Focus on translating the microbiome

Cheaper and faster sequencing is galvanizing the study of the human microbiome. Indeed, researchers have generated more than 3.5 terabytes of human microbiome information in the past 15 years—a staggering slew of sequences that is more than 1,000 times the amount of data produced by the Human Genome Project. This has been mirrored by a rapid increase in publications year-on-year [**Data page, p. 277**], encompassing work in microbiology, ecology, immunology, pharmacology, human physiology, metabolism and disease, and the intersections between all of these areas. As yet, little has been discussed concerning how our increasing understanding of the relationships between humans and their 'second genome' can be translated into new therapeutic approaches. This Focus highlights progress in microbiome research and how these data might enable a better understanding of human disease and the rational design of new therapeutic modalities.

Microbe-based therapies are of course nothing new, with preserved milk fermented by bacteria (yogurt) being known for its health-giving properties for centuries. Nowadays probiotic science has advanced considerably and was already a huge industry before cheap sequencing enabled the microbiome revolution with the concomitant realization of the potentially beneficial effects of modulating the gut microbiota. Charles Schmidt traces the development of probiotics from their conception over a century ago to the present day, as researchers move away from vague health claims toward pinning down mechanisms. [**News Feature, p. 279**] This shift in emphasis is in part due to regulatory agencies preventing food manufacturers from making specific health claims absent clinical evidence. The profiling technologies that are providing unparalleled details of the microbiome are now being applied in probiotic research, and bolstering the field are recent clinical trial results demonstrating what had been reported anecdotally for almost 50 years: that transplanting the fecal microbiota of healthy individuals can cure recalcitrant intestinal infections. [**Feature, p. 309**]

To provide a snapshot of seminal papers in the field, we surveyed scientists who work on different aspects of the human microbiome and asked them which papers published in the past 15 years, since the inception of this field, have been the most influential. [**Feature, p. 304**] Perhaps surprisingly for a burgeoning research literature, only a few papers dominated responses. The top five papers highlighted by survey respondents catalog the immense diversity of human gut microbiota or investigate the links between microbiota dysbiosis and disease.

Thus far, the standard approach to treating bacterial infections has been antibiotic treatments, with problems arising from the emergence of resistant strains. Another route to therapeutic intervention, however, may be to simply modulate the human microbiota to outcompete organisms that mediate pathogenic effects. Taking a look at commercial efforts to modulate the microbiome, Bernat Olle outlines the spectrum of microbiome modulators possible, from ecosystem level interventions to targeted approaches. He also provides an overview of some of the main startups that are exploiting this newfound knowledge to develop products against intestinal disorders, and touches on the regulatory and proprietary issues that surround commercialization of the technology. [**Feature, p. 309**]

Surprisingly, intellectual property surrounding microbiome products is less uncertain than it was for products based on monoclonal antibodies, RNA interference or stem cells. This may be an advantage as these latter products required businesses to negotiate thickets of cross-licensing arrangements and burdened them with high royalty stacks on the resulting products. Our survey of the patent databases yields a variety of recent patent applications in the field. [**Patent Table, p. 318**]

Going forward, several challenges face those who want to translate basic biology findings associated with the human microbiota. Discussions with nine experts from academia and industry [**Feature, p. 304**] reveal that we still lack sufficient cultured microbiota organisms to understand the functions of the microflora, that we face technological barriers to unraveling the functions associated with the microbiome and that good model systems for functional studies are crucial for progress.

To rationally design microbiome-based therapies to address chronic disease, we will need a clearer understanding of the mechanisms that underpin dysbiosis (pathological imbalances in the microbiota) and how these relate to dysfunction. Identifying mechanisms usually means reductive biology and bespoke animal models, but the generation, maintenance and availability of germ-free models remains problematic. [**Editorial, p. 263**]

There is little doubt that we are gradually beginning to uncover ways in which we might exploit a better understanding of the intersection between humans and their microbes to treat disease. The articles presented in this issue focus on how knowledge of the microbiome can be translated into new approaches for therapeutic intervention. But clearly microbiome research will open up many new lines of investigation in other biotech areas as well (e.g., companion animals, livestock and plants). In plant biotech, for example, increased understanding of the composition and functions of root-associated microbes could eventually result in new approaches to improving pathogen resistance (*Science* **332**, 1097–1100, 2011) or even improving yield and drought resistance.