In the pursuit of personalized medicine; New technologies to study the gut microbiome

Humans have a symbiotic relationship with microbes that reside in and on our bodies. The human digestive tract contains as many as 10^{14} of bacterial cells, making it one of the densest and most diverse microbial communities on earth. The gut microbiota has recently gained attention from medical researchers, as disruptions have been shown to be associated with a variety of human diseases. With increasing interest in the microbes residing within the gut, new multidisciplinary technologies have arisen with the singular purpose of better understanding the importance of microbial communities on host health.

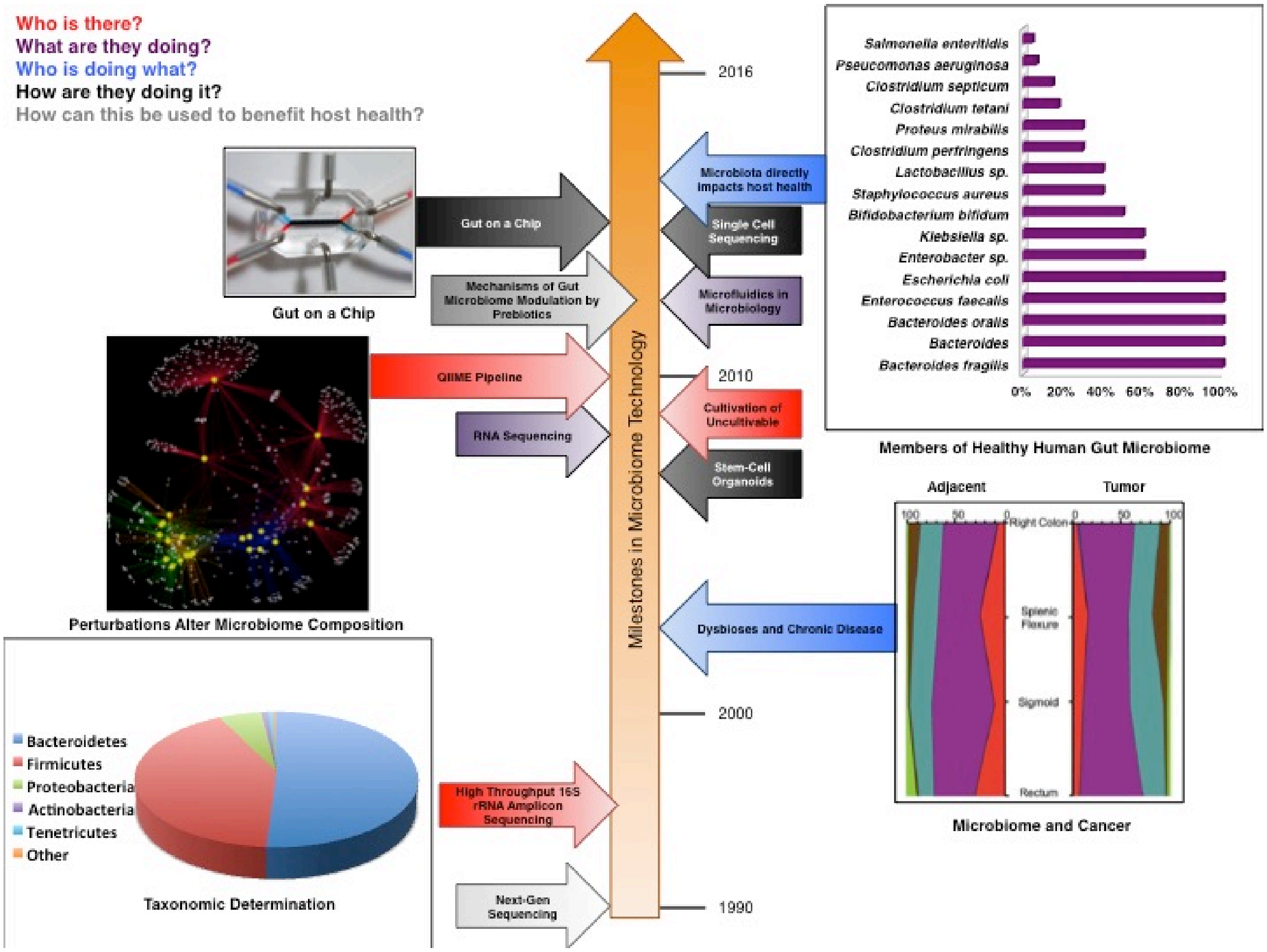

Fig. 1. Timeline of Major Advancements on Gut Microbiota Studies. With improvements to sequencing technology, studies of complex microbial communities have become more affordable, resulting in an explosion of new technologies surrounding the gut microbiome. New multi-disciplinary technologies are continually emerging, allowing scientists to identify specific interactions in microbial communities that may lead to the development of novel therapeutics for a

wide range of human diseases.

Technological advancements have permitted researchers to answer some of the big questions surrounding the gut microbiome: “Who is there?” “What are they doing?” “How are they doing it?” “Can the microbiome be modulated to promote or restore host health?” (Fig. 1)

High throughput sequencing technologies are important tools in microbiome studies. The most commonly used method to identify composition of complex microbial communities (“Who is there?”) involves sequencing variable regions in the universally conserved (shared among all bacteria) ribosomal genes. Deeper resolution of community composition can be achieved using Whole Genome Shotgun (WGS) sequencing, easily resolving sub-species variation and identifying DNA viruses, a feat unattainable by sequencing ribosomal genes alone. WGS also provides insight into the function of the community (“What are they doing?”), revealing overrepresented genes within the population. Sequencing total mRNA present in the community allows further exploration of microbial function. Technologies like nuclear magnetic resonance (NMR) and mass spectrometry (MS) have seen recent improvements and are now being employed to study microbial metabolomics. Together these technologies can provide a wealth of data regarding what microbes are doing, but are unable to fully resolve how these behaviors are controlled.

To understand microbial function, cultivation of individual microbes is imperative. Gut microbes require very specific growth conditions. Many are highly sensitive to oxygen.   Furthermore even with advanced cultivation techniques, a percent of gut bacteria remain uncultivable. Use of germ free animals has made it possible to cultivate difficult-to-grow microbes; however performing functional analyses within live animals is challenging. Novel *in-vitro* systems (iChip/I-tip) can be used to isolate and culture individual “uncultivable” microbes, providing a platform to improve functional studies. Cutting edge gastrointestinal simulators offer a way to study microbial interactions, metabolism, and behavior under highly controlled conditions, further increasing cultivation efficiency for difficult-to-grow microbes. Unfortunately, *in vitro* systems alone do not yield insight into how microbes interact with their hosts, or how they may be able to provide health benefits.

With improvements in compositional studies and cultivation technologies, it has become possible to identify beneficial modulators of the gut microbiota (prebiotics) designed to promote growth of specific microbes, or initiate precise changes within the community as interventions for diseases associated with gut microbial imbalances. Additionally, these technological advancements improve the capacity to identify novel probiotic microbes that may be used as specific disease interventions by modulating host gene expression and gut microbial composition.

By modulating the microbiota, researchers can determine the impact of specific microbial communities, probiotics and prebiotics on the host. These studies can be performed in germ free animals, however the cost and space requirement to perform experiments in live animal models is often prohibitive. Recent breakthroughs in stem cell technology and tissue engineering allow for the growth of fully differentiated micro-organs (organoids) from epithelial stem cells harvested from small or large intestine; retaining the genetic background of their donor. Emerging organoid technology will provide a platform for research toward personalized medicine, allowing for the study of many treatment types simultaneously without the time, space, or financial constraints imposed by live animal model research.

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