Biotechnology and Biological Sciences Research Council

Report of the BBSRC

Understanding the mechanisms of the gut-immunology-brain axis: a community building workshop

Held on 28 March 2023

Contents

Introduction

On 28 March 2023, BBSRC held a hybrid workshop to identify the research and innovation challenges and community needs to build a vibrant interdisciplinary community to advance understanding of the mechanisms of the gut-immunology-brain axis (GIBA).

The GIBA is a complex network of direct and indirect bidirectional communication routes involving multiple biological systems and signalling pathways such as neural, endocrine, metabolic and immune pathways.

Understanding the biological mechanisms of the GIBA and how it is modulated by lifestyle and other factors is not well understood, but it is an emerging area of research with potential to improve physical, cognitive and mental health across the lifecourse.

BBSRC recognises that research on the GIBA will require new interdisciplinary partnerships and integrated approaches across biological systems and disciplines, as well the use and development of high-quality methodologies and tools to advance the field.

The purpose of the workshop was to provide an opportunity to bring together researchers from across disciplines and sectors to:

- facilitate networking, knowledge exchange and to foster the formation of new interdisciplinary collaborations
- explore the opportunities, challenges and the research and innovation community needs to advance understanding of the GIBA and inform future activities

Key findings

A wealth of information was collected during discussions throughout the workshop and also from the previously held meeting of the BBSRC GIBA Steering Group. Some of the key findings are highlighted below:

- **interdisciplinary research networks:** establishing understanding and creating collaborative opportunities was identified as being vital to forming clear routes of knowledge exchange of research expertise, existing resources (tools, technologies, data) and skills, as well improving standards and reproducibility across the diverse disciplines and sectors of the GIBA field

- **understanding the causal biological mechanisms:** identifying the key mechanisms and their actions on systems and health across the whole lifespan. Focussing on building understanding of the normal process (as opposed to specific disease pathways), their stability or how they change over time was highlighted as being particularly important

- **better use of existing resources:** will provide a faster route to identify the most promising pathways, interactions and potential targets for mechanistic study or validation, as well as encouraging integrative approaches, e.g., population and patient cohorts, UK Biobank, toolkits, experimental models. It was noted networks could promote awareness, access and sharing of available materials and resources

- **experimental models:** this includes animal models, *in vitro* systems such as organoids, lab-on-a-chip and microfluidics, and *in silico* models:
  - determining the most appropriate **animal model** to use or develop, the variability of models in different environments and translatability to humans were considered key challenges. However, there are opportunities to increase the genetic diversity of models, to repurpose and optimise

existing models as well as investigating new model organisms to improve translation of research across other organisms and humans
- **organoids** were viewed as both an existing resource that should be utilised more, but also as a significant new, emerging and exciting tool and technology that could help to advance the GIBA field and translation to human. Developing new *in vitro* models closer to human biology, use of models in combination, functional assays and standards would be particularly impactful

- **development of non-invasive techniques:** identified as an inexpensive and convenient route to obtain different and 'cleaner' samples, repeat sampling as well rapidly expanding cohort availability for studies. Examples included ingestible swallowing devices (capsules) to provide real-time monitoring or to capture intestinal fluid or biopsies at different locations along the GI tract, non-invasive imaging techniques and portable blood chemistry

- **data and data integration:** focussing on data integration to enable better exploitation of existing datasets was consistently highlighted as a significant opportunity for more cost effective and rapid identification of the most promising mechanisms, pathways and interactions or targets for validation. However, many challenges were posed such as the quality and accessibility of data, lack of integrated datasets and bioinformatics expertise, and the necessary tools, skills and training required to enable biological interpretation

- **role of AI:** this was highlighted as an important emerging key technology and tool to better manage, analyse and integrate data sets to advance GIBA research, for example making datasets more user friendly, linking biological with behavioural data, identifying patterns, but this would require high quality data and more training and capacity building opportunities to develop AI skills

- **role of BBSRC:**
  - provide a continuation of funding opportunities to encourage interdisciplinary research and innovation, from catalyst funding to support networking, new collaborations and pump priming/seed funding, to larger/longer term investments and programmes and follow-on funding to encourage cross-sectoral approaches to overcome the challenges associated with the translation of basic research to application and successful commercialisation or policy impact
  - provide training opportunities to develop the next generation of researchers to bridge across disciplines and sectors, developing interdisciplinary skills and bilingualism, for example support a GIBA centre for doctoral training
  - engage with other funders to seek opportunities for collaborative partnerships and activities, gain knowledge of the research landscape and avoid duplication, e.g., UKRI councils, Alan Turing Institute, international funders

BBSRC understanding the mechanisms of the gut-immunology-brain axis: a community building workshop.

Participants

Participation was by registration only. There were 77 participants at the workshop (one third of which attended virtually) drawn from a diverse range of academic research disciplines and career stages and representatives from industry, clinicians, gov depts, other funders, and learned societies. A list of attendees is provided in **Annex 1**.

Scope and process of the workshop

The workshop programme was informed by the BBSRC GIBA Steering Group. The group was established to advise BBSRC on the focus and design of the community building workshop to deliver the most beneficial outcomes for both the participants and BBSRC. The membership of the GIBA Steering Group is provided in **Annex 2**.

The workshop programme can be found in **Annex 3**. It was designed to introduce the topic via some setting the scene presentations, followed by three breakout sessions where participants discussed and identified the current opportunities, challenges, and tools and technologies required to advance GIBA research and innovation.

In total there were 7 breakout groups per session (5 in-person and 2 virtual groups). Miro boards were used to facilitate and capture the discussions. After each breakout session, there was a review period to give participants time to look at the outputs from the other breakout groups and to add further comments to the Miro board.

During the day participants were also given time to meet and network and invited to 'soapbox'[1].

To round the day off, there was a quick Q&A session using Mentimeter. The following questions were posed to the participants:

a) What do you think will be the disruptors or trends that will revolutionise GIBA research and innovation?

b) Following this workshop, what sort of activities would you like BBSRC to do?

c) What will help the GIBA field to move forward?

d) What GIBA research and innovation should BBSRC prioritise and in what time frame?

e) Where could we see the maximum impact of GIBA research?

f) What are the broader social and ethical factors for which we need to be cognisant?

g) Who do BBSRC need to work with to help advance GIBA research & innovation and why? *(For example, key industrial players, centres of excellence)*

h) After hearing all the discussions from today - If you have one research question you would like to investigate, what would it be?

The outputs can be found in **Annex 4**.

[1] A 'soapbox' is a voluntary, quick one-minute statement with no Q&A. For example, it can be used to express a comment, view, or idea, or to request to talk to someone with specific expertise in the break etc.

Summary of workshop discussions

A summary of the key findings from workshop discussion Miro boards is presented below. The breakout group discussions created a substantial amount of data and there were often overlap of topics between opportunities and challenges, as well as whether these were short-term or longer term. Where possible the main challenges and opportunities for each topic have been identified.

1. Collaboration

Challenges:

It was acknowledged that the GIBA research is a complex area spanning across different systems and requires multiple disciplines and expertise to advance the field. Although, there are currently some pockets of GIBA research within the UK, the workshop participants noted the following challenges:

- research is being conducted in siloes with many universities not structured for this type of cross-faculty collaboration which could in part be result of how universities measure success of their researchers (e.g., encouraging individuals to become leaders rather than rewarding teamwork) and the Research Excellence Framework (REF). It would be very beneficial if the next REF assessment includes a section on “Team” in the same way it has a section on “Impact” to encourage universities to value collaborative work
- assembling real interdisciplinary teams that can address gut to brain is difficult
- there is a lack of common language
- it is difficult to know what other research has been done to avoid unnecessary duplication
- it is unclear what resources (samples, data, tools and technologies) are available and how to access them
- inter- and multi-disciplinary approaches are needed for better study design and translation of research into application and potential impact
- there is a lack of funding for partnership opportunities

Opportunities:

A strong and consistent theme running throughout the workshop was the importance of providing opportunities to encourage networking and new collaborations, and bring together various disciplines, including stakeholders such as patient groups, industry and charities to establish interdisciplinary teams within and across research organisations.

<u>Short-term (1-2 years) opportunities</u>

Creating opportunities to bring together the current expertise to develop GIBA research culture in the UK via collaborative networks or consortia would provide the following outcomes:

- a better understanding of our strengths and diversity of expertise
- build commitment, shared language and research capacity
- determine the current status of GIBA research in the UK by reviewing existing knowledge and resources (e.g., models, tools, methods, data) to:
  - inform where we are and what to focus on next
  - understand community needs
  - leverage existing resources, enabling people to share resources and skills in the future
- facilitate interdisciplinary approaches which will help to develop the right research questions and study design
- identify known and potential communicators to promote the field
- encourage exchanges to develop skills and training across disciplines and sectors

- improve methodologies, standards and reproducibility to make studies and data more interoperable
- provide opportunities to collaborate with industry and other stakeholders
- increase translation
- enable more targeted/fast paced research to accelerate the UK GIBA field

It was also noted that:

- bioinformatics expertise within the network/consortia approach is essential
- need to ensure stronger engagement with the neuroscience community (much of the discussion at the workshop was centred on the gut, microbiome and immune interactions)
- the recently funded BBSRC/MRC Interdisciplinary Networks could provide a good template for potential GIBA networks/consortia

Medium-term (3-5 years) opportunities

Longer-term opportunities would embed interdisciplinary collaborations and approaches to enable:

- improved study design with a more holistic, balanced approach taken by biologists, neuroscientists, microbiologists, clinicians, nutritionists, etc to better define outcomes, drive translation and deliver impact
- more collaborations with industry and other stakeholders, e.g., public and patient involvement
- international collaborations, e.g., with Ireland, USA, Sweden and other European countries

2. Approaches

2.1 Mechanistic research

There was a strong consensus from workshop participants that understanding the biological mechanisms and signalling pathways across the GIBA is vital to advance research and innovation in this area. To date there has been much focus on correlative and large cohort descriptive studies, and it is now timely for more research on understanding the cause, actions and effects. This would provide the following potential outcomes:

- identify key mechanisms and their actions on systems and health across the whole lifespan – focussing on building understanding of the normal process and the stability or changes of these over time was highlighted as being particularly important, rather than on specific disease focussed pathways
- increase understanding of how physiological changes influence behaviour and vice versa
- move away from the tendency to identify patterns and develop cross-validation of measures
- develop a more accurate idea of causation from longer term studies (confounders and complexity)
- improve identification of specific targets and interventions, such as probiotics
- provide understanding of why interventions work (or not)
- create a strong evidence base for causality and potential intervention routes
- increase translation of findings
- increase in healthy life years

2.2 Utilise existing resources

Utilising existing resources was clearly identified by workshop participants as a key short term-opportunity as it would provide a faster route to identify the most promising pathways and interactions and potential targets for mechanistic study or validation. Examples suggested were:

- the UK has a wealth of population cohort studies, such as ALSPAC, EPIC, Lothian Birth Cohorts, TwinsUK, Understanding Society, Whitehall 2 Study and the newly established Adolescent Health Study which bioscientists should utilise more. In particular, it was noted that the UK Biobank provides a rich biological and health data resource, e.g., imaging, metabolomics, cognition and lifestyle data. Opportunities should be sought to engage to influence the collection of samples (types and protocols) and data to help understand normal processes and define the pathways across GIBA and how stable these are over time. In the longer term this would also enable a larger more holistic picture to be incorporated which could include social and environmental factors
- from existing data, establish a catalogue of metabolites to help define what the 'playground' is for the thousands of metabolites
- funded genetic/genome resources such as the 100,000 genomes project to investigate, for example, a set of genes influencing/defining key microbiotal relationships
- utilise appropriate patient cohorts, for example, ileostomy patients as a proxy for understanding healthy gut function such as nutrient absorption. This would encourage an integrative approach from clinical through to molecular and cellular biology
- engage with existing intervention studies/trials to gain access to and expand sample collection to enable cause/effect studies (e.g., blood, blood cells, mucus, stool bank) and analytical methods (e.g., metabolomic profiling, single cell analysis)
- repurpose the use of experimental models for GIBA research such as mouse knockouts or pre-clinical models

However, it was noted that there would be other available resources, but it was often difficult to know what these are and how to access them.

2.3 Other Approaches

There were a number of other research approaches identified during the course of workshop discussions.

Short-term opportunities

- natural experiments
- biomimetics, e.g., hibernating animals
- consider providing support for:
  - companion animal microbiome study and citizen science, e.g., dog genome project
  - investigating causal pathways and scaling up to higher-order organisms e.g., pigs
  - human interventional approaches to access different parts of the GIBA system (GI tract, mucus, blood, blood cells, stool bank, brain scans etc) to advance mechanistic research
  - investigation of GI tract using minimally invasive methods
  - adding to other trials or studies for the collection of relevant samples for GIBA research
  - microbiome genome wide association studies

Medium term opportunities

- provide evidence in the mammalian system that the gut and microbiome affect brain and behaviour in both fundamental and translation research
- co-monitoring/scanning of gut with other organs like the brain (already being done) but improving those studies to look more closely at mechanistic mediation between the brain and gut
- the development of a UK gut microbiome cohort using available funding opportunities. The USA and Dutch have large microbiome cohorts supporting such an approach and the UK is lagging behind. Currently the UK has a lot of observational data but is lacking in mechanistic insights and functional understanding of microbiome e.g., the microbiome is the same, but metabolites are

different. We need to develop genuine multidisciplinary approaches to bridge some of the immediately identifiable problems
- need better understanding of variation within people (most current research focuses on between-people differences), both across the lifespan and shorter time periods e.g., the role of circadian rhythms
- need populations and data that have defined diets within the UK e.g., vegan
- studies into long covid - overlaps gut (ACE2 and gastro issues), immunology and brain (brain fog and psychiatric conditions)
- evidence based probiotic diets
- microbiota and its influence on anti-depressant medication
- bacteriophage therapy, helminths and the GIBA
- look at underexplored areas, such as viruses, phages, fungi and archaea and have more focus on bacterial strains rather than species and genera by using whole-genome shotgun sequencing
- utilise medical technologies for brain circuitry

3. Tools and technologies

Workshop participants agreed that there are many existing tools and technologies used across the different disciplines to enable interrogation of biological mechanisms and pathways, cells and systems; human trials to assess health, cognitive, stress, nutrition, sleep; and to capture, analyse and interpret data.

There are opportunities to repurpose and use experimental models and existing toolkits from across the disciplines to further GIBA research such as for vagus nerve stimulation, or utilising new and emerging technologies such as organoids, bioprinting, behavioural measure technologies and citizen science apps

However, some overarching challenges were highlighted, particularly the need for:

- standard policies for labs, equipment, protocols to ensure data is consistent and replicable
- tools to standardise data capture, analysis and interpretation
- an inventory of the tools available which could be shared for GIBA research
- training opportunities for all career levels for different technologies (e.g., via knowledge exchange, short course grants, networks/networking opportunities)

3.1 Models

The topic of models was consistently identified and discussed throughout the workshop as a challenge but also as an area of significant opportunity: enabling some rapid research gains by using existing resources, but also a significant area of emerging tools and technologies to deliver translation and impact in GIBA research.

3.11 Animal models

Challenges:

It was agreed that mammalian models are a valuable tool to obtain fundamental mechanistic understanding. However, there are particularly challenges associated with their use such as determining the most appropriate model to use or develop, the variability of models in different environments (e.g., housing, lab conditions, handling, diet) affecting reproducibility of results, interspecies differences and the translation of findings into the human.

The longer-term challenges highlighted were that animal models are currently 'too clean' and that laboratory settings will result in false phenotypes which will differ from wild-type microbiomes; greater

genetic diversity of and within models is needed, as well as access to and sharing of existing and new animal models.

It was also noted that mouse and human microbiota are very different whereby some microbiome species, such as *Candida*, do not colonise in rodents. As a result, even humanised mouse models have limitations.

Short-term opportunities:

- optimising pre-clinical models and improving links to clinical models
- investigate new model organisms to improve translation of research to other organisms
- use or repurpose existing mouse models, for example:
  - GABA receptor knockout mice developed to study the brain also have changes in inflammation which could be beneficial GIBA research
  - mouse models of immune disorders could be used to understand immune to brain communications
  - model of animals with behavioural and emotional differences to, for example, investigate gut immune functions
- networks could share material and resources, such as models of leaky gut, depression
- more fine-scale manipulation of the microbiome in animal models beyond probiotics, antibiotics and faecal microbiota transplants by applying current technology in novel ways, e.g., using CRISPR-Cas technology to control gene expression and modulate the production of metabolites and proteins, and also using bacteriophages that infect and eliminate specific species/strains

Medium-term opportunities:

- animal health reports of lab animals could be mandatory
- as there are limitations on how much can be learnt from lab-based mice models, other models could be investigated such as companion animals and larger animals, e.g., pigs, cows

3.12 Organoids, lab-on-a-chip and microfluidics

These were viewed as both an existing resource that could be utilised more, but also as a significant new, emerging and exciting tool and technology that could help to advance the GIBA field and translation to human.

Challenges

- developing *in vitro* systems and use of primary tissues
- knowing what models are currently available
- need to be improved to be more representative of physiological models
- gut-on-a-chip models are currently limited by the immune element
- developing models of the vagus nerve
- use of models in combination, e.g., brain-on-a-chip coupled with a system flowing from the gut to assess the ability of GIBA models to translate to human studies

Current opportunities

- as *in vitro* models improve, increasing complexity can be added and challenged to find out what individual components are doing (via an element of trial and error)
- advance *in vitro* models to be closer to human biology
- develop better and more appropriate models such as organoids
- organoids, gut- and brain-on-a-chip models are already being developed and used, there is opportunity to progress within these to connect human cells, nerve cells and microfluidics

Emerging opportunities

- development of organoids using pluripotent stems cells, enteric nervous system of an individual cultured with colon epithelium of another or same individual. This will elucidate specific communication between different systems
- development of functional assays that measure the impact of an intervention in a model system e.g., obtain functional readouts using electrophysiology on organoids
- foster collaborations with the USA - they potentially have more advanced models

3.2 Imaging

Imaging technologies were considered important to move the GIBA field forward. The following existing and evolving tools and technologies highlighted were:

- whole body imaging
- brain scans
- real-time imaging at the cellular and spatial level
- MEG analysis
- *In situ* Raman spectroscopy
- non-invasive and portable blood chemistry using radiofrequency and 5G technology

However, it was acknowledged that more technology development is needed to make imaging more consistent and accessible. Some examples of new and emerging imaging technologies and needs identified are:

- advancements in non-invasive imaging techniques which would also rapidly expand cohort availability for sample collections, e.g., for gut permeability
- smaller/cheaper *in situ* metabolomics in the brain
- develop imaging system and confocal microscopes to look at the immune changes
- live *in vivo* imaging in the brain for measuring e.g., neuroinflammation, metabolites
- multimodal imaging in animal models
- the opportunity for using AI for imaging
- *in situ* Raman spectroscopy
- non-invasive and portable blood chemistry using radiofrequency and 5G technology
- nanotechnology, although further resolution is needed

3.3 Sampling methods and tools

This discussion focused mainly on the many challenges of collecting human intestinal microbiome samples. Currently, researchers obtain samples from stools, mucosal biopsies and intestinal aspiration using techniques such as colonoscopy or endoscopy. However, these methods are all unable to accurately reflect the composition of the intestinal microbiome. To support more gastrointestinal sampling studies (as opposed to 'straight to stool' studies) including those from the small intestine, there is a real need for development of alternative, non-invasive technologies to improve accuracy, enable collection of samples from different sites along the GI tract and rapidly expand cohort availability for sampling.

Short term challenges

- development of non-invasive technologies: while upper GI tract and microbiome samples are obtainable via colonoscopy and endoscopy patients, collection of healthy samples is very difficult due to the invasive nature of these procedures. There are other issues, such as cross-contamination and the bowel preparation required before these procedures (fasting, use of laxatives and antibiotics). It also requires establishing collaborations with surgeons which can also

be difficult. Using post-mortem samples are an option, but these need to be taken with 3 days of death and requires establishing connections with pathologists

- the collection of faecal samples is the most common method used for investigating the microbiome as it is non-invasive, inexpensive, convenient for repeated sampling and thus can be used more widely. However:
  - there are significant differences between faecal and mucosal microbiota content
  - it cannot be used to determine microbiome composition at different sites along the GI tract
  - different collection, transportation and storage conditions may significantly alter the characteristics of the microbial sample
- collection of faecal, blood and immune markers are usually obtained from patients based on disease, but other samples are needed for comparative studies, e.g., poor vs healthy diet, different population groups

Opportunities

- utilise appropriate patient cohorts (e.g., ileostomy patients) as a proxy for understanding healthy gut function such as nutrient absorption etc.
- utilise new or emerging tools and technologies such as:
  - ingestible swallowing devices such as capsules that can observe or capture intestinal fluid or biopsies at different locations along the tract, and can provide real-time monitoring such as pH, changes to microbial composition and metabolites *in situ*
  - GM microbes as sensors
  - smart toilet

3.4 Single cell technologies

The advances in single cell technologies were considered to enable greater access to analyse and understand individual cell biology. Some examples are:

- single cell genomics for functional insights
- multi-omics conducted in a single cell
- neuro-modulating *in vivo* targeting single cell
- single cell sequencing of ganglia
- single cell bacteriomics/karyotes at a complex community level
- digital twin

3.5 Data and data integration

During the workshop, significant discussion centred on the challenges and opportunities posed by the quality, access, integration and analyses of data and the development and use of tools, technologies and skills required to address these.

Challenges

- consistent sharing and accessibility of data and lack of integrated data sets, particularly for people who are not dedicated bioinformaticians
- the current mechanisms to share human data need to be improved, including ensuring the relevant permissions are in place to facilitate sharing
- more accessibility to advanced bioinformatics tools for multi-omic integration
- need the tools and training to allow biological interpretation
- lack of bioformaticians and informaticians that appreciate the biology

Opportunities

- make more use of existing data for a more cost effective and rapid identification of associations or targets for validation and to eliminate ‘dead-end’ enquiries to determine the most promising pathways and interactions
- focus on data integration to enable better exploitation of existing datasets
- map or mine data from existing larger scale studies (e.g., population data) to identify knowledge gaps and generate hypotheses
- more and better integration of epigenomics data
- study the virome and mycobiome in existing datasets
- leverage large microbiome data collection from human longevity studies to advance understanding of:
  - age-related changes and the influence of other factors
  - stability of markers over time
  - causality physiology and function, e.g., which microbe is associate with which product and its action
- use of AI (see 3.6)
- stronger adoption of FAIR principles

Needs

- catalyst funding is needed to support multidisciplinary projects with a data hub to enable the integration of data sets
- different types of data from the same individuals
- common ground learning for computational and biological research
- advanced analysis tools or the development of a toolkit and statistical models to get more out the data
- GIBA research would greatly benefit from input from statisticians, especially in field of modelling and integrating multidisciplinary data
- BBSRC to support the establishment of an open data sharing platform to use on multidisciplinary data sets to help with developing new hypotheses in GIBA research. Could potentially use available data management systems such as Pioneer or Insight which can be adapted to other systems. This would need a management or advisory group to determine the type and format of available data, including the provision of metadata. However, this would require resource to maintain and manage the site and sustainability would be a key issue

3.6 Role of AI and data

While the use of AI was considered by workshop participants as an important emerging tool to be used to advance GIBA research, it was primarily discussed as a key technology to better manage, analyse and integrate data sets:

- simplify datasets as large datasets can be 'noisy'
- make datasets more user friendly, e.g., human atlas
- link datasets, particularly in terms of GIBA research linking biological with behavioural datasets
- identify patterns and correlations although causality still needs to be studied

The following research community needs were identified:

- more work needs to be done to improve the quality of the collection and use of the data first, before engaging with AI
- better statistical models are needed to understand human data first and then interrogate using AI
- more accessible AI tools

- both AI and computational tools to bridge across immunology, neuroscience and informatics
- more training and people with AI skills
- working in partnership with the Alan Turing Institute

Some potential areas of interest to use AI were identified:

- AI could be used to reduce the problem down to a size that is tractable by average lab capability, rather than major programme scale endeavour
- a quick win would be to train AI using the pathways that have already been identified
- AI and other technologies could potentially help in nutritional assessment and improve the ability to measure food consumption reliably in humans which is a major challenge for the nutritional science community
- digital twin could be developed at the cellular or system level or to guide interventions, diet and predictions
- analysis of biological age versus chronological age
- imaging

4. Translation

Workshop discussion focussed on ways to navigate the 'valley of death' that often exists between translating basic research to application and successful commercialisation or policy impact (e.g., product development, clinical trials, policy intervention). The GIBA field needs to clearly define its importance as biological determinant of physiology and provide strong causal evidence to demonstrate that the gut and microbiome affects brain health and behaviour across the lifecourse in both fundamental and translation research.

Long-term translational challenges for the GIBA field going forward

- translation from experimental models (e.g., cell, animal, *in silico*) to humans to populations: it was suggested that a stronger approach would be to better understand human data first to inform experimental model design or re-design, the experimental research can elucidate the mechanistic understanding to provide the causal research evidence required to then translate back into testing the data or studying in a human model, intervention trial or population study. This could require reiterative cycles
- activities and funding routes need to support inter- and multi-disciplinarity research as these approaches are essential to enable better study design and to bridge the 'valley of death' in translation
- more research is needed in the pre-clinical and translational stage with appropriate support available to enable this
- need continuation of transnational opportunities and funding
- anticipating the impact of research studies, and getting input from potential users such as industry, clinicians, patient groups and policy makers to help co-design the project or get buy-in to help bridge the valley of death in translation

Opportunities

- use more appropriate models: a key example of this is organoids which are currently available and being rapidly developed and will assess the ability of GIBA models to translate to human studies
- translate research to other organisms: take a comparative biology approach and develop a 'chain' of understanding across animal models to identify the conserved or different pathways to facilitate understanding in humans, e.g., *c.elegans* to mouse to pig to humans

- integrating different data sets to identify causation and provide a stronger evidential route to translation
- BBSRC should:
  - encourage and support inter- and multi-disciplinary and cross-sectoral approaches for better study design and increase potential translational pathways to enable greater impact
  - establish consortia to establish bridges to aid translation

5. Funding

When discussing challenges and opportunities, workshop participants were requested not to just ask for more funding or substantial large investments, but to focus on what types of funding would be most useful and impactful to stimulate and advance GIBA research and innovation:

- catalyst funding to support interdisciplinary networks and encourage new collaborations and partnerships across the GIBA disciplines and sectors is required to drive forward this exciting field of research and innovation. Support for 3-5 years was suggested
- there needs to be a continuation of opportunities from funding pump-priming activities for small projects with the potential to lead to a larger research proposal, to longer term funding such as the BBSRC Longer Larger (LoLa) grants scheme
- grant applications/funding schemes need to place more emphasis on team working/expertise and be less focussed on the Principal Investigator
- training:
  - the next generation of researchers to bridge across disciplines and sectors, developing interdisciplinary skills and bilingualism
  - GIBA is an area that would strongly benefit from centres for doctoral training
  - at all career levels is essential on different technologies
- some specific barriers were identified:
  - funding barriers due to experimental design, for example the need for statistical power vs cost, the number of animals required and ethical concerns etc
  - trying to do multidisciplinary research is difficult with smaller amounts of funding. For example, a grant application combining both neuroscience and immunology expertise and resources will be more expensive than single discipline approaches
  - need to have reviewers that understand and can comment on the whole interdisciplinary grant is difficult, i.e., need more generalists over specialists
- higher risk funding - trial randomisation of funding within the fundable list was suggested

6. Things to avoid

BBSRC should endeavour to engage with other funders to gain knowledge of the research landscape and activities to avoid duplication.

BBSRC should not support the following:

- siloed studies as single discipline approaches should not be encouraged as a way to advance to GIBA research and innovation
- activities and funding routes that do not support inter- and multi-disciplinarity research as these approaches are needed to enable better study design and to overcome the challenges associated with the translation of basic research to application and successful commercialisation or policy impact
- projects or intervention studies that are not mechanistic based or include significant mechanistic understanding

- small (underpowered) and undirected intervention studies to avoid publication of confusing results and reduce the amount of research which may follow these 'red-herrings' and are not reproducible
- research using non-human models which do not have a human relationship explanation as to why that is necessary or when the study could be conducted in humans to avoid unnecessary duplication
- large descriptive surveys and correlation studies as there are more effective use of time and funding
- more microbiome sequencing as this is now viewed as 'stamp collecting' and we need to understand the function of the microbiome and the mechanisms by which it influences health

GIBA workshop participant list

First name	Last name	Organisation	Participated
Katie	Adolphus	University of Leeds	in person
Zubair	Ahmed	University of Birmingham	virtually
Ezra	Aksoy	Queen Mary University of London	in person
Kirstie	Atkins	Action for Pulmonary Fibrosis	virtually
Catrin	Bailey	BBSRC	in person
Melissa	Basso	University of Surrey	in person
Alexandre	Benedetto	Lancaster University	in person
Paul	Blair	University College London	in person
Doug	Brown	British Society for Immunology	in person
Phil	Burnet	University of Oxford	in person
Mohsin	Butt	Barts and The London School of Medicine and Dentistry	in person
Simon	Carding	Quadram Institute Bioscience	virtually
Livia	Carvalho	Queen Mary University of London	virtually
Meral	Celikag	University College London	in person
Kathrin	Cohen Kadosh	University of Surrey	in person
Erika	Coletto	Quadram Institute Bioscience	virtually
Daniel	Commane	Northumbria University	in person
John	Cryan	University College Cork	virtually
Giuseppe	D'Agostino	University of Manchester	in person
Simon	Daniels	Royal agricultural university	in person
Christina	Dardani	University of Bristol	in person
Chiara	de Lucia	King's College London	in person
Sebastiaan	De Schepper	UK Dementia Research Institute/UCL	in person
Franziska	Denk	King's College London	in person
Niharika	Duggal	University of Birmingham	in person
Marc-Emmanuel	Dumas	Imperial College London	in person
Deborah	Dunn-Walters	University of Surrey	in person
Louise	Dye	University of Leeds	virtually
Sally	Eldeghaidy	University of Nottingham	virtually
Caryl	Evans	King's College London	in person
Karen	Finney	MRC	in person
Gary	Frost	Imperial College London	in person
Chris	Gill	Ulster University	virtually
Jef	Grainger	BBSRC	in person
Beth	Greenhough	University of Oxford	in person
Sarah	Harding	Dstl	virtually
Isabelle	Hautefort	Earlham Institute	in person
Matthew	Hepworth	University of Manchester	in person
Aleksandra	Jatkowska	University of Glasgow	virtually
Louisa	Jenkin	BBSRC	in person
Katerina	Johnson	University of Oxford / Leiden	virtually

First name	Last name	Organisation	Participated
Nicola	Johnstone	University of Surrey	in person
Uzma	Khan	University of Glasgow	virtually
Meena	Kumari	University of Essex	in person
Nikki	Mackie	BBSRC	virtually
Lewis	Mattin	University of Westminster	in person
Simon	McArthur	Queen Mary University of London	in person
Neil	McCarthy	Queen Mary University of London	in person
Katie	McDermott	University of Leeds	virtually
Ekaterina	Nesterenko	Science Foundation Ireland	virtually
Joana F	Neves	King's College London	in person
Vincent	O'Connor	University of Southampton	in person
Christine	Ozolins	Exsurgo Limitd	in person
Aimee	Parker	Quadram Institute Bioscience	in person
Lee	Parry	Cardiff University	in person
Michelle	Pelta	Imperial College - Age Epidemiology Unit	in person
Giorgia	Perri	Newcastle University	virtually
Martyn	Pickersgill	University of Edinburgh	virtually
Fränze	Progatzky	Francis Crick Institute	in person
Vicky	Ratcliffe	Dstl	in person
Natalie	Rouse	BIC Innovation	virtually
Sadhana	Sharma	BBSRC	in person
Paul	Shiels	University of Glasgow	in person
Soraya	Shirazi-Beechey	University of Liverpool	virtually
Ravinder	Singh	MRC	virtually
Jonathan	Swann	University of Southampton	in person
Jerome	Swinny	University of Portsmouth	in person
Jessica	Teeling	University of Southampton	in person
Ceri-Wyn	Thomas	BBSRC	virtually
Lizzie	Treadwell	BBSRC	in person
Kieran	Tuohy	University of Leeds	in person
David	Vauzour	University of East Anglia	virtually
Claudia	Viggiano	ESRC	virtually
Emily	Whittle	BBSRC	virtually
Emma	Wightman	Northumbria University	virtually
Thomas	Wileman	Quadram Institute Bioscience	in person
Yuning	Zhang	University of Southampton	in person

Membership of the BBSRC GIBA steering group

Name	Organisation
Deborah Dunn-Walters (Chair)	University of Surrey
John Cryan	University College Cork
Katerina Johnson	University of Oxford
John McLaughlin	The University of Manchester
Paul Shiels	University of Glasgow
Jonathan Swann	University of Southampton

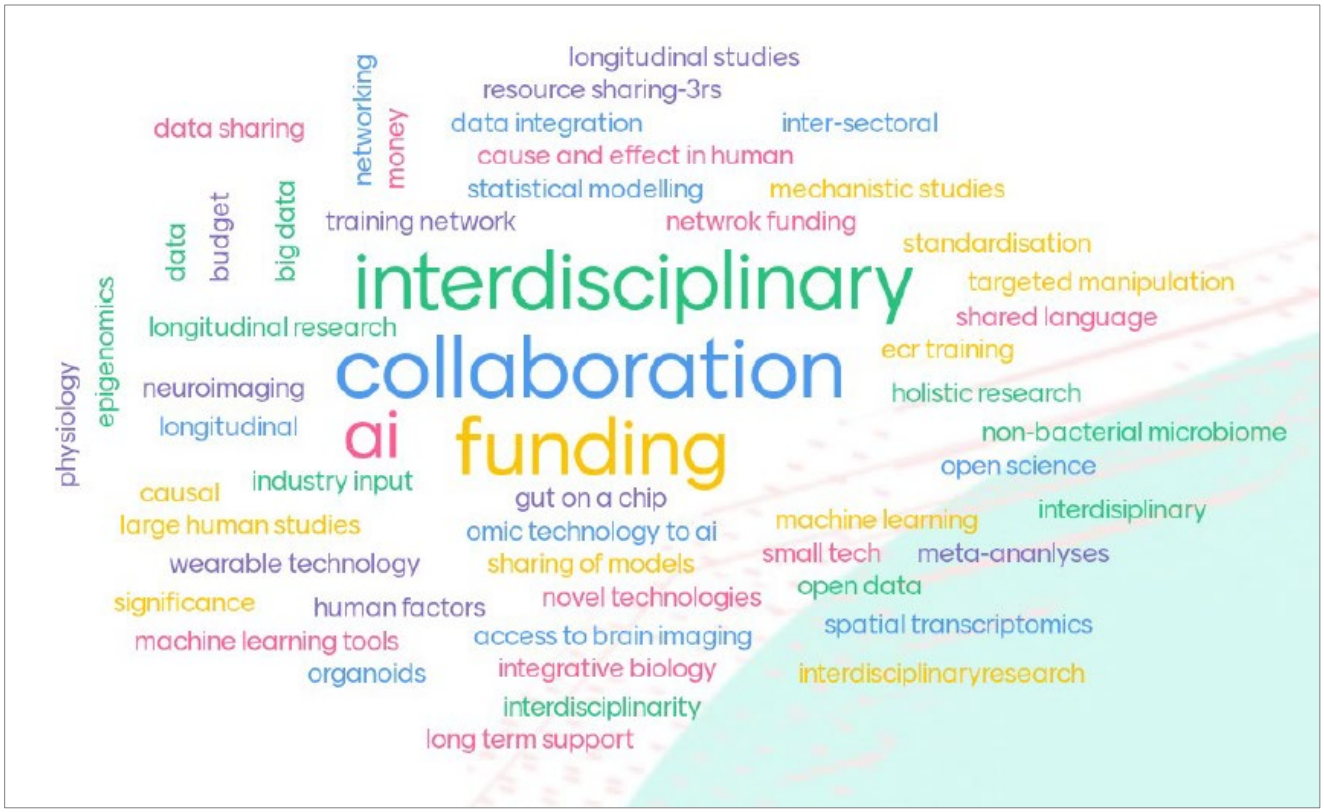
GIBA workshop programme

Time	Activity
9:30 – 10:00	Arrival and registration
10:00 – 10:05	Welcome Workshop Chair: Professor Deborah Dunn-Walters, University of Surrey
10:05 – 10:15	Introductory BBSRC presentation Louisa Jenkin Senior portfolio manager, Bioscience for an Integrated Understanding of Health
10:15 – 11:15	Presentations: • Professor John Cryan, University College Cork Microbiota-Immune-Brain interactions: A lifespan perspective • Professor Philip Burnet, University of Oxford Gut-Immunology-Brain axis: Manipulation with bacteria-based interventions
11:15 – 11:35	Coffee / screen break
11:35 – 13:00	Breakout session #1 • Quick roundtable introductions [5 minutes] • What are the current opportunities in GIBA research and innovation? [40 minutes] • What are the current challenges to GIBA research and innovation? [40 minutes]
13:00 – 14:00	Lunch break
14:00 – 14:15	Review of morning breakout session [15 minutes]
14:15 – 14:55	Breakout session #2 • Quick roundtable introductions [5 minutes] • What tools and technologies are required to support GIBA research & innovation? [35 minutes]
14:55 – 15:05	Review of afternoon breakout session [10 minutes]
15:05 – 15:25	Tea / screen break
15:25 – 15:50	Mentimeter Q&A session [25 minutes]
15:50 – 16:00	Next steps Louisa Jenkin

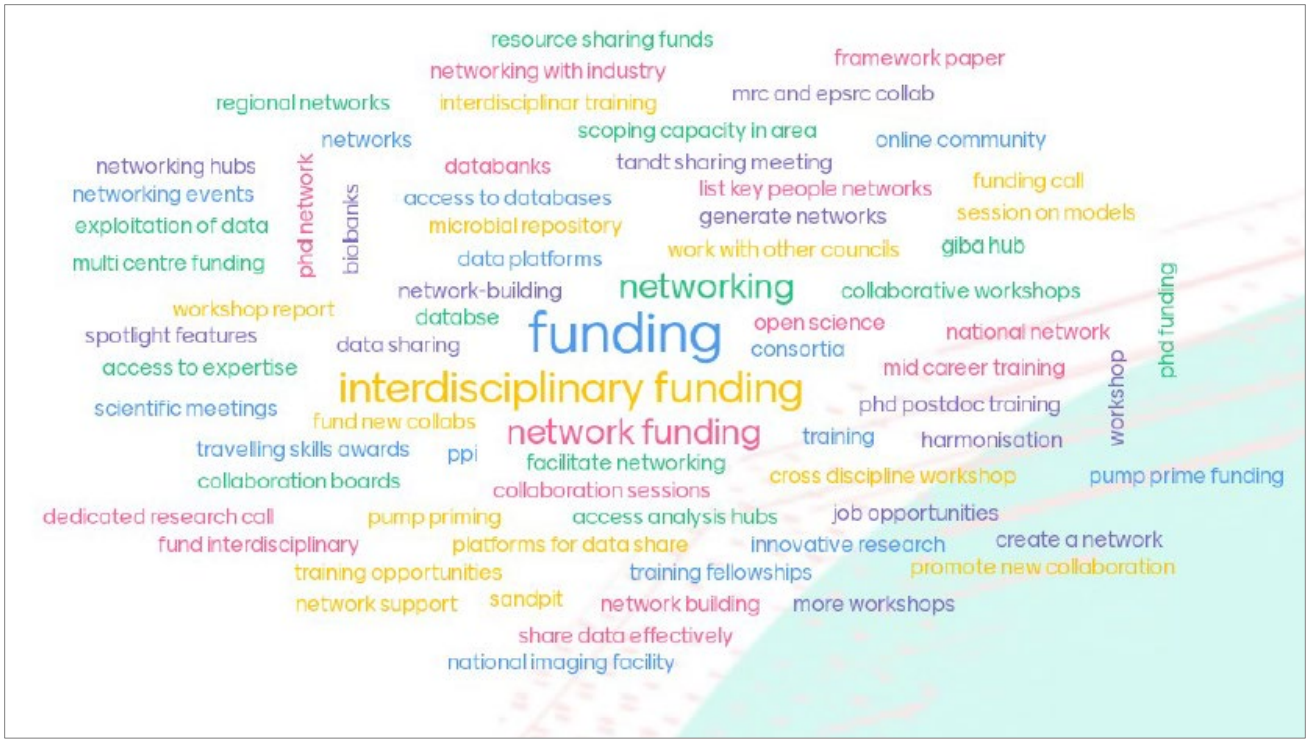
GIBA workshop Mentimeter Q&A session

The workshop participants were asked the following 8 questions:

a) What do you think will be the disruptors or trends that will revolutionise GIBA research and innovation?

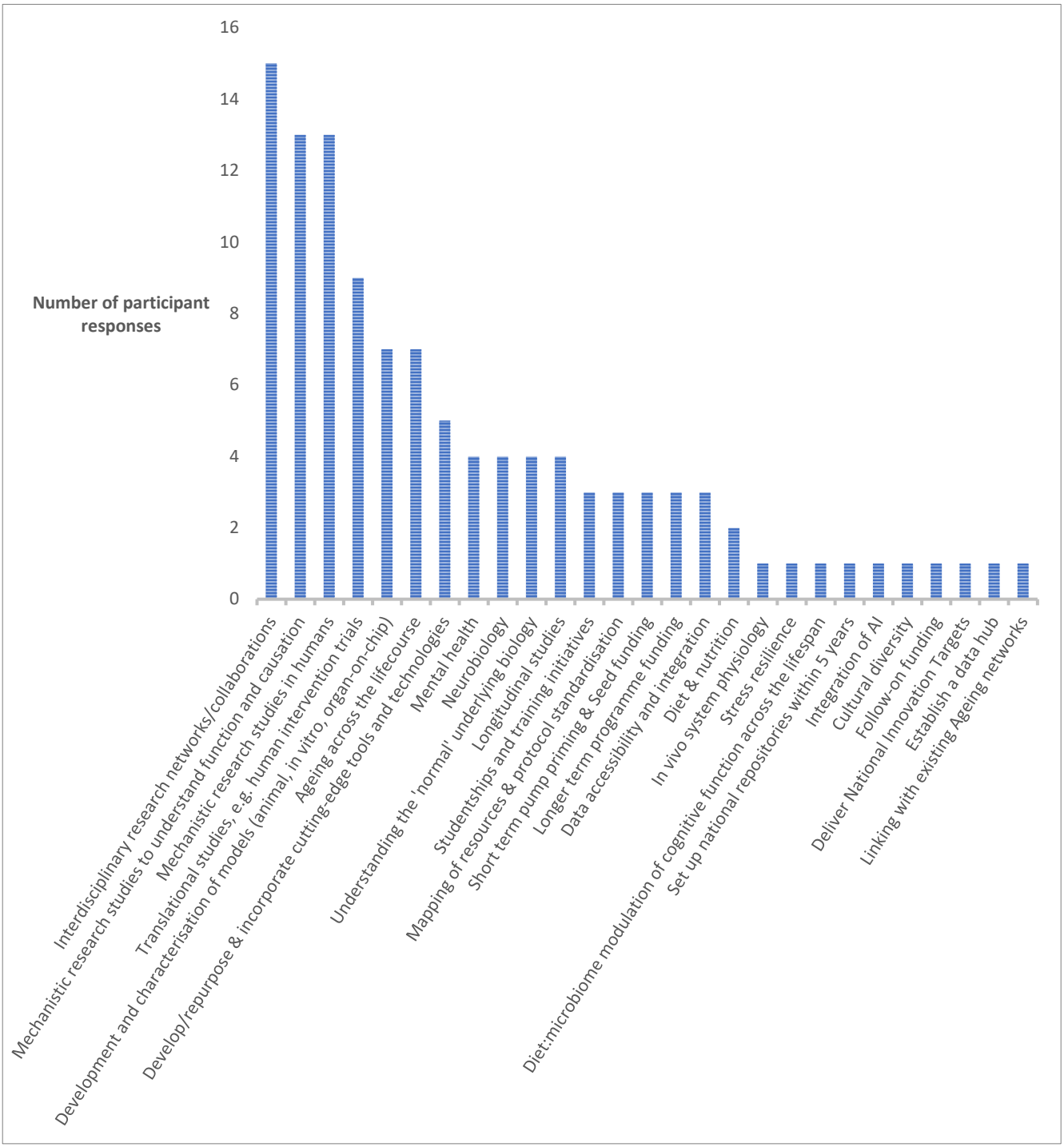


b) Following this workshop, what sort of activities would you like BBSRC to do?



c) What will help the GIBA field to move forward?

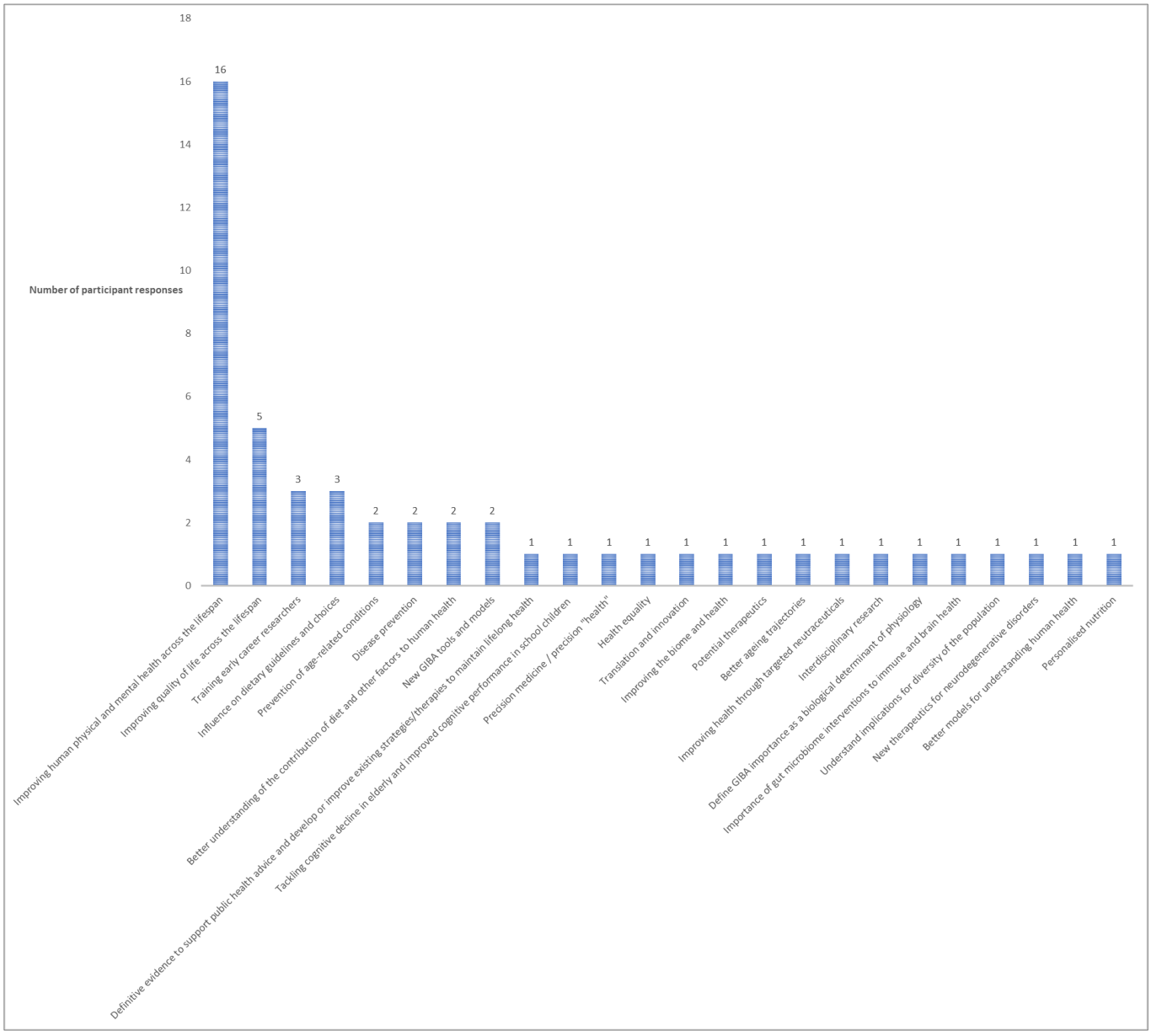
d) What GIBA research and innovation should BBSRC prioritise and in what time frame?



A timeline was indicated for a few of the suggested priorities:

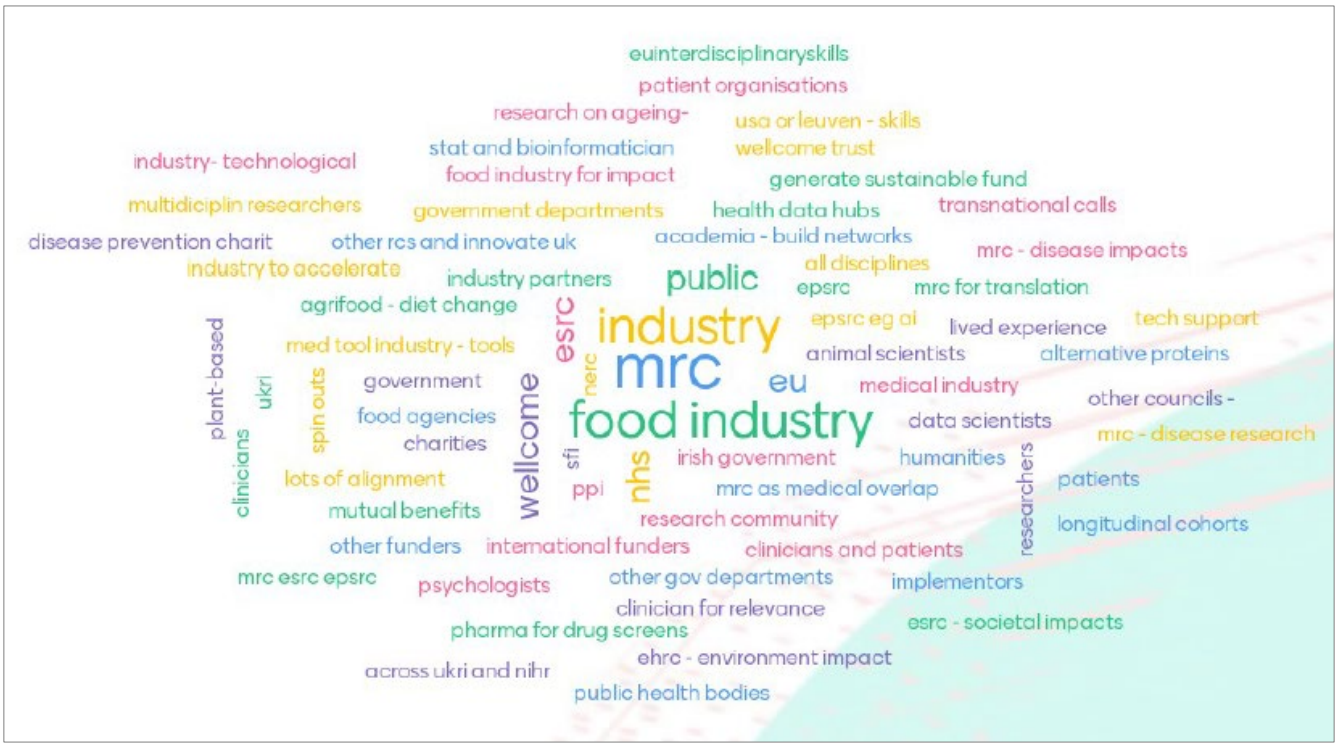
Short term	Long term
Networks, cross disciplinary team science	Cross disciplinary networks funded for 3-5 years
Explore options for collaboration and sharing data, tools and technologies	Consortium building across disciplines for 5 year funding cycles
Holistic research that maximises the material generated	Follow on funds and longer term funding/ programme grants for established research
Short term pump priming	Look at developing focus on microbiome functions, pathways to intervention and translation.PPI key
Understanding the 'normal' underlying biology	Human longitudinal multidisciplinary studies and big data collection
Develop & incorporate cutting-edge tools and technologies	Large scale human trials, initially focussing on healthy populations in order to understand the healthy biome
Align with 3Rs to improve human physiologically relevant ex vivo/in vitro models	Human studies with mechanistic insight, 5 years
Big data gathering, annotating, sharing and analysis within two years	Cause and effect intervention studies in human partricipants over the next five years
Seed funding and mid term funding to startup research	Mechanistic human studies 5-8 years
Human mechanistic studies	Human interventions, looking at differences in sex and populations over 5 years
	Healthy ageing (long term)
	Set up national repositories within 5 years
	Neurodevelopment, neurological disorders, neurodegeneration - next 5 years

e) Where could we see the maximum impact of GIBA research?



f) What are the broader social and ethical factors for which we need to be cognisant?

g) Who do BBSRC need to work with to help advance GIBA research & innovation and why? (For example, key industrial players, centres of excellence)



h) After hearing all the discussions from today - If you have one research question you would like to investigate, what would it be?

GIBA

How are the gut, brain, immunology systems actually connected?

How do these separate systems communicate with each other? What are the common communicating pathways and receptors across the GIBA system? Is there 'common language within systems and between systems and are they bidirectional? Are they age-dependent?

How important is the first 1000 days in the human gut-immune-brain development process?

How does early life experience impact lifetime GIBA responses?

How does the GIBA system change with age?

Does GIBA affect nutrients uptake and influence appetite regulate, leading to weight gain or loss?

What novel approaches need to be developed to manipulate brain-gut communication?

What do the public understand about GIBA and how - if at all - does it shape their behaviour?

Role of the microbiome in GIBA

What is a healthy microbiome?

What are the mechanisms by which the microbiome affects the body?

How does the microbiome influence normal brain and behaviour function? What component of gut microbiome has biggest influence on brain function?

How does the gut microbiota influence the brain in ageing and disease?

What are the relationships between the microbiome and ageing and diseases of old age?

What are the main effectors of gut/ microbiome changes in the brain?

How does the microbiome influence vagus nerve activity?

How does the gut microbiota impact cognition?

How does the gut microbiota affect responses to neurotrauma?

What are the microbiome mechanisms underlying different individual responses to diet and different diseases development?

How can we unravel whether it is the bacteria or the metabolites that are having an effect?

What are the microbiome-derived chemical messengers and their targets involved in the GIBA?

How do the bacterial metabolites in the gut interact with the vagus nerve, immune system etc to affect the brain and behaviour in healthy individuals?

How do fungus-immune interactions in the gut impact human brain function and disease risk?

How do microbial metabolites impact on the human ageing process?

What are the mechanistic actions and definitive causation of microbial metabolites in immunity and brain?

What is the relationship between microbiome and gender, ethnic diversity and chronobiology?

What is the role of the microbiome in immune system modulation?

Is gut microbiome more connected to brain than other microbiomes?

What is the role of the mycelial cell wall in neuroinflammation?

If we model the dynamic cellular relationships in villi such as short-lived epithelia vs long-lived neurons and persistent immune cells - what memory develops and transmits?

Role of immune system

How important is gut health to immune function?

What is the role of immunological mechanisms on cognitive functions?

What are the effects of inflammation on the microbiota and the knock-on effects on mucosal-neuronal signalling?

How does the immune system contribute to brain function and what is the role of the gut microbiota in this process? How does age modify this response?

Why do several gut inflammation diseases manifest in ilium – is it a clock component, metabolite profile etc?

How does local immune response in gut interact with immune response in the blood and brain (which can be very different)?

Could comorbidities of inflammatory disease give us insight into immune mechanisms?

Which immune cells are mediating in terms of stress etc?

Role of neurobiology

What is the role of the nervous system in Peyer's patch B cell immune function?

How does the peripheral nervous system orchestrate GIBA?

How do neurons communicate with epithelial cells and immune cells in the gut?

What is the role and mechanisms by which neurotransmitters in the gut can affect the brain e.g., via vagal signalling or precursors travelling across blood-brain barrier?

What are the key mechanisms and role of vagal signalling in GIBA?

The effect of diet

What are the impacts of specific diet/microbiome/immune/behaviour crosstalk on cancer risk.

Can dietary modulation of the microbiome reduce, retard or prevent cognitive decline in an at-risk population via GIBA?

How do different diets impact the gut microbiome, brain and inflammation?

What is the mechanistic relationship between diet, gut signalling and the brain?

How does altering the microbiota with dietary interventions affect health and metabolic function in the long term?

How do GI cells respond to complex nutritional stimulations?