MRC Laboratory of Medical Sciences

Clinical impact of LMS Research

Research Group	Summary
Lila Allou Genomic variation and disease	The knowledge gained from our research could lead to the diagnosis of a substantial portion of the 300 million undiagnosed patients with rare diseases and the development of innovative therapeutic strategies for cancer patients. In particular, our research aims to deepen our understanding of the functional consequences of genetic structural variations (SVs), the development of new tools for the clinical interpretation of SV effects, and the characterisation of potential SV-derived therapeutic targets in cancer. Our lab focuses on investigating SVs impacting noncoding DNA sequences and uses a combination of mouse and human models, genome-editing technologies, single-cell sequencing, and proteomics.
Luis Aragon DNA motors	Our research aims at bridging fundamental genome biology and translational medicine. We aim to understand how proteins involved in genome organisation interact with DNA to preserve genome integrity. We focus on the Structural Maintenance of Chromosomes (SMC) complexes (cohesin, condensin, and Smc5/6) and on topoisomerases. We employ a combination of biochemical, biophysical, single-molecule, and cellular approaches, to uncover how these molecular machines maintain chromosomal architecture and repair DNA damage. Translationally, our work is relevant for developmental disorders and cancer, where these complexes malfunction. We are also investigating DNA sensors, such as cGAS, which detect cytoplasmic DNA and trigger innate immunity responses, and consequently this work is relevant to autoimmunity, inflammation, and ageing. Through high-throughput biochemical screens, we aim to identify inhibitors of cGAS and viral modulators of SMC complexes, opening routes to novel antiviral and anti-inflammatory therapies rooted in a deep mechanistic understanding of genome–protein modulators.
Wiebke Arlt Steroids and metabolism	Our research investigates the role of steroid biosynthesis and metabolism in human health and disease. Our work targets both rare adrenal and gonadal disorders and common conditions associated with increased cardiometabolic disease risk, such as polycystic ovary syndrome, endocrine hypertension and adrenal incidentaloma. A major focus area is the role of androgens in women and how tissue-specific steroid metabolism and action links to metabolic health and disease. In our group clinician scientists, biochemists, biologists and computer scientists work together and learn each other's scientific languages. We use detailed human physiology and experimental medicine studies for metabolic *in vivo* phenotyping, in combination with human-based ex vivo and *in vitro* studies. We pioneer the use of steroid metabolomics, the combination of multi-steroid profiling by mass spectrometry and

	steroid data analysis by machine learning approaches. This helps us to identify disease- and mechanism-specific steroid “fingerprints”.
Alexis Barr Cell cycle control	Our research aims to understand how cells control their replication, such that the right number of cells forms in the right place, at the right time. This is vital for normal development and tissue homeostasis. Dysregulated cell replication can lead to over-replication, the basis of cancer. We investigate how cancer cells have lost control of cell replication and use that knowledge to identify points of intervention to prevent tumour growth. Many new drugs that target cell replication are successfully being used in cancer treatment. However, these don’t work in all cancer types and drug resistance is a huge barrier to their effectiveness. We are working to understand which tumours will respond to which drugs and how to overcome the emergence of resistance. Since cell replication is dysregulated in all cancer types, our work has broad importance. We have experience of working in breast, lung and bladder cancer.
Petter Brodin Systems immunology	Our systems immunology research addresses critical gaps in understanding immune development and function across the lifespan. For example, our ISAC project, the world's largest paediatric pan-cancer immune monitoring study, is generating insights into immune responses during cancer treatment that could inform immunotherapy strategies and predict treatment outcomes in children with solid tumours. Using our Born Immune birth cohort, we are studying microbial factors that shape early immune development and may prevent inflammatory conditions in infants. We also hope to explain the mechanisms underlying sex-differences in immune function. Ongoing projects aim to reveal how testosterone and oestrogen directly modulate innate immune responses, such as interferon pathways, explaining sex-based differences in infection susceptibility, vaccine responses, and autoimmunity. Together, these projects provide mechanistic understanding of immune regulation at critical life stages, during early development, cancer treatment, and across hormonal transitions, with potential to improve paediatric cancer care, optimise infant nutrition and microbiome interventions, and personalise medical approaches based on hormonal status.
André Brown Behavioural phenomics	We build technology for large-scale behavioural screening. Using the nematode *C. elegans*, which is small enough to behave freely in 96-well plates, we can run ten thousand behaviour assays per day. What is it good for?

	Genetic diseases and drug repurposing: *C. elegans* has homologs for about half of human genes, and we can create new disease models in weeks. Our throughput allows testing of essentially all approved drugs in a day. This enables systematic, *in vivo* discovery of repurposing candidates, complementing *in vitro* and AI-driven approaches. Psychopharmacology: Most first-in-class psychiatric drugs were discovered through phenotypic screens or serendipity. The shift to target-based R&D in pharma has coincided with a decline in productivity. Our platform delivers *in vivo* neuroactivity readouts with near *in vitro* throughput. We are exploring natural products from fungi (the next psilocybin?), plants (the next caffeine?), and bacteria (the next ivermectin?). Neglected tropical diseases: Over a billion people suffer from nematode infections, with rising drug resistance. By combining synthetic biology with high-throughput worm screening, we aim to discover and engineer new worm-killing proteins.
David Carling Cellular stress	We study the role of the enzyme AMPK (AMP-activated protein kinase) in regulating metabolism. AMPK acts as the cell's energy sensor, monitoring the level of ATP and coordinating metabolic pathways to ensure ATP levels are sustained. Dysregulation of energy metabolism occurs in a wide range of human diseases, including cancer, obesity and neurodegeneration. Our work aims to provide fundamental information on how AMPK regulates metabolic pathways, and how this can be harnessed in treating or preventing metabolic diseases. This knowledge is essential for the development of new and improved strategies for combatting these conditions. We use a combination of approaches and techniques, ranging from structural studies, cell-based assays and *in vivo* mouse models. We collaborate with Pharma to explore the therapeutic utility of small molecule modulators of the AMPK pathway.
Helena Cochemé Redox metabolism	Our research investigates the role of redox biology in health and disease. Reactive oxygen species (ROS) can cause oxidative stress and damage but are also essential as cellular messengers in physiological redox signalling. Dysregulation of redox signalling has been implicated in the pathophysiology of many conditions, as well as in ageing. Redox reactions are also key from a pharmacological perspective, as the mechanism of covalent binding for many drugs in the clinic. We combine advanced redox proteomics with genetic knock-in approaches, enabling us to achieve detailed mechanistic insight into the contribution of redox signalling across a range of biomedical contexts. We use multiple systems in our research, from cells and *in vivo* pre-clinical models (including *Drosophila*) to patient samples, allowing us to span fundamental discovery science through to translational applications.

	Recent clinical work has studied mitochondrial dysfunction in the immune system of patients with alcoholic hepatitis, underlying their susceptibility to infections.
Louise Fets Drug transport and tumour metabolism	Our research aims to understand the role of transporter proteins in cancer. This class of membrane proteins can influence drug response in two ways: either directly, by transporting a drug into or out of a cell; or indirectly, by shaping the metabolic state of the cell, which in turn alters the efficacy of that therapy. Transporter expression in cancer is highly heterogeneous, so by better understanding of which transporters influence drug activity and how they do this, we may be able to better predict drug response and design more personalised treatment strategies for patients. While we are interested in a range of therapeutic drugs and cancer types, to date, our work mainly focuses on ovarian and lung cancer.
Jesús Gil Senescence	Our research aims to understand how cellular senescence is controlled and can be targeted. Cellular senescence is a stress response that plays important pathophysiological roles. Importantly, senescent cells accumulate and contribute to cancer, ageing, and multiple age-related pathologies. We take advantage of a combination of approaches, including functional screens to identify novel regulatory mechanisms relevant to senescence. As part of our studies, we are also identifying targets or drugs that can be used to eliminate senescent cells or modulate their effects. Importantly, such drugs (referred to as senotherapies) can be used to treat a broad range of diseases, including idiopathic pulmonary fibrosis, metabolic disease, and cancer. We have experience in conducting drug and genetic screens and testing modulators of senescence for their effects in ageing, cancer, and liver disease.
Petra Hajkova Reprogramming and chromatin	We are interested in the flow of epigenetic information across the germline cycle and between the generations, and how this can be influenced by the environment. We investigate how DNA and histone modifications change when new germ cells are formed in the developing embryo and what changes are necessary for the nascent germ cells to undergo meiosis and to produce mature gametes. We are particularly keen to understand the development and long-term stability of the epigenetic information in the oocytes, the mechanistic implications for the age-related rapid decline in the oocyte quality and how this can be influenced by the environment. Our work has direct implications for our understanding of infertility and female reproductive potential. Epigenetic information (DNA and histone modifications) is responsive to environmental stimuli. As a parallel interest of my team, we are looking at the mechanistic underpinning of the cross-talk between metabolism and epigenetic regulation. This has direct implications for

	our understanding of epigenetic changes observed in disease and during aging.
Carl Jenkinson Vitamin D and bioanalysis	Our research aims to investigate the role of vitamin D metabolism on health outcomes using mass spectrometry as a translational application tool. Vitamin D has skeletal and extra-skeletal actions, and its deficiency can have wide ranging impacts across health. Mass spectrometry enables refined analysis for the quantitation of metabolic pathways spanning synthesis, activation and inactivation. This approach can define the metabolism, transport, localised action and excretion of analytes through the measurements of different biological sample matrices. Translational application of analytical methods across observational and clinical trial studies aim to characterise the role of vitamin D in health, including sex specific and ageing related health and disease. This includes defining optimal levels for population groups and addressing the impact of supplementation. A further objective is to establish more accurate approaches for defining vitamin D status through identification of novel biomarkers to generate clinical diagnostic methods.
Boris Lenhard Computational regulatory genomics	We investigate how genes are regulated during development, differentiation and disease, using computational and experimental genomics. We study how promoters and enhancers cooperate to control transcription, and how the architecture of regulatory landscapes enables precise patterns of gene expression across tissues and developmental stages. A particular focus is on long-range regulation, where clusters of enhancers spanning hundreds of kilobases interact with a single developmental gene within structures known as genomic regulatory blocks (GRBs). This research has direct relevance to human disease. Many genetic variants associated with complex disorders lie in non-coding regions, often far from the genes they affect. By modelling the organisation of enhancers within GRBs, we have shown that disease-associated mutations in type 2 diabetes, obesity, and schizophrenia act on distant developmental regulators rather than on the nearest genes. This has led to the identification of previously unrecognised disease mechanisms involving long-range misregulation of key transcription factors. Going forward, we aim to develop innovative computational approaches of analysing multiomic and comparative data to understand how disruptions of long-range regulatory architecture contribute to heritable developmental disorders, particularly those affecting the nervous system and body patterning and applying it to clinical data.
Enrique “Fadri” Martinez-Perez Meiosis	We investigate the mechanisms that ensure the accurate transmission of the genome from parents to offspring, which is essential for fertility and to prevent genetic diseases caused by aneuploidy such as Down’s syndrome.

	We focus on understanding how proteins that bind DNA to control the structure and function of chromosomes ensure the successful completion of meiosis, the specialised cell-division program that produces haploid gametes from diploid germ cells. To this end, we combine multiple experimental approaches including biochemistry and single molecule imaging of meiotic proteins with *in vivo* studies of meiosis in the nematode *C. elegans*. We also use worms to determine if mutations identified in infertile patients impair meiosis. In this way, we hope to understand the molecular mechanisms behind human infertility and to contribute to international efforts for the genetic diagnosis of infertility. This knowledge is required to design interventions aiming to restore fertility to patients carrying mutations that hinder the meiotic programme.
Matthias Merkenschlager Lymphocyte development	We explore how genetic variation impacts disease susceptibility, progression and reversal. Cohesin is a protein complex that holds sister chromatids together; it facilitates genomic functions ranging from gene expression to genome replication and repair, and is mutated in multiple cancer types, including acute myeloid leukaemia (AML). We found that cohesin mutations confer a selective advantage to leukemic stem cells by dampening inflammation and increasing self-renewal. Of relevance to patient stratification, mutation type can affect drug efficacy. Inherited cohesin mutations cause Cornelia de Lange Syndrome. We investigate whether correcting mutations can reverse disease in pre-clinical model. The *IKZF1* gene encodes a gene regulatory protein and is recurrently mutated in acute B cell progenitor leukaemia (B-ALL). Towards new treatments for B-ALL we investigate the impact of *IKZF1* mutations in B-ALL. A new direction of research is the sex-specific impact of human genetic variation with implications for diagnosis and treatment of X-linked diseases.
Vicki Metzis Development and transcriptional control	Our lab investigates how regulatory DNA sequences control gene expression during development. Using mouse genetic models, and embryonic stem cells differentiated into defined cell types, we study the mechanisms that establish the mammalian body plan. By dissecting how regulatory DNA orchestrates these processes, we aim to uncover fundamental rules of cell fate specification, with direct relevance to engineering cell types on demand. This work is of growing importance as mutations in noncoding DNA sequences are increasingly recognised as a key driver of human disease, yet predictive frameworks to interpret their impact are lacking. Through genome engineering and quantitative *in vitro* models, we are building platforms to connect regulatory sequence variation to developmental outcomes. These efforts open new opportunities for

	modelling human disease and ultimately for translating genomic discoveries into therapeutic strategies.
Declan O'Regan Computational cardiac imaging	We use clinical imaging of the heart and circulation to construct dynamic digital models of health and disease states in large populations. This helps us to discover mechanisms of aging, discover new genetic mechanisms in heart disease, and make accurate predictions of disease trajectory. Using machine learning to interpret this data is helping to accelerate discovery of new treatments for preventable heart diseases. We collaborate with Pharma in early target prioritisation research for drug therapies and develop AI technology for use in the clinic.
Michelle Percharde Chromatin and development	We investigate the role and regulation of mobile parts of our DNA, called transposable elements (TE), in early development and disease. TEs are normally suppressed in adult cell types, and their reactivation can lead to TE copy-paste mobilisation through the genome, DNA damage, mutations and innate immune activation. However, TEs also become de-repressed and play essential roles in normal embryogenesis. As well as studying healthy TE regulation and function, we are starting to investigate TEs in pathologies where they are dysregulated, such as in cancer, senescence, infertility, or inflammation. TEs may thus be novel therapeutic targets to ameliorate disease.
David Rueda Single molecule imaging	Our laboratory's translational research focuses on applying single-molecule microscopy and RNA technologies to address biomedical challenges. First, we are developing highly sensitive diagnostic platforms based on fluorogenic RNA aptamers, enabling rapid and precise detection of nucleic acids and biomarkers. Second, we are engineering next-generation fluorogenic RNA aptamers optimised for multispectral live-cell imaging, providing powerful tools to visualise and track dynamic gene expression in real time. These efforts have recently been spun out into a startup company, Irida, which is advancing these technologies towards commercial applications. Third, we are engineering novel Cas9 variants with enhanced fidelity, aiming to deliver safer and more accurate gene-editing tools for therapeutic use. Together, these projects bridge fundamental discovery with translational impact.
Karen Sarkisyan Synthetic biology	Our group focuses on developing new technologies to program cellular processes. We use protein engineering, modelling, and synthetic biology to create genetic circuits that predictably change gene expression and metabolism. In the past, our work focused on systematic understanding of mutational effects in proteins through high-throughput genotype-

	phenotype mapping, and on creating imaging technologies based on self-sustained luminescence. Our current focus is on designing molecular building blocks to engineer new traits in organisms. Our main models are bacterial and plant cells, which we use for prototyping genetic circuits, and for production of novel compounds with potential clinical applications. We then combine them with animal models to test effects on animal physiology and behaviour.
William Scott Genomics of obesity	We study how adipose tissues remodel in human obesity and weight loss, and how this leads to the development and remission of diabetes, by integrating findings from human tissues and experimental models. This approach has enabled us to define critical tissue injury and repair pathways linked to clinical outcomes. Building on our discoveries, we are using cell screens to identify proteins and compounds that modify these pathways; and ii. machine learning to simulate how pathways, cells, tissues, and individual patients will respond to targeted therapeutic interventions. Ultimately, we aim to accelerate the development of pharmaco-therapies that target adipose tissues to treat diabetes and other adverse complications of obesity.
Christian Speck DNA replication	Our team studies how DNA replication is controlled, because this process is essential for maintaining genome stability and supporting healthy ageing. When replication goes wrong, it can contribute to rare conditions such as Meier-Gorlin Syndrome and one of the most common health problems, cancer. By combining cutting-edge computational tools, biochemistry, and genomics, we are uncovering novel regulators of DNA replication and revealing how mutations in these proteins can lead to disease. We also work with collaborators to develop new small molecules and peptides that block DNA replication, with the goal of creating new cancer therapies. In addition, the team studies how DNA replication factors influence telomeres, discovering new regulatory circuits that are misregulated in cancer.
Mikhail Spivakov Functional gene control	Our lab uses wet-lab and computational approaches to study how DNA regulatory elements, such as gene enhancers, control gene expression and how this goes wrong in disease, such as common pathologies of the immune and cardiovascular system and cancer. As part of this research, we develop approaches to interpret the function of non-coding variants detected from GWAS studies using insights from statistical genetics, epigenomics and gene regulatory network analysis. We are also interested in how enhancers find their target genes (which may be megabase pairs away from them), as well as the role these elements play in early development, cytokine response (with implications for autoimmunity) and cancer drug resistance.

Juanma Vaquerizas Developmental epigenomics	In our laboratory, we focus on understanding the fundamental mechanisms that govern gene regulation during development. We utilise and develop advanced genomics and epigenomics approaches to examine how changes in the genetic and epigenetic landscapes influence development and disease. For example, by employing state-of-the-art single-cell methodologies, including single-cell multiome, we can map gene regulatory networks with high confidence. These techniques enable us to identify key regulatory elements and pathways that are disrupted in various conditions, which then allows us to link genetic variation to the underlying mechanisms causing the disease. We have already employed such approaches to study male infertility, congenital kidney malformations, and Diamond-Blackfan anaemia. Importantly, our research approach is applicable to a wide range of other diseases, offering the potential to uncover novel insights and therapeutic strategies across various conditions. By bridging fundamental research with clinical applications, we aim to advance human health and improve patient outcomes.
James Ware Cardiovascular genomics precision medicine	Our overarching research aims are to understand the impact of genetic variation on the heart and circulation, and to use genome information to improve patient care. Our work can often be immediately translated to the clinic. We have returned a genetic diagnosis to many families with previously unexplained heart disease, with immediate impact on their care. Our work to improve genetic variant interpretation has led to tools that are in routine clinical use and cited in international guidelines & best practice documents for genetic diagnostic testing. Beyond diagnosis, we are evaluating genomic biomarkers (both rare variants that cause monogenic disease, and polygenic scores) for precision medicine, with applications in prognostication and therapeutic stratification. In the longer-term, some of the new genes & pathways that we have identified as contributing to cardiovascular disease are promising therapeutic targets and may eventually lead to new treatments.
Dominic Withers Metabolic signalling	We study two interrelated areas: 1) the mechanisms regulating food intake with a view to understanding the regulation of bodyweight and 2) the role of inflammation in tissues including the liver and adipose tissue in the ageing process. Our work on the control of feeding behaviour focuses on the role of the brain and in particular the signals and neuronal pathways that are involved in nutrient sensing, sensory perception of food and food choice.

	Our work on ageing is underpinned by our previous work that has shown that nutrient sensing pathways control healthspan and lifespan. In particular, we are interested in the interplay between metabolic signalling and the inflammatory processes that drive age-related disease and multi-morbidity. We use a range of approaches including cutting edge neuroscience techniques, detailed *in vitro* mechanistic studies and *in vivo* physiology in mice. Our overarching aim is to discover new ways of treating obesity and delaying the ageing process in humans.