**Milner Therapeutics Consortium call 2021**

**Disease areas** Oncology | Neuroscience | Immunology & Inflammation | Infectious Disease | Metabolic & Cardiovascular disease | Neuromuscular | Rare disease | 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, but approaches that are particularly relevant in a disease area are also highlighted within that topic.

**Oncology**

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

**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
* Retrotransposons and LINE1 elements
* **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)

**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
* Mechanisms to circumvent IO resistance
* Tumour microenvironment related to immunology including spatial distribution and relation to outcome
* Macrophage biology
* Overcoming T cell exhaustion; enhancing antigen presentation
* CD3 engagers
* small molecule immune-modulators and combinations with immunotherapies

**Technologies and approaches in oncology**

* Identifying and targeting early-stage disease
* Preventing overtreatment
* Methods to better understand tumour microenvironment
* **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)

**Neuroscience**

**Relevant companies: Astex, Bristol Myers Squibb, Eisai, Eli Lilly and Compnay, J&J Innovation, Shionogi**

**Diseases of interest**

* **Neurodegenerative disorders** **(e.g.** **Alzheimer’s and Parkinson’s diseases**, **Huntington’s, FTD, ALS and dementia)**
* **Genetic diseases with a neurodegenerative component** e.g. lysosomal storage diseases, mitochondrial diseases, leukodystrophies, CMT, poly Q diseases and MS)
* Repeat expansion disorders
* **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)
* Addiction (e.g. drug abuse, opioid, alcohol, gambling)

**Target identification and validation, approaches to therapeutic 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**
* **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
* *In vivo* chimeric human iPSC rodent models
* *In vivo* transdifferentiation 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)
* 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

**Novel modalities**

A full list of modalities is at the end of this appendix. 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**

**Disease areas**

* **Immuno-oncology \*see also oncology**
* **Neuroinflammation\*see also neuroscience**
* **Gastro-intestinal** **disease**

IBD, IBS,Crohn’s Disease, ulcerative colitis, refractory coeliac disease, cilial 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
* Senescence
* T cell exhaustion
* Regulatory T cells
* Regulatory B cells
* Myeloid cells that might promote immune resolution
* Nucleic acid sensing
* Microbiome (for IBD and IBS)
* Complement
* Il-23 Pathway (includingsmall molecule and other oral approaches for this pathway)

**Technologies and modalities**

* Senolytic / senomorphic approaches to resolve fibrosis and inflammation
* Diagnostic tests to validate known prognostic disease biomarkers

**Infectious disease**

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

* 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 includesmolecules / pathway expertise in “HIV Cure” approaches (latency reversing agents, bNAbs, 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 that selectively suppress excessive inflammation caused by respiratory infections; Ideas for host immune system modulation to develop novel anti-viral, anti-bacterial, antifungals or antimalarial; Clinical/translational researches 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 Bronchiestasis patients and polymicrobial infection; Concepts of biofilm formation or persistence (excluding general drug resistance mechanism)

* Global Public Health
* Novel dengue virus antivirals or vaccines

**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

**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

**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 Dx 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 simulates human gut microbiota

**Metabolic and cardiovascular disease**

**Relevant companies: J&J Innovation, Pfizer, AstraZeneca**

* Metabolism and cardiovascular risk factors
* NASH and NAFLD (including targeting senescence to improve metabolic dysfunction)
* Diabetic/chronic kidney disease, AKI
* Common retinal conditions: Age-Related Macular Degeneration (Wet, Dry / Intermediate, Geographic Atrophy), Diabetic Macular Edema / Diabetic Retinopathy, Glaucoma
* Rarer inherited retinal diseases: e.g. Stargardt Disease, Retinitis pigmentosa
* Pulmonary hypertension and adjacencies, including Idiopathic Pulmonary Fibrosis
* 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

**Musculoskeletal**

**Relevant companies: Shionogi, Pfizer**

Novel drug targets or lead compounds for sarcopenia

Neuromuscular disease

**Rare disease**

**Relevant company: Pfizer**

Haematology, neuro-muscular, gene therapy

* Including emerging science on repeat expansion diseases, DNA damage response, replicative stress and cellular senescence

**Reproductive medicine & maternal health**

**Relevant company: Ferring**

* Infertility (female and male)
* Maternoembryonic crosstalk and Implantation
* Preeclampsia and placental biology
* Preterm birth

**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
* Mechanisms to aggregrate or stimulate datasets in a coherent way
* Applications of AI in chemistry and other disciplines

**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

**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
* Approaches to improve understanding causal links between non-coding elements and gene expression

**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
* 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* transdifferentiation of cells e.g. astrocytes to neurons

**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

**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
* Solid state stabilization of proteins to enable high-concentration parenteral delivery
* Biomolecular condensates
* Lipid nano particles
* Technologies directed toward enhancing GI absorption of poorly absorbed compounds or enabling novel delivery methods (colonic, intraoral, subcutaneous, intra-tumoral)

**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
	+ 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)
	+ T-cell engagers, BiTEs
	+ RNA-stabilizing or editing technologies, coupled with improved delivery e.g. to brain

**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