

# MILESTONES

simply the production of a bacteriocin. A second pair of unrelated papers set out to understand how enteropathogens could overcome colonization resistance. In separate mouse studies and using different enteropathogens (*Citrobacter rodentium* or *Salmonella*), it was shown that intestinal inflammation altered the composition of the host's microbiota and made them susceptible to colonization by the invading bacteria. In both cases the bacteria needed to be able to elicit gut inflammation in order to establish themselves — in other words, this appeared to be a case of the enteropathogen co-opting the host's immune response to its advantage.

Colonization resistance has proved to be a useful model for understanding the dynamics of microbial communities in the gut and other barrier surfaces, such as the skin, however in one sense it is strikingly similar to the much earlier ecological concept of 'allelopathy'. Initially outlined in the 1930s to describe interactions between certain plant species, allelopathy was later broadened to describe the suppression of any competitor organism

by another through the generation of biologically active factors.

As we teeter towards the dangers of a post-antibiotic era, further insights

from the study of colonization resistance could offer the hope of novel antimicrobial therapies.

Zoltan Fehervari, *Nature Immunology*

**ORIGINAL ARTICLES** Corr, S. et al. Bacteriocin production as a mechanism for the anti-infective activity of *Lactobacillus salivarius* UCC118. *Proc. Natl Acad. Sci. USA* **104**, 7617–7621 (2007) | Lupp, C. et al. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of *Enterobacteriaceae*. *Cell Host Microbe* **16**, 119–129 (2007) | Stecher, B. et al. *Salmonella enterica* serovar Typhimurium exploits inflammation to compete with the intestinal microbiota. *PLoS Biol.* **5**, 2177–2189 (2007).

**FURTHER READING** Bohnhoff, M. et al. Effect of streptomycin on susceptibility of intestinal tract to experimental *Salmonella* infection. *Proc. Soc. Exp. Biol. Med.* **86**, 132–137 (1954) | van der Waaij, D. et al. Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. *J. Hyg.* **69**, 405–411 | Freter, R. Experimental enteric *Shigella* and *Vibrio* infections in mice and guinea pigs. *J. Exp. Med.* **104**, 411–418 (1956) | Bohnhoff, M., Miller, C. P. & Martin, W. R. Resistance of the mouse's intestinal tract to experimental *Salmonella* infection: factors responsible for its loss following streptomycin treatment. *J. Exp. Med.* **120**, 817–828 (1964) | Yamazaki, S., Kamimura, H., Momose, H., Kawashima, T. & Ueda K. Protective effect of bifidobacterium monoassociation against lethal activity of *Escherichia coli*. *Bifidobacteria Microflora* **1**, 55–60 (1964) | O'Mahony, C. et al. Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF- $\kappa$ B activation. *PLoS Pathog.* **4**, e1000112 (2008) | Winter, S. E. et al. Gut inflammation provides a respiratory electron acceptor for *Salmonella*. *Nature* **467**, 426–429 (2010) | Thiennimitr, P. et al. Intestinal inflammation allows *Salmonella* to use ethanolamine to compete with the microbiota.

*Proc. Natl Acad. Sci. USA* **108**, 17480–17485 (2011) | Fukuda, S. et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* **469**, 543–547 (2011) | Kamada, N. et al. Regulated virulence controls the ability of a pathogen to compete with the gut microbiota. *Science* **336**, 1325–1329 (2012) | Buffie, C. G. et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature* **517**, 205–208 (2015) | Sassone-Corsi, M. et al. Microcins mediate competition among *Enterobacteriaceae* in the inflamed gut. *Nature* **540**, 280–283 (2016) | Rivera-Chávez, F. et al. Depletion of butyrate-producing *Clostridia* from the gut microbiota drives an aerobic luminal expansion of *Salmonella*. *Cell Host Microbe* **19**, 443–454 (2016) | Faber, F. et al. Host-mediated sugar oxidation promotes post-antibiotic pathogen expansion. *Nature* **534**, 697–699 (2016) | Byndloss, M. X. et al. Microbiota-activated PPAR- $\gamma$  signaling inhibits dysbiotic *Enterobacteriaceae* expansion. *Science* **357**, 570–575 (2017) | Becattini, S. et al. Commensal microbes provide first line defense against *Listeria monocytogenes* infection. *J. Exp. Med.* **214**, 1973–1989 (2017) | Caballero, S. et al. Cooperating commensals restore colonization resistance to vancomycin-resistant enterococcus faecium. *Cell Host Microbe* **21**, 592–602 (2017) | Zhu, W. et al. Precision editing of the gut microbiota ameliorates colitis. *Nature* **553**, 208–211 (2018) | Zmora, N. et al. Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. *Cell* **174**, 1388–1405 (2018) | Litvak, Y. et al. Commensal *Enterobacteriaceae* protect against *Salmonella* colonization through oxygen competition. *Cell Host Microbe* **25**, 128–139 (2019).

## MILESTONE 14

# Functional human microbiota analyses in vivo using 'omics technologies

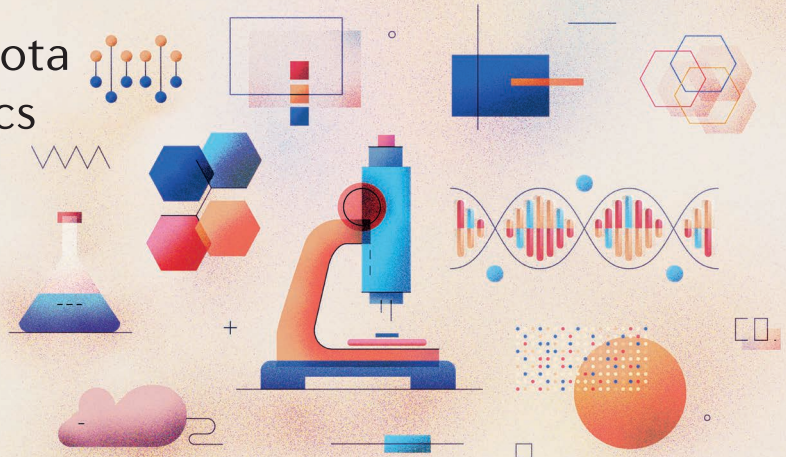
Eline Klaassens and colleagues applied a metaproteomics approach to uncultured faecal microbiota, providing the first insights beyond taxonomic identification. This was followed by numerous studies using 'omics methods, such as metabolomics and metatranscriptomics, as well as the development of multi-omics pipelines; methods that are still uncovering the functions of the microbiota today.

**ORIGINAL ARTICLE** Klaassens, E. S., de Vos, W. M. & Vaughan, E. E. Metaproteomics approach to study the functionality of the microbiota in the human infant gastrointestinal tract. *Appl. Environ. Microbiol.* **73**, 1388–1392 (2007).

**FURTHER READING** Verberkmoes, N. C. et al. Shotgun metaproteomics of the human distal gut microbiota. *ISME J.* **3**, 179–189 (2008) | Jansson, J. et al. Metabolomics reveals

metabolic biomarkers of Crohn's disease. *PLoS ONE* **4**, e6386 (2009) | Martin, F. P. et al. Topographical variation in murine intestinal metabolic profiles in relation to microbiome speciation and functional ecological activity. *J. Proteome Res.* **8**, 3464–3474 (2009) | Franzosa, E. A. et al. Relating the metatranscriptome and metagenome of the human gut. *Proc. Natl Acad. Sci. USA* **111**, 2329–2338 (2014) | Bouslimani, A. et al.

Molecular cartography of the human skin surface in 3D. *Proc. Natl Acad. Sci. USA* **112**, 2120–2129 (2015) | Heintz-Buschart, A. et al. Integrated multi-omics of the human gut microbiome in a case study of familial type 1 diabetes. *Nat. Microbiol.* **2**, 16180 (2016) | Franzosa, E. A. et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat. Microbiol.* **4**, 293–305 (2019).



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