how bacteriophages may interact with mammalian cells and the responses they induce are needed.

HYPOTHETICAL GENE POTENTIAL

A final hypothetical alternative for bacteriophage uptake and internalisation by mammalian cells is the potential for gene delivery and transduction. Once internalised, there exists the possibility for bacteriophages to deliver their genetic material into the mammalian cell allowing for the transcription and translation of virally encoded DNA by the eukaryotic cellular machinery – a process more broadly known as 'transduction' (*Merril*, 1974; *Tao* et al., 2013).

Bacteriophages have indeed been used as viral gene delivery vectors and nanocarriers, primarily due to their ease of use, capacity for nucleic acid packaging and their relative safety in humans (*Karimi* et al., 2016). To accomplish this, a process known as 'phage-display' is used for the targeted delivery of phage-carried nucleic acids and proteins to specific mammalian cells (*Ivanenkov* and *Menon*, 2000; *Pranjol* and *Hajitou*, 2015). In this process bacteriophages are engineered to display ligands on their capsids that are complementary to mammalian cell surface integrins. Phage-displayed ligands then bind to these integrins and trigger receptor-mediated endocytosis of the bacteriophage particle on contact with the mammalian cell. These bacteriophage capsids can be recombinantly packaged with DNA, RNA, or proteins for the targeted delivery of genes and

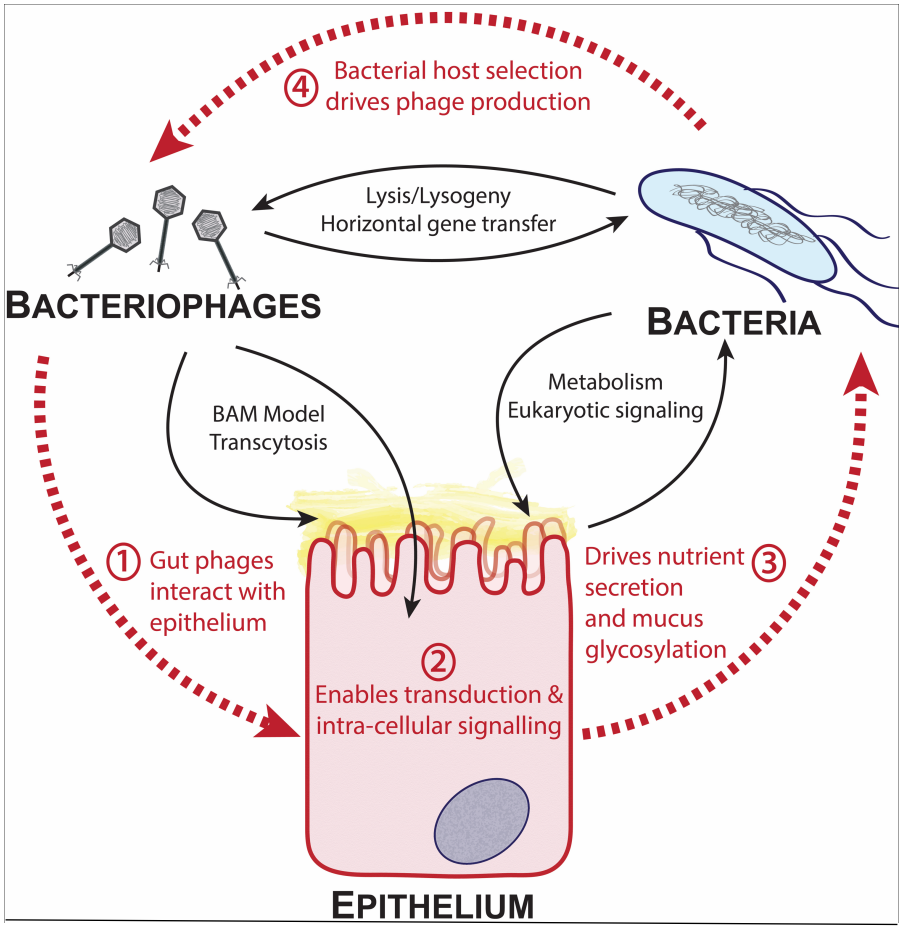

Figure 2: Model of tripartite symbioses in the human gut and the potential for the delivery and transduction of bacteriophage-encoded nucleic acid material to the mammalian cell. (Taken from Barr, 2019).

enzymes into the mammalian cells of interest. Using these approaches, engineered bacteriophage particles have successfully been used to transduce mammalian cells to correct metabolic deficiencies (*Geier* et al., 1973; *Merril* et al., 1971), elicit antibody response (*Tao* et al., 2013), and to deliver reporter genes or enzymes (*Poul* and *Marks*, 1999). These studies demonstrate the capacity for bacteriophage-encoded genetic material to be delivered to and transduce mammalian cells.

This leads to a major hypothesis as to whether the uptake and internalisation of naturally occurring bacteriophage populations within the human gut are capable of transduction (Figure 2). As theses gut bacteriophages are known to be internalised and transcytosed at consistent levels (*Nguyen* et al., 2017) and studies have shown engineered bacteriophage particles can deliver and transduce cells (*Geier* and *Merril*, 1972) this mechanistic route for natural bacteriophage populations to transduce the mammalian host remains and open possibility.

When considering the enormous diversity of bacteriophage populations within the human gut and the large

hypothetical genes they encode – more commonly referred to as 'viral dark matter' – this is an intriguing hypothesis to explore further. A clear understanding of the cellular and molecular interactions between these bacteriophage particles and mammalian cells will be required to elucidate any novel symbioses.

LITERATURE

Barr, J.J., Auro, R., Furlan, M., Whiteson, K. L. L., Erb, M. L. L., Pogliano, J., Stotland, A., Wolkowicz, R., Cutting, A. S. S., Doran, K. S. S., Salamon, P., Youle, M., and Rohwer, F.: Bacteriophage adhering to mucus provide a non-host-derived immunity. Proc. Natl. Acad. Sci. USA 110, 10771-10776 (2013).

Barr, J.J., Auro, R., Sam-Soon, N., Kassegne, S., Peters, G., Bonilla, N., Hatay, M., Mourtada, S., Bailey, B., Youle, M., Felts, B., Baljon, A., Nulton, J., Salamon, P., and Rohwer, F.: Subdiffusive motion of bacteriophage in mucosal surfaces increases the frequency of bacterial encounters. Proc. Natl. Acad. Sci. USA 112, 13675-13680 (2015).

Barr, J.J.: A bacteriophages journey through the human body. Immunol. Rev. 279, 106-122 (2017).

Barr, J.J.: Missing a Phage: Unraveling Tripartite Symbioses within the Human Gut. mSystems 7, e00105-19 (2019).

Bichet, M.C., Chin, W.H., Richards, W., Lin, Y.-W., Avellaneda-Franco, L., Hernandez, C.A., Oddo, A., Chernyavskiy, O., Hilsenstein, V., Neild, A., Li, J., Voelcker, N.H., Patwa, R., and Barr, J.J.: Bacteriophage uptake by mammalian cell layers represents a potential sink that may impact phage therapy. iScience 24, 102287 (2021a).

Bichet, M.C., Patwa, R., and Barr, J.J.: Protocols for studying bacteriophage interactions with *in vitro* epithelial cell layers. STAR Protoc. 2, 100697 (2021b).

Blasius, A.L. and Beutler, B.: Intracellular Toll-like Receptors. Immunity 32, 305-315 (2010).

Bloch, H.: Experimental investigation on the relationship between bacteriophages and maligant tumors. Arch. Virol. 1, 481-496 (1940).

Bosch, T.C.G., Augustin, R., Anton-Erxleben, F., Fraune, S., Hemmrich, G., Zill, H., Rosenstiel, P., Jacobs, G., Schreiber, S., Leippe, M., Stanisak, M., Grötzinger, J., Jung, S., Podschun, R., Bartels, J., Harder, J., and Schröder, J.-M.: Uncovering the evolutionary history of innate immunity: the simple metazoan Hydra uses epithelial cells for host defence. Dev. Comp. Immunol. 33, 559-569 (2009).

Carraway, K.L., Ramsauer, V.P., Haq, B., and Carothers Carraway, C.A.: Cell signaling through membrane mucins. Bioessays 25, 66-71 (2003).

Clooney, A.G., Sutton, T.D.S., Shkoporov, A.N., Holohan, R.K., Daly, K.M., O'Regan, O., Ryan, F.J., Draper, L.A., Plevy, S.E., Ross, R.P., and Hill, C.: Whole-Virome Analysis Sheds Light on Viral Dark Matter in Inflammatory Bowel Disease. Cell Host Microbe 26, 764-778 (2019).

Dabrowska, K, Opolski, A., Wietrzyk, J., Switala-Jelen, K., Boratynski, J., Nasulewicz, A., Lipinska, L., Chybicka, A., Kujawa, M., Zabel, M., Dolinska-Krajewska, B., Piasecki, E., Weber-Dabrowska, B., Rybka, J., Salwa, J., Wojdat, E., Nowaczyk, M., and Gorski, A.: Antitumor activity of bacteriophages in murine experimental cancer models caused possibly by inhibition of beta3 integrin signaling pathway. Acta Virol. 48, 241-248 (2004a).

Dabrowska, K., Opolski, A., Wietrzyk, J., Switala-Jelen, K., Godlewska, J., Boratynski, J., Syper, D., Weber-Dabrowska, B., and Gorski, A.: Anticancer activity of bacteriophage T4 and its mutant HAP1 in

mouse experimental tumour models. Anticancer Res. 24, 3991-3995 (2004b).
Geier, M.R. and Merril, C.R.: Lambda phage transcription in human fibroblasts. Virology 47, 638-643 (1972).
Geier, MR., Trigg, M.E., and Merril, C.R.: Fate of bacteriophage lambda in non-immune germ-free mice. Nature 246, 221-223 (1973).
Górski, A., Wazna, E., Dabrowska, B.-W., Dabrowska, K., Switała-Jeleń, K., and Miedzybrodzki, R.: Bacteriophage translocation. FEMS Immunol. Med. Microbiol. 46, 313-319 (2006).
Gregory, A.C., Zablocki, O., Zayed, A.A., Howell, A., Bolduc, B., and Sullivan, M.B.: The Gut Virome Database Reveals Age-Dependent Patterns of Virome Diversity in the Human Gut. Cell Host Microbe 28, 724-740 (2020).
Hsu, B.B., Gibson, T.E., Yeliseyev, V., Liu, Q., Lyon, L., Bry, L., Silver, P.A., and Gerber, G.K.: Dynamic Modulation of the Gut Microbiota and Metabolome by Bacteriophages in a Mouse Model. Cell Host Microbe *25*, 803-814 (2019).
Ivanenkov, V.V. and Menon, A.G.: Peptide-mediated transcytosis of phage display vectors in MDCK Cells. Biochem. Biophys. Res. Commun. 276, 251-257 (2000).
Karimi, M., Mirshekari, H., Moosavi Basri, S.M., Bahrami, S., Moghoofei, M., and Hamblin, M.R.: Bacteriophages and phage-inspired nanocarriers for targeted delivery of therapeutic cargos. Adv. Drug Deliv. Rev. 106, 45-62 (2016).
Lehti, T.A., Pajunen, M.I., Skog, M.S., and Finne, J.: Internalization of a polysialic acid-binding Escherichia coli bacteriophage into eukaryotic neuroblastoma cells. Nature Commun. 8, 1915 (2017).
Liang, G., Zhao, C., Zhang, H., Mattei, L., Sherrill-Mix, S., Bittinger, K., Kessler, L.R., Wu, G.D., Baldassano, R.N., DeRusso, P., Ford, E., Elovitz, M.A., Kelly, M.S., Patel, M.Z., Mazhani, T., Gerber, J.S., Kelly, A., Zemel, B.S., and Bushman, F.D.: The stepwise assembly of the neonatal virome is modulated by breastfeeding. Nature 581, 470-474 (2020).
Lillehoj, E.P., Kim, H., Chun, E.Y., and Kim, K.C.: Pseudomonas aeruginosa stimulates phosphorylation of the airway epithelial membrane glycoprotein Muc1 and activates MAP kinase. Am. J. Physiol. Lung Cell. Mol. Physiol. 287, L809-L815 (2004).
Maynernis-Percaxhs, J., Castells-Nobau, A., Arnoriaga-Rodriguez, M., Maldonado, R., and Fernandez-Real, J.-M.: Caudovirales bacteriophages are associated with improved executive function and memory in flies, mice, and humans. Cell Host Microbe 30, 340-356 (2022).
Merril, C.R., Geier, M.R., and Petricciani, J.C.: Bacterial virus gene expression in human cells. Nature 233, 398-400 (1971).
Merril, C.R.: Bacteriophage interactions with higher organisms. Trans. NY Acad. Sci. 36, 265-272 (1974).
Nguyen, S., Baker, K., Padman, B.S., Patwa, R., Dunstan, R.A., Weston, T.A., Schlosser, K., Bailey, B., Lithgow, T., Lazarou, M., Luque, A., Rohwer, F., Blumberg, R.S., and Barr, J.J.: Bacteriophage Transcytosis Provides a Mechanism To Cross Epithelial Cell Layers. MBio, 8, e01874-17 (2017).
Norman, J.M., Handley, S.A., Baldridge, M.T., Droit, L., Liu, C.Y., Keller, B.C., Kambal, A., Monaco, C.L., Zhao, G., Fleshner, P., Stappenbeck, T.S., McGovern, D.P.B., Keshavarzian, A., Mutlu, E.A., Sauk, J., Gevers, D., Xavier, R.J., Wang, D., Parkes, M., and Virgin, H.W.: Disease-Specific Alterations in the Enteric Virome in Inflammatory Bowel Disease. Cell 160, 447-460 (2015).
Poul, M. a, & Marks, J. D.: Targeted gene delivery to mammalian cells by filamentous bacteriophage. J. Mol. Biol. 288, 203-211 (1999).
Pranjol, M.Z.I. and Hajitou, A.: Bacteriophage-derived vectors for targeted cancer gene therapy. Viruses 7, 268-284 (2015).
Sanchez, S.E., Cuevas, D.A., Rostron, J.E., Liang, T.Y., Pivaroff, C.G., Haynes, M.R., Nulton, J., Felts, B., Bailey, B.A., Salamon, P., Edwards, R.A., Burgin, A.B., Segall, A.M., and Rohwer, F.: Phage Phenomics:

Physiological Approaches to Characterize Novel Viral Proteins. J. Vis. Exp. 100: e52854 (2015).

Scarpellini, E., Ianiro, G., Attili, F., Bassanelli, C., De Santis, A., and Gasbarrini, A.: The human gut microbiota and virome: Potential therapeutic implications. Dig. Liver Dis. 47, 1007-1012 (2015).

Singh, P.K. and Hollingsworth, M.A.: Cell surface-associated mucins in signal transduction. Trends Cell. Biol. 16, 467-476 (2006).

Sutton, T.D.S. and Hill, C.: Gut Bacteriophage: Current Understanding and Challenges. Front. Endocrinol. 10, 784 (2019).

Sweere, J.M., Van Belleghem, J.D., Ishak, H., Bach, M.S., Popescu, M., Sunkari, V., Kaber, G., Manasherob, R., Suh, G.A., Cao, X., de Vries, C.R., Lam, D.N., Marshall, P.L., Birukova, M., Katznelson, E., Lazzareschi, D.V., Balaji, S., Keswani, S.G., Hawn, T., Secor, P.R., and Bollyky, P.L.: Bacteriophage trigger antiviral immunity and prevent clearance of bacterial infection. Science 363, eaat9691 (2019).

Tan, X., Sun, L., Chen, J., and Chen, Z.J.: Detection of Microbial Infections Through Innate Immune Sensing of Nucleic Acids. Annu. Rev. Microbiol. 72, 447-478 (2018).

Tao, P., Mahalingam, M., Marasa, B.S., Zhang, Z., Chopra, A.K., and Rao, V.B.: In vitro and in vivo delivery of genes and proteins using the bacteriophage T4 DNA packaging machine. Proc. Natl Acad. Sci. USA, 110, 5846-5851 (2013).

Thompson, L.R., Zeng, Q., Kelly, L., Huang, K.H., Singer, A.U., Stubbe, J., and Chisholm, S.W.: Phage auxiliary metabolic genes and the redirection of cyanobacterial host carbon metabolism. Proc. Natl Acad. Sci. USA, 108, E757-E764 (2011).

Van Belleghem, J.D., Clement, F., Merabishvili, M., Lavigne, R., and Vaneechoutte, M.: Pro- and anti-inflammatory responses of peripheral blood mononuclear cells induced by Staphylococcus aureus and Pseudomonas aeruginosa phages. Sci. Rep. 7, 8004 (2017).

Van Belleghem, J.D., Dąbrowska, K., Vaneechoutte, M., Barr, J. J., and Bollyky, P. L.: Interactions between bacteriophage, bacteria, and the mammalian immune system. Viruses 11: 10 (2019).