Horizon Scanning Series
The Future of Precision Medicine in Australia

Microbiome

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What is the microbiome and its relevance to precision medicine?

We define the "microbiome" as the holistic and mechanistic study of the interactions and processes inherent to a microbial community (micro-), placed in context with the physiochemical attributes of their surrounding environment (-biome). The human microbiome is a measurable, functional and dynamic interface between our genes, the environment we live in, and the lifestyle choices we make.

One can envisage a future where the microbiome status of individuals can be assessed as part of routine GP visits from non-invasive samples (e.g. oral, skin, and stool swabs, breath and urine samples) and the information is used for their risk stratification and clinical management. From the assessment and management of the gut microbiome for digestive diseases, to the oral microbiome with respect to cardiovascular disease and rheumatoid arthritis risk and attenuation, and the skin microbiome to thwart the progression of skin lesions to keratoses and cancers, the microbiome offers new opportunities for the diagnosis, treatment and prevention of diseases, especially those with limited genetic penetrance. As such, the microbiome is likely to be a key contributor to precision medicine because it can be predictive, personalized and preventative.

While the impetus to study the microbiome across the industrial, environmental and health sciences has been triggered by technological advances in DNA/RNA sequencing and computational biology; expertise and technological advances in microbiology, cellular imaging, and biomolecule analyses (e.g. proteins and metabolic products) will be critical to success. As such, microbiome research will help promote new opportunities and synergies in ***Biological Sciences, Immunology and Infectious Diseases,*** **and** ***Medicinal Chemistry and Pharmaceutical Genomics***.

Current state of play in Australia and overseas

Over the last decade, efforts supported via the US-NIH Human Microbiome Program (HMP), and the EU-funded Metagenomics of the Human Intestinal Tract (MetaHIT) program, in collaboration with Chinese collaborators (e.g. Chinese Academy of Sciences, Shanghai Jiao Tong University, and Beijing Genomics Institute) have led the way in improving our awareness and understanding of the human microbiome, and its relationships with health and disease. The overwhelming amount of research effort has been directed to the microbiome of the lower gut, and principally via the analyses of stool samples[1,2]. More recently, greater emphasis has been directed to other body sites (e.g. skin, oral cavity and urogenital tract)[3,4] as well as various cohorts differing in age, indigenous populations, and non-Western ethnic groups adopting a Western lifestyle[5-7]. There is also now an increasing degree of focus towards translating these advances in fundamental understanding into medical practice, principally via integration with other molecular, genetic and clinical data [8,9]. As an example, the 2015 expenditure by the US-NIH on human microbiome research exceeded US$200 million (Lita Proctor, Chair trans-NIH Microbiome Working Group, NHGRI/NIH, pers. comm.) and continues to increase.

Australia has a long and prominent history in medical microbiology research, including Florey's role in the discovery of penicillin; Fenner's development of the myxoma virus for biocontrol of rabbit populations; Marshall's and Warren's identification and demonstration of the role of *Helicobacter*

pylori in gastric diseases, and Frazer's and colleagues development of novel vaccine technologies for the prevention of HPV-mediated cancers. In their own way, these outcomes result directly from approaches consistent with our definition of "microbiome research", so the Australian health research landscape has long recognised the merit and value in this research field. However, the adaptation and use of those technologies now underpinning microbiome research has been gradual in Australia during the last decade, essentially supported via small investigator-initiated clinical research project grants, and/or via collaborations with overseas partners (e.g. NHMRC-EU projects). Although engagement and (minor) contributions to the large international initiatives outlined above have been mediated via these investigator-initiated collaborations, a consortium-led initiative representing a uniquely Australian position and contribution to these global endeavours has been lacking.

Ten-year Trajectory

Host-microbe interactions have long been recognized as a factor contributing to the onset and progression of many acute and chronic diseases, including immune-mediated diseases and cancers. Indeed, recent studies using animal models provide strong evidence that many diseases once thought to be "non-communicable" are now transmissible via the "transplant" of the microbiota[10,11]. While much excitement and optimism has resulted from these reported observations the **key knowledge gap** that remains is the conceptualisation of the role(s) of the microbiota in the progression and/or prevention of chronic diseases. Many of these "commensal" microbes either remain elusive to culture, their genetic potential is identifiable but remains functionally cryptic, and furthermore microbes often function within the context of a community to affect host phenotype[10,12,13].

Globally, it is highly likely that more outcomes of microbiome research will translate into clinical diagnostics and therapies within the next 10 years. Two recent examples setting the stage include a microbiome profiling tool to monitor "dysbiosis score" for irritable bowel syndrome patients; and the use of "faecal microbiota transplantation" (FMT) as a first line clinical intervention for the displacement of chronic, antibiotic resistant *Clostridium difficile* infections[14,15]. However and despite the current optimism, in particular, for the use of FMT to treat a broader range of digestive and other metabolic diseases, the clinical results to date for other conditions are modest at best, constrained by our current understanding of the microbiome from both a donor and recipient context; and requiring further advances in approach from an ethical, legal and social perspective[16].

In summation, the Australian biomedical research landscape can continue to play a globally dominant role in the translation of the microbiome into medicine; but will depend on expanding our scope of research to more fully consider the commensal microbiota; and identifying priorities and marshalling resources into sound flagship projects that are globally recognised for their eco- and ethno-regional characteristics.

Opportunities, Challenges and Risks of Human Microbiome Research in Australia

The opportunity is that scientific, medical, social, and commercial value will flow to those groups who both understand and dissect host-microbe interactions, and then can productively manipulate them, at an organismal or systems level. A working example of how human microbiome research can help deliver outcomes relevant to human health and well-being, using the current and emerging networks of researchers centred in Queensland is shown in Figure 1.

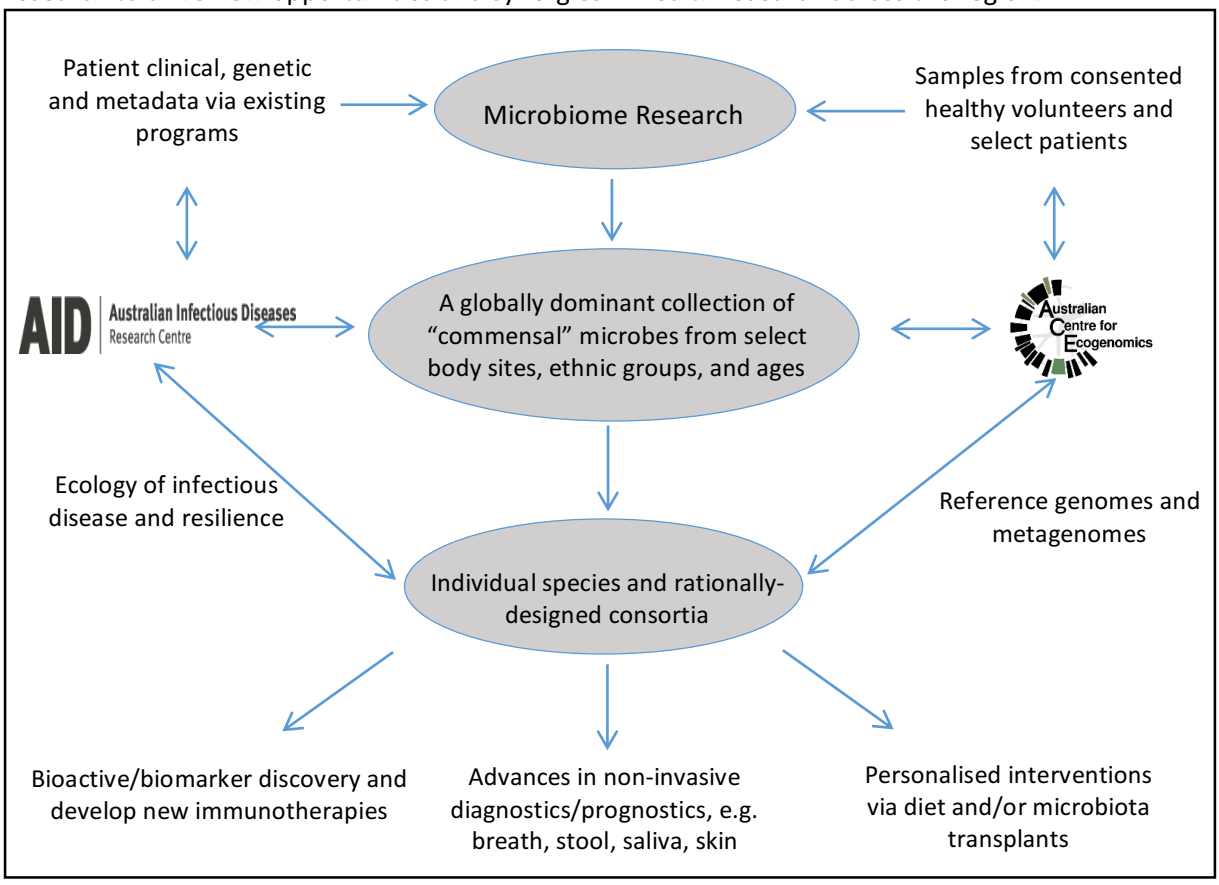
Importantly, the cross-sectional comparisons undertaken to date shows the human microbiome is not universal: its diversity and functional potential is affected by ethnicity, cultural behaviours (including diet, antibiotic use, traditional medicines) and environment (built/urban compared to rural/natural)[17].

Microbiome research has also revealed that much of the genetic content of the microbiota is still "dark matter": cryptic, and still largely ignored in terms of it evolution, functional attributes, and impacts on our health and well-being[12,13]. As such, an eco-regional frame of reference is warranted to facilitate the development of key databases and outputs listed in Figure 1 that are "fit for purpose". For these reasons, Australia offers a number of globally unique attributes and thereby opportunities for real impact from microbiome research via medicine and community health. These attributes include:

- Australia is a thriving first-world and multicultural society, now comprised of a unique diversity of ancient, indigenous populations; European migrants, and in recent decades, growing communities of representing ethnic groups originating from middle- and southeast Asia and the Pacific.
- Common to all these ethnic groups are the burdens of many, but not all, chronic "Western" immune-mediated and metabolic diseases and cancers, and at rapidly increasing incidence rates, suggesting a non-genetic basis for their penetrance into these communities. There is a strong interest across the medical communities that the microbiome is the "new frontier" that needs to be charted and understood, to realise new breakthroughs in the diagnosis, prevention and treatment of these diseases.

- The Australian clinical setting already has provisions in place for the collection and processing of numerous types of biological samples for existing diagnostic tests. As such, the access and supply of samples that can be utilized for microbiome assessment are not rate-limiting to making systematic and innovative advances in our understanding of the human microbiome.

- Our geographical location ensures our research and medical infrastructure encompasses both temperate and tropical environments, providing opportunities for Australian microbiome research to drive new opportunities and synergies in health research across the region.



- Australia's historical prominence for innovations in agriculture and food production are continued drivers for the demand and uptake of our commodities into new markets across Asia and the Pacific. However and at the same time, persons are becoming more aware of "what you eat becomes what you are" both in Australia and abroad. Microbiome research provides opportunity to further establish and sustain recognition of the nutritional and commercial value of Australian produce, both for mass and niche markets, locally and abroad.

- Again linked with food animal production and veterinary sciences, Australia possesses infrastructure and intellectual capabilities that can be harnessed to provide step advances in our understanding and management of the human microbiome for health and well-being, using "large" animals rather than rodents for models of nutrition and physiology[10].

In many respects **the challenges** facing microbiome research in Australia are neither unique nor new to Australian science. Most Western countries, as well as Japan, China and India possess some form of national human microbiome initiative. However, Australia still does not have a clear national profile or identity in this field, despite the recognised contributions of individual research groups. Our connections with overseas initiatives are principally based on specific researcher-to-researcher networks. As such, we lack influence and recognition, relative to our capabilities and opportunities, to be globally and regionally influential.

- At least some of these challenges arise from the types of funding schemes historically favoured in Australia, especially with respect to fundamental and "discovery" research often being the domain of small investigator project grants, rather than larger scale consortium-based projects.

- Developing the economies of scale in research infrastructure that has driven and will further advance the large-scale, population-based microbiome research in North America and Europe remains a challenge in Australia, but should not be an excuse for doing nothing.
- Australia would also be considered deficient in the provision of key infrastructure widely used in human microbiome research. In particular, Australia possesses a dearth of facilities to sustain and use animal models that are germ-free (devoid of microbes) or gnotobiotic (colonised with individual or defined consortia of microbes). These types of facilities for rodents and larger animals (pigs) are definitive in terms of dissecting cause-versus-consequence relationships, and viewed critical for publication in high impact journals.
- The most powerful and translatable research of the human microbiome is likely to arise from longitudinal studies, structured as either inception cohort studies and/or placebo-controlled randomised control trials. The challenge is acquiring the necessary funding for these types of trials *per se,* let alone adding the microbiome as a primary outcome measure, remain a challenge.
- Our relatively limited industry base, and local cultural attitudes towards investment of venture capital and/or other forms of university-industry partnerships are impediments to both discovery and translational research.

Currently, microbiome data are really only assessed in the context of dedicated clinical trials. However, it can be anticipated that with the dramatic reduction in prices of the necessary molecular testing, and by data linkage can develop utility for use in the clinical setting. Therefore, translation of microbiome data and knowledge into medicine, requires data integration, via its linkage with the records produced from primary through to tertiary health care systems. However to achieve that, further progress is needed with the ethical, legal and social issues of health record data collection and management.

Risks

Over the last decade, human microbiome research has become a hot topic in terms of professional and media reportage, and the social interest in its findings. Commensurate with that is the risk that the role of the human microbiome in health and disease is overhyped (over-promises and under-delivers), especially via sources tangentially or remotely affiliated with the Australian scientific community and/or professional medical organisations. Fortunately, the interest in the human microbiome embedded within the Australian practitioner and clinical research communities provides avenues to mitigate this risk but need to be further developed, by fusing the appropriate expertise in microbial, genomic and clinical sciences together, to generate and provide evidence-based information for various stakeholder groups.

Another major risk facing Australia, justified in part by the opportunities and challenges outlined earlier, is to minimise investment or to use a "fast follower" rationale to support human microbiome research. Australia and Australians possess unique ethnic and eco-regional needs and opportunities with respect to individual and community health, which should be the focus of Australian-led initiatives and consortia.

Collectively then, the major risk is to do nothing more substantial in human microbiome research and sustain the current status quo. The international advances and awareness generated from the studies of the human microbiome will continue to grow, and without an Australian "footprint" create an increasing vacuum of knowledge and information directly provided by Australia's scientific and medical professions, which will be filled by others.

Required resources or changes to support implementation

A consensus working group to produce a decadal plan for Australian microbiome research relevant to precision medicine. The group would be comprised of subgroups representing clinical sciences and microbiological expertise, which can effectively coalesce a "bench to bedside" approach to national priorities. As such, the objectives of this relatively small working group are:

- to establish how a nationalized framework supporting an **Australian human microbiome project** could be formulated to provide the reference information and bioresources needed for our key ethnic groups, and at specific ages, with the contributions advancing and adding value to precision medicine via primary health care;
- **defining integrative human microbiome projects** that specifically address priority non-communicable diseases and cancers affecting a broad cross-section of Australian society, including our indigenous communities, leading to outcomes that improve clinical management and decision making in secondary and tertiary health care.
- **provide recommendations that address technology gaps in the form of research infrastructure** to ensure the biology of microbiome research is transcendant beyond its foundational roots in genomic sciences, and competitive on an international scale. These include but are not limited to specialized facilities for animal models, as well as technologies supporting innovations in biomolecule analyses, data integration and analyses.
- **align activities with the emergent basic/clinical/translational funding schemes** in terms of how projects of varying scales (e.g. national through to investigator led) should be developed in unison with the evolution of the directed and peer-reviewed funding schemes via Federal agencies and the Medical Research Future Fund.

Enhance and improve engagement with professional national and specialist medical organisations (e.g. Australian Medical Association, Gastroenterological Society of Australia, Arthritis Australia, State Cancer councils, etc.,). These activities could be encouraged via ensuring grant funding opportunities require and actively support efforts in stakeholder outreach and education programs of relevance to both professional organisations, as well as the general public.

In summation, human microbiome research can support precision medicine throughout the various arms of the health sector, but requires a sustained effort to support it as both a distinct field of research (e.g. distinct and separate from infectious disease and clinical microbiology research) that delivers both new diagnostic and therapeutic options for chronic diseases. No small amount of the expertise required resides in non-medical research sectors, and should be encouraged to forge new collaborations and partnerships.

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