Milner Therapeutics Consortium call 2022

Disease areas
- Neuroscience | Immunology & Inflammation | Infectious Disease | Oncology |
- Metabolic & Cardiovascular disease | Musculoskeletal and Rare disease | Microbiome |
- Reproductive medicine | Technologies

Cross-cutting themes
- Senescence | Fibrosis | RNA | Epigenetics | Chromatin

Key approaches
- Disease model development | Novel modalities | Computational research and AI | RNA technologies

This full list of topics is organized by disease areas. Please note that topics which are of interest to several companies are highlighted in bold. There is a full list of technologies at the end of this list and the approaches that are particularly relevant in a disease area are also highlighted in bold within that topic.

Neuroscience

Relevant companies: Astex, Bristol Myers Squibb, Eisai, Eli Lilly and Company, J&j Innovation, Shionogi, Astellas

Diseases of interest
- Neurodegenerative disorders (e.g. Alzheimer’s and Parkinson’s diseases, Huntington’s, FTD, ALS (including ALS-C9orf72), dementia and other diseases that involve degeneration of motor neurons)
- Genetic diseases with a neurodegenerative component e.g. lysosomal storage diseases, mitochondrial diseases, leukodystrophies, CMT, poly Q diseases and MS
- Repeat expansion disorders
- Retinal degeneration disorders
- Hearing loss owing to hair cell degeneration or ribbon synapse loss
- Mood disorders (e.g. major depression, anxiety, ADHD, autism, PTSD, bipolar disease, schizophrenia)
- Neuropathic and chronic pain
- Neurological disorders (such as epilepsy, sleep-wake disorders inc. sleep disorders linked to neurodegenerative pathology /diagnosis)
- Sleep apnoea, including identifying contributing factors, resistance mechanisms to current therapies, muscle control in the upper airway, drug repurposing
- Addiction (e.g. drug abuse, opioid, alcohol, gambling)

Target identification and validation, approaches to therapeutics intervention and disease understanding
- UPR/proteostasis, mitochondrial function, autophagy, lysosomes, intracellular trafficking, inflammation, DNA damage repair, ferroptosis
- Astrocyte biology in maintenance of brain homeostasis and mechanisms to restore normal astrocyte function
- Lipid homeostasis
- Cell senescence
• Contraction or removal of expanded nucleotide repeats
• Sporadic Alzheimer’s disease target ID using gene profiles from patient samples; target validation (in animal models or iPSCs); methods for patient stratification and biomarker identification in response to HDAC2
• Neuroinflammation e.g. mechanisms in neurodegeneration and mood disorders
• Synaptic plasticity e.g. in mood disorders
• Glymphatic clearance
• Gut:brain axis and the role of the microbiome as a biomarker, e.g. in Parkinson’s Disease
• Neuronal regeneration and repair, including neurogenesis

Technologies and approaches
• Cellular and in vivo models that are better predictive of disease, including human and patient iPSC derived neurons/glia, organoids, microfluidic-based cellular model systems
• Biophysical, cellular, imaging and functional assays to study ion channels, including those present in the lysosomal pathway
• CRISPR screens in organoid models or using neurons derived from iPSCs for target ID and validation
• In vivo chimeric human iPSC rodent models
• In vivo trans-differentiation of cells e.g. astrocytes to neurons
• Novel in vitro model systems translatable to human biological processes
• Genetics and biomarkers (including digital) for the early detection/diagnosis of disease and patient stratification, e.g. for Parkinson’s and rarer proteinopathies
• Novel ‘omics approaches (including lipidomics, metabolomics and proteomics) for target ID and validation and pre-clinical and clinical biomarker discovery
• Imaging receptor occupancy using PET in animal models of CNS disease
• Assessing functional connectivity using fMRI and EEG in animal models of CNS disease
• Targeted modulation of gene transcription and translation (including endogenous non-coding RNA / RNA regulation/epigenetics
• Cell and Gene Therapy, including technologies for targeting the blood-brain barrier and specific cell types
• AAV mediated gene therapy in the CNS, retinal degenerative diseases or hearing loss (e.g. hair cell regeneration or ribbon synapse regeneration)
• T cell engagers
• BiTEs

Novel modalities
A full list of modalities is at the Technologies list. In the context of neuroscience, there is interest in coupling novel chemical or biological entities, cellular or genetic approaches with improved mechanisms for delivery to the brain.

Digital therapeutics
• Novel evaluation methods or technologies for cognitive functional domains in CNS diseases
• Digital solutions e.g. smartphone applications, computer software (In particular for Alzheimer’s disease and dementia)
• Non-drug treatments for CNS diseases or chronic pain e.g. smartphone applications, computer software
• Medical devices for non-drug treatments (e.g. Virtual Reality-based therapeutics for chronic back pain)

**Immunology & inflammation**

**Relevant companies:** Bristol Myers Squibb, Ferring, GSK, J&J, Pfizer, Astellas, Eli Lilly and Company

**Disease areas**

- **Immuno-oncology** *(see also oncology)*

- **Neuroinflammation** *(see also neuroscience)*

- **Gastro-intestinal disease**
  IBD, IBS, Crohn’s Disease, ulcerative colitis, refractory coeliac disease, celiac disease; Approaches targeting the adaptive immune pathway; Approaches to enhance Treg function and abundance and activation of co-inhibition pathways; Looking beyond live microbial consortia to specific small molecule therapeutics that target pathogenic strains and metabolites derived from microbial strains, intestinal fibrosis

- **Rheumatology**
  Systemic rheumatic diseases; Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, SLE and LN, Sjogren’s syndrome, Scleroderma, Polymyositis; Targeting mechanisms that address adaptive and innate immunity activation as well as adaptive counter-regulation; Complement mediated alternative pathway activation; Nucleic acid sensing; Novel combination approaches; Novel targets to address for SLE and LN

- **Dermatology**
  Psoriasis, Atopic Dermatitis, Hidradenitis suppurativa; palmoplantar pustulosis, Alopecia, Vitiligo, Hiradenitis Suppurativa; Acne, pemphigus and systemic approaches to these diseases

- Lung immunity
- Heart disease and inflammation
- Fibrosis and inflammation
- Immunology & Inflammation in reproductive medicine and women’s health: decidualization and immune resistance
- Peanut allergy and celiac disease (including antigen specific and other immune modulating treatments)
- ANCA associated vasculitis
- Autoimmune diseases with defined autoantigens
- Pathways that are specific to patient-stratified populations in inflammatory disease

**Biological understanding and therapeutic approaches:**

- Innate and adaptive immunology
- Non-immune side of immunology: stromal interactions and tissue barrier function
- Tissue-immune system crosstalk in disease pathology: tissue-resident immune cells
- Immunomodulation, including novel targets in innate lymphoid cells
• Senescence
• T cell exhaustion
• Regulatory T cells, including engineered or optimized Tregs
• Regulatory B cells
• Myeloid cells that might promote immune resolution including engineered or optimized macrophages
• Biological pathways that selectively govern the induction of immunoregulatory cells, such as Tregs, macrophages, mesenchymal stem cells, dendritic cells and regulatory innate lymphoid cells
• Nucleic acid sensing
• Microbiome (for IBD and IBS)
• Complement
• IL-23 Pathway (including small molecule and other oral approaches for this pathway)
• Immune system modulation through the manipulation of mitochondria

Technologies and modalities
• Senolytic / senomorph approaches to resolve fibrosis and inflammation
• Diagnostic tests to validate known prognostic disease biomarkers
• RNA as a therapeutic modality
• Immune cell reprogramming

Infectious disease

Relevant companies: GSK, J&J, Shionogi, Pfizer

• SARS-COV-2
• HBV and HIV

HBV Immune therapeutics (TLR/RIG-I agonists, immune activation in the liver, checkpoint and MDSC inhibitors); and HBV antivirals (targeting cccDNA, replication inhibitors, HBX pathway, nucleic acid therapeutics). For HIV, this includes molecules / pathway expertise in “HIV Cure” approaches (latency reversing agents, bNAb, immune clearance of reactivating cells; and Novel HIV vaccine approaches (therapeutic or prophylactic Vx; also interest in cure instead of chronic treatment)

• Respiratory Pathogens
  • Targets for pan-respiratory infections
  • novel influenza antivirals (especially Influenza B)
  • novel rhinovirus or human metapneumovirus antivirals / host pathways implicated in viral pathogenesis; novel inhibitors of pNTM (human non-tuberculosis mycobacteria)
  • novel host targets or therapeutics that selectively suppress excessive inflammation caused by respiratory infections, including suppression of ARDS
  • Ideas for host immune system modulation to develop novel anti-viral, anti-bacterial, antifungals or antimalarial
  • Clinical/translational research for an identification of etiological factors affecting severities and outcomes of infectious diseases
• Antibacterial resistance and hard to treat microbial infection
  Novel compound or technology (Vaccines also in scope), in particular to control Pseudomonas
  aeruginosa infection; Infection following acute exacerbation of COPD, infection in CF or non-CF
  Bronchiectasis patients and polymicrobial infection; Concepts of biofilm formation or persistence
  (excluding general drug resistance mechanism)

• Global Public Health
  • Novel dengue virus or pan-flavivirus antivirals or vaccines
  • MRSA (Methicillin resistant Staphylococcus aureus)
  • Chlamydia
  • ETEC (enteropathogenic E. Coli)

Therapeutic approaches
• Pathogen and host targets
• Understanding of the immune pathways that need to be increased or decreased to reach a
  sweet spot between fighting infection or conversely limiting tissue damage
• Targets and strategies that can be used for other diseases e.g. pan-respiratory
• RNA vaccines
• RNA as a drug

Technologies
• Development of smart pills e.g. to improve/ensure compliance of HIV patients
• New technology that would induce immune response in mucus in mouth and at local infection
  site
• New (humanised) models to study chronic viral infection of hepatitis B, papilloma virus
• New pre-clinical models for human rhinovirus infection

Oncology

Relevant companies: Astex, AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, Ferring, GSK, J&J
Innovation, Pfizer, Astellas

Cancer types
• Hematologic malignancies (e.g. B-cell malignancies, multiple myeloma, myeloid malignancies, AML)
• Lung
• Colorectal
• Breast
• Ovarian
• Prostate
• Bladder
• Gastrointestinal
• Sarcoma
• Pancreatic cancer
• Any tumour type where there is a recognisable targetable sub-population of interest
• Novel targets in indications with limited existing, targeted therapies, e.g. small cell lung cancer or
  glioblastoma
Target identification and validation, approaches to disease understanding and therapeutic intervention

- DNA damage response
- Chromatin regulation
- Epigenetics
- Cell cycle
- Cellular senescence
- Fibrosis
- Understanding the role of the microbiome
- Protein homeostasis and degradation
- Validated and novel E3 ligands and/or tissue or disease specific E3 ligands
- Novel approaches to target undruggable proteins
- Retrotransposons and LINE1 elements
- Cell surface proteins expressed specifically on solid tumour cells
- Tumour heterogeneity and evolution
- Tissue-immune system crosstalk and tissue-resident immune cells
- Tumour microenvironment
- Tumour intrinsic biology
- Long-term survivors
- Mechanisms of drug tolerance and drug-tolerant persister cells (DTPs)
- Screening platform for multi-specific antibodies, i.e. antibodies that bind more than one antigen
- Technologies that impact mitochondrial protein homeostasis, DNA variation and mutation

Immuno-oncology

- Immune senescence
- Immune Therapy
- Developing next-generation I-O therapies
- Directed T cell therapies
- Regimens that trigger potent, specific T cell immunity
- Immune biomarkers, including minimally invasive biomarkers of immune cell activity in the tumour microenvironment
- Biomarkers related to detection of CCR8 expressed by cells in the tumour microenvironment and/or in circulating PBMCs and plasma
- Mechanisms to circumvent IO resistance
- Tumour microenvironment related to immunology including spatial distribution and relation to outcome
- Macrophage biology
- Natural killer cell biology
- Immune cell reprogramming
- Overcoming T cell exhaustion; enhancing antigen presentation
- CD3 engagers
- Small molecule immune-modulators and combinations with immunotherapies
- Novel approaches to modulate the tumour microenvironment
- Mitochondrial biology involved in immunometabolism, particularly in T cell activation and macrophage differentiation

Technologies and approaches in oncology

- Identifying and targeting early-stage disease
- Preventing overtreatment
• Methods to better understand tumour microenvironment, including spacial analyses
• New approaches to local therapy
• Single cell sequencing e.g. to understand resistance
• Direct tumour targeting
• Liquid biopsies and cfDNA
• Cell and gene therapy
• Novel and rational combination/synthetic lethality-driven treatments
• Improved models of disease (e.g. patient-derived)
• Innovative target identification and validation using novel technologies or model systems
• Microbiome
• New imaging approaches
• RNA as a drug, small molecule RNA binders
• Novel modalities (e.g. PROTACs, ADCs, Small molecule chaperones, Protein stabilisers, Protein degraders, Nitrases)
• Screening platform for multi-specific antibodies, i.e. antibodies that bind more than one antigen
• Technologies that impact mitochondrial protein homeostasis, DNA variation and mutation

Metabolic and cardiovascular disease

Relevant companies: J&J Innovation, Pfizer, AstraZeneca, Eli Lilly and Company

• Metabolism and cardiovascular risk factors
• Heart failure
• Pulmonary hypertension and adjacencies, including Idiopathic Pulmonary Fibrosis
• NASH and NAFLD (including targeting senescence to improve metabolic dysfunction)
• Cachexia
• Obesity
• Diabetic/chronic kidney disease, AKI
• Common retinal degeneration conditions: Age-Related Macular Degeneration (Wet, Dry / Intermediate, Geographic Atrophy), Diabetic Macular Edema / Diabetic Retinopathy, Retinal neuroprotection
• Rarer inherited retinal diseases: e.g. Stargardt Disease, Retinitis pigmentosa
• Gene therapies
• Extended release technologies

• Type 1 Diabetes
  • BMs/tests that anticipate β-cell destruction
  • Treatments suppressing impact of environmental triggers
  • Treatments suppressing immune activation
  • Treatments that maintain normal insulin production in those susceptible to T1D
  • Adjunctive therapies to insulin in T1D that result in substantial HB1Ac lowering
  • Clinical data sets
• Type 2 Diabetes
Musculoskeletal
Relevant companies: Shionogi, Pfizer, Eli Lilly and Company, Astellas
Novel drug targets or lead compounds for sarcopenia
Neuromuscular disease
Duchenne muscular dystrophy
Mitochondrial biology, including Ca$^{2+}$ signalling and biology, and apoptosis

Rare disease
Relevant company: Pfizer, Astellas

Rare haematology
Rare cardiac disorders
- Rare inherited, dilated & arrhythmogenic hypertrophic cardiomyopathy; Amyloid light-chain amyloidosis (AL-Amyloidosis); Rare heart rhythm disorders
  - Novel concepts underlying the cause of disease such as mutant or modifier genes or signaling pathways
  - Novel treatments that reverse existing pathology

Rare renal disorders
- Focal Segmental Glomerulosclerosis, IgA Nephropathy, Alport Syndrome, or Autosomal Dominant Polycystic Kidney Disease:
  - Novel targets/pathways to improve glomerular filtration
  - Mechanisms to reduce IgA deposition or slow renal decline post deposition
  - Mechanisms to reduce cyst size, growth, formation and downstream effects on renal function

Rare metabolic/ endocrine diseases
Neuromuscular disease
- Emerging science on repeat expansion diseases, DNA damage response, replicative stress and cellular senescence
- AAV based approaches for gene therapies

Microbiome

Relevant companies: Ferring, J&J, Shionogi

- Gut dysbiosis, host-microbiome signals
- Role of microbiome in uro-oncology
- Respiratory microbiome
- Studies supporting microbiome treatment as strategy for other disease areas
- Microbiome-based solutions for prevention/interception of childhood allergic disease or celiac disease
- Novel microbiome targets and/or diagnostics for adenoma occurrence or recurrence
- Technology that lets probiotic bacteria settle at specific sites in the human gut
  - In vitro models of human gut microbiota
  - In vivo models that simulate human gut microbiota
**Novel methods and technologies across all disease areas**

This list includes novel methods and technologies that are potentially relevant across different disease areas and are of interest for many of the Consortium companies. Please also see the technologies that are particularly relevant to specific disease areas.

There is strong interest in teams who are developing technologies, methods or modalities in other disciplines and working with researchers to apply these in disease biology.

**Computational biology**
- Novel approaches for interpreting cfDNA
- Immunoinformatics methods
- Translational expression methods in single cells
- Differential expression and crosstalk in organoid or complex cell models
- **Novel approaches to guide unique gene editing capabilities**
- AI and Machine Learning for drug discovery, biomarkers and novel applications
- AI or another technology to analyse chemical or protein structure for potential toxicological profile
- **Mechanisms to aggregate or stimulate datasets in a coherent way**
- Applications of AI in chemistry and other disciplines
- In silico approaches for the design of functional proteins
- In silico chemical synthesis to identify chemical structures with reduced off target toxicity of a known compound or small molecule
- Methods for studying the biology of DNA nucleotide repeats and their contribution to disease

**Sequencing, multi-omic approaches and protein biochemistry**
- Proteomics, Epigenomics or Metabolomics
- Integrative multi-omics approaches
- Immunophenotyping (single-cell and spatial ‘omics)
- Single cell genomics and proteomic platforms
- scRNAseq multiplexing
- Novel high throughput proteomics platform with high sensitivity

**RNA drug discovery**
- Technology to predict secondary and tertiary structures of RNA molecules (mRNA, non-coding RNA etc.)
- Technology to identify secondary and tertiary structures of RNA molecules (SHAPE technology, DMS technology etc.)
- Small molecule RNA binders and inhibitors
- RNA as small molecule target
- Approaches to improve understanding causal links between non-coding elements and gene expression
- Efficient mRNA modification technologies
- Novel approaches that enable in vivo mediated cellular reprogramming
- Novel non-viral vectors or lipid nanoparticles
Disease models
There is strong interest in models that are patient-derived and have been demonstrated to be disease relevant. Key considerations will include how well the model reflects and predicts disease pathology, how well it can be used for screening assays and whether it could be scalable.

- Organoids in which genetic changes have been causally linked to disease phenotypes (n.b. consideration of model limitations will be important)
- Senescence models e.g. to study senomorphic or senolytic agents
- Tissue slice methods and tissue explants
- Functional Genomics and phenotypic models
- Microphysiological systems for safety/metabolism for screening
- *in vitro/ex vivo* reconstitution of 3D tumours or other disease models
- Cell and Gene Therapy
- *In vivo* trans-differentiation of cells e.g. astrocytes to neurons
- Organ-on-a-chip technology that can be used to test pharmacokinetics (e.g. culture of intestinal, renal and hepatocyte cells)

Structural biology
- Materials science/surface chemistry for EM-grids
- Accessing reagents for stabilising individual proteins and protein complexes and/or increasing the size of proteins for EM (Antibodies, Aptamers, Nanobodies, Darpins etc)
- Incorporation of non-standard amino acids into proteins
- Novel methods for purifying/isolating/stabilising membrane proteins for structural studies (EM/X-ray)
- New expression systems, including cell free technologies, for membrane proteins
- Emerging protein structure determination platforms
- Next generation platforms for protein structure prediction

Imaging technologies
Super resolution imaging platforms (such as 3D bioprinter, intelligent image analysis tools, tissue imaging and real time single cell sorting/ purification based on machine learning)

Targeted delivery approaches
- Technologies for targeting the blood-brain barrier and specific cell types
- Technologies to deliver peptides or nucleotides to specific tissues or organs
- Novel approaches to enable peptide delivery to cells
- Novel technologies to improve peptide pharmacokinetics after oral or parental delivery
- Solid state stabilization of proteins to enable high-concentration parenteral delivery
- Biomolecular condensates
- Lipid nano particles (LNPs) or other non-viral based technology for gene modulation in cells
- Technologies directed toward enhancing GI absorption of poorly absorbed compounds or enabling novel delivery methods (colonic, intraoral, subcutaneous, intra-tumoral)
- Drug delivery systems using nasal aerosol
- Novel modalities that enable disease or tissue specific gene expression
- Approaches to enable multiple exposures to (redosing with) AAV based vectors

Systems biology tools to evaluate pharmacologic/toxicologic responses
Chemistry and novel drug modalities

- Chemical biology tools to expand FBDD capabilities: Biological validation of novel binding sites; Cellular target engagement tools
- Chemoproteomics: Novel target ID (oncology and CNS), particularly for targets where we can deploy CryoEM (ion channels / GPCRs)
- Medicinal Chemistry: High throughput experimentation – automation for fragment elaboration, Reaction prediction, Encoded library technology
- Non-invasive approaches the quantitatively monitor the toxicology phenotype of a new therapeutic
- Novel approaches to predict ligand affinity
- Biomaterials the increase engraftment, survival and function of transplanted cells
- PROTACs and compounds that induce protein degradation or stabilization
- Molecular glues
- Small molecule chaperones
- Nitrases, a recently identified enzyme class with reported role in Parkinson’s disease
- Antibody-drug conjugates (ADCs)
- ASO - ligand conjugates: antisense oligos with receptor binding moiety appended to facilitate internalisation
- Bi- and tri-specific antibodies
- Conjugated oligos (RNA / DNA)
- RNA as a drug
- T-cell engagers, BiTEs
- RNA-stabilizing or editing technologies, coupled with improved delivery e.g. to brain
- Gene therapy technologies to drive differentiation, maturation or cell function

Devices and non-drug technologies

- Digital solutions e.g. smartphone applications, computer software (In particular for Alzheimer’s disease and dementia)
- Companion digital therapeutics that enhance delivery of care
- Controlled release technologies for drug delivery
- Drug delivery device technologies