Scottish Cell Biology Meeting 2026 Programme – 4th September 2026 Abstract booklet

Talks

Keqin Li, University of Glasgow
Title: Live-imaging tumour cell death uncovers a pro-tumourigenic role of apoptosis
Although apoptosis is considered anti-tumorigenic, paradoxically, increased tumour apoptosis correlates with poor prognosis. By combining Drosophila's unrivalled genetics with advanced live/dead biosensors, we generated a unique tumour model wherein oncogenesis can be precisely spatially and temporally controlled, allowing in vivo live-imaging of growing neoplasms. We demonstrate that genetically-complex, patient-derived tumour genotypes frequently exhibit high oncogenic apoptosis, which is mechanistically distinct from physiological apoptosis. Quantification of neoplastic outgrowth and basal tumour apoptosis across our collection of tumour genotypes revealed that aggressive outgrowth was generally associated with high cell death. Interestingly, suppression of apoptosis within tumour models with high cell death had no effect on tumour size, belying an anti-tumourigenic role for apoptosis. Strikingly, irradiation increases apoptosis and neoplastic outgrowth, even in tumour genotypes with minimal outgrowth and cell death, suggesting apoptosis is promoting tumourigenesis. Through our live-imaging of macrophage recruitment, we propose a pro-tumourigenic role for apoptosis via tumour-associated macrophage efferocytosis.

Farzaneh Seyedshahi, CRUK Scotland Institute
Title: MUL-T: Decoding Spatial Cellular Architecture in Multiplexed Tissue Images
Understanding tissue organisation in multiplexed imaging requires modelling both cellular phenotypes and their spatial context. Existing approaches typically rely on handcrafted features, such as marker intensity statistics or cell-type proportions, which often fail to scale or generalise across cohorts with heterogeneous marker panels. We introduce MUL-T, a lightweight transformer framework that reframes tissue architecture as a masked contextual prediction task over discrete cell tokens. By learning contextualised [CLS] embeddings without task-specific supervision, the model captures higher-order cellular interactions while remaining computationally efficient. We evaluate MUL-T on several clinically relevant downstream tasks, including core-level tumour pattern classification, patient-level grading, PD-L1 positivity prediction, and cross-dataset treatment response prediction. Across tasks, MUL-T consistently outperforms classical feature-based baselines and achieves performance comparable to a foundation ViT model, despite substantially fewer parameters and lower training cost.

Luis Pardo, University of Glasgow
Title: The synthesis and trafficking of extracellular matrix proteins through the secretory pathway is regulated by subcellular localisation of mRNA translation mediated by the Ccr4-not complex.

The flux of newly synthesized proteins through the secretory pathway is highly regulated to ensure proper folding and post-translational modifications in the ER and Golgi, thus avoiding ER stress and consequent inhibition of mRNA translation through the unfolded protein response. Despite this mechanism being well characterized, the coupling between mRNA translation and protein flux through the ER-Golgi remains poorly understood. We report the role of the translation inhibitor complex Ccr4-not in regulating the early stages of extracellular matrix (ECM) protein synthesis in the cytosol. Combining polysome profiling and digital droplet PCR we have determined that Ccr4-not disruption increases the number of polysomal mRNAs encoding ECM

components in the cytosol, while reducing it in the ER. These changes in translation dynamics promote the accumulation of ECM proteins in the Golgi and ER which are subsequently routed for degradation in the lysosomes, leading to defects in cell adhesion, migration and matrix remodelling.

Taryn Wilson, University of Strathclyde

Title: Sex- and Cell-Type-Specific Mitochondrial Responses to NFE2L2 Inhibition and Oestrogen in Human Cardiac Cells Under Hypoxia

Background: Pulmonary arterial hypertension (PAH) causes right ventricular (RV) failure, which determines mortality. Mitochondrial dysfunction, oxidative stress, and fibroblast activation drive RV maladaptation, while sex differences implicate oestrogen and NFE2L2 signalling.

Methods: Male and female cardiac fibroblasts and cardiomyocytes were exposed to normoxia or hypoxia and treated with vehicle, ML385, 17Î²-oestradiol (E2), or ML385+E2. Confocal imaging assessed mitochondrial superoxide, membrane potential, and network morphology using MitoSOX, TMRM, and MitoTracker Green. Immunofluorescence assessed stress, mitochondrial, proliferative, and fibrotic markers.

Results: ML385 increased superoxide and reduced membrane potential and TFAM, with hypoxia amplifying these effects. E2 partially preserved mitochondrial function, particularly under hypoxia. Cardiomyocytes showed greater membrane-potential loss, whereas fibroblasts displayed broader stress and remodelling responses. Male fibroblasts showed stronger superoxide and stress responses, while E2 protection was greater in female cells.

Conclusions: NFE2L2 inhibition exposes mitochondrial vulnerability, while E2 provides sex- and cell-dependent protection relevant to RV remodelling in PAH.

Mark Kelly, University of St Andrews

Title: Dysregulation of the de novo synthesis of phosphatidylethanolamine in β-catenin-driven Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide, consisting of multiple subtypes with varied therapeutic responses. Identifying metabolic alterations associated with these genetically distinct subtypes is important for improving therapeutic outcomes. Cancer cells undergo metabolic reprogramming to support tumour growth, and these metabolic alterations are often linked to specific genetic mutations. Therefore, investigating subtype-specific metabolic changes may reveal new biomarkers and therapeutic targets for HCC. In this study, plasma samples from genetically engineered mouse models (GEMMs) of HCC were analysed using LC-MS-based metabolomics through targeted and untargeted approaches. Untargeted profiling and structural elucidation identified ethanolamine phosphate as a metabolite potentially consumed by β-catenin-driven tumours. Ethanolamine phosphate is an important intermediate in the synthesis of phospholipids such as phosphatidylethanolamine. This study explores the biological impact of the dysregulation of the de novo synthesis of phosphatidylethanolamine using in vitro models to better understand its role in HCC metabolism.

Rosie Gallagher, University of Dundee

Title: A High-throughput analysis of Hes-7 dynamics in hiPSC-derived Somitoids

Somitogenesis is the process by which the paraxial mesoderm forms somites, precursors of bones and skeleton. The segmentation clock coordinates this through the spatiotemporal timing of oscillations of different clock genes. Human characterisation has been enabled by human-induced pluripotent stem cell (hiPSC)- derived organoids (somitoids), though these have not

been staged across the segmentation clock cycle at scale. A high-throughput system was developed in which hiPSC-derived somitoids were cultured in 384-well plates with a programmable feeding schedule to stagger the initiation of oscillations. An automated pipeline reconstructed Hes7-Achilles oscillations through image processing, segmentation, and analysis. Results showed that staged feeding distributes the Hes7-Achilles signal across the segmentation clock cycle. Media changes during oscillation cause phase resets, whilst plate perturbation induces partial phase resets. Taken together, this research shows that media change can serve as a periodic stimulus for studying the segmentation clock

James Gray, University of Dundee
Title: Understanding RNA-TDP43 interactions in ALS
TDP-43 is a key regulator of RNA biogenesis and is mislocalized from the nucleus to the cytoplasm in >90% of people with motor neuron disease (MND). This causes toxic TDP-43 aggregation and loss of RNA-processing, including mis-splicing of STMN2 a central pathogenic event in disease. While TDP-43 loss-of-function and aggregation is a defining hallmark of MND, the controlling mechanisms are poorly understood. We previously showed that inhibiting the poly-ADP-ribose polymerase Tankyrase reduces cytoplasmic TDP-43 accumulation and neurotoxicity, implicating Tankyrase as a regulator of this transition. Here, we show that Tankyrase binds the first RNA recognition motif (RRM1) of TDP-43 using an ankyrin repeat cluster that is weakly utilised by most canonical substrates. Tankyrase binding displaces RNA, remodels RRM1, and promotes aggregation of full-length TDP-43. These findings link loss of RNA binding to TDP-43 aggregation and reveal a unique interaction interface to selectively target gain- and loss-of-function pathologies underlying MND.

Dan Sarni, University of Edinburgh
Title: A progeria syndrome links DNA hypermethylation to age-related pathology
What if DNA methylation changes aren't just ticking of our biological clock but rather the rust breaking the gears? Ageing is characterised by declining tissue function and regenerative capacity which underlie many chronic diseases. Experimentally establishing the mechanistic basis for such tissue ageing presents substantial challenges, given decades-long timescales and multifactorial origins. Epigenetic alterations have been proposed to have a key aetiological role, but whether they are correlative or causal remains a key unanswered question, as does their contribution to specific age-related pathologies. In this work, we establish a novel epigenetically-driven accelerated ageing syndrome. We demonstrate that DNMT3A gain-of-function mutations in Heyn-Sproul-Jackson syndrome recapitulate age-related gains in DNA methylation, cause multilineage stem cell dysfunction, and phenocopy aspects of ageing in humans and mice. We also show that region-specific DNA hypermethylation at lineage-specific genes can explain reduced stem cell output and lineage skewing. Hence, starting from a Mendelian disorder, we implicate DNA methylation-mediated stem cell dysfunction in the aetiology of medically important age-related haematological, bone and metabolic pathologies.

Vincenzo Ruscica, University of Glasgow
Title: XRN1 supplies free nucleotides to feed alphavirus replication
The 5'-to-3' exoribonuclease XRN1 is a key regulator of mRNA decay with proposed roles in viral infection. We previously showed that Sindbis virus (SINV) induces widespread host mRNA degradation accompanied by increased XRN1 association with cellular RNAs, yet its precise contribution remains unclear. Here, we show that XRN1 catalytic activity is essential for replication of multiple alphaviruses, highlighting the importance of RNA degradation for viral infection. XRN1 preferentially binds transcripts degraded during infection and relocalises to viral replication centres, placing RNA decay near the viral replication machinery. Consistently,

nucleotide-recycling kinases also accumulate in viral factories, facilitating conversion of RNA decay-derived monophosphorylated nucleotides into triphosphorylated nucleotides for viral RNA synthesis. Finally, uridine analogue labelling revealed incorporation of host RNA-derived nucleotides into viral RNA, supporting a model in which XRN1 promotes alphavirus replication by degrading host mRNAs near viral factories, thereby increasing local nucleotide availability to fuel genome replication.

Matthew Walker, University of Glasgow
Title: Developing a model of breast cancer dormancy in the bone marrow
Bone marrow is the most common secondary site for breast cancer metastasis and recurrence after dormancy. Within this niche, mesenchymal stem cells (MSCs) communicate with breast cancer cells via extracellular vesicles (EVs), regulating tumour dormancy. Our previous work showed MSC-derived EV metabolites induce a slow-growing MCF-7 phenotype. We aim to develop a bone marrow-mimetic dormancy model using synthetic EVs loaded with these metabolites, interacting with MCF-7 spheroids and MSCs in a 2.5D/3D system, integrated into an organ-on-chip platform for screening breast cancer recurrence. Methods include MCF-7 culture, immunostaining, confocal microscopy, nanoparticle tracking analysis, and qPCR, with statistical analysis using ANOVA-based approaches in GraphPad Prism. Results show synthetic EVs mimic natural EV size, remain stable at 4°C, and are efficiently taken up by MCF-7 cells. Metabolites increase dormancy markers (p27, COUP-TFI) and reduce Ki-67 expression. Overall, synthetic EVs act as effective delivery vehicles and support development of a dormancy-on-chip model.

Chiara Cazzaniga, University of Dundee
Title: UBE2Q1 cooperates with ZER1/ZYG11B in CUL2-dependent N-terminal degron targeting of JAK2
Ubiquitylation regulates protein stability through the coordinated action of E1, E2, and E3 enzymes. Non-canonical ubiquitylation extends the ubiquitin code beyond lysine residues to include serine, threonine, tyrosine, and other hydroxyl-containing biomolecules. This added layer of complexity defines an emerging and technically challenging frontier in ubiquitin biology. We have recently identified non-canonical activity within the UBE2Q family of ubiquitin-conjugating enzymes (E2s), demonstrating their ability to catalyse serine and threonine ubiquitylation (Rehman et al., 2024). Among these, UBE2Q1 is essential for early embryonic development and embryo implantation; however, the molecular mechanisms, substrates, and cognate ubiquitin ligases (E3s) that underpin its non-canonical activity remain unknown. Here, we identify UBE2Q1 as a previously unrecognised component of the CUL2-dependent N-degron pathway. Using integrated transcriptomic and proteomic profiling of UBE2Q1-knockout HeLa cells, as well as biochemical approaches, we find that UBE2Q1 cooperates with the CUL2 substrate adaptors ZER1 and ZYG11B to promote degradation of a variety of N-degron-containing proteins. Together, these findings identify UBE2Q1 as an E2 enzyme functioning with CUL2–ZER1/ZYG11B complexes to regulate N-degron-mediated protein turnover and provide mechanistic insight into how UBE2Q1 and non-canonical ubiquitination contribute to protein homeostasis.

Rhea Couper, University of Strathclyde
Title: Investigating Glucose Metabolism & Lipolysis in Cultured 3T3-L1 Adipocytes Using SRS & Zinc-alpha2-glycoprotein (ZAG)
Heterogeneity is a feature across many cells and tissue types, and adipose tissue is no exception, with adipocytes of different sizes within a single fat depot exhibiting distinct metabolic and functional properties. Clinically, the association between a greater number of large adipocytes and metabolic dysregulation contributes to the risk of developing insulin resistance

and T2D. Hence an understanding of defective and heterogenous adipocyte metabolism at single-cell level is urgently required. I have utilised SRS to analyse individual cells, circumventing the barriers of population averaging in tissues, using Glucose-D7 to trace and investigate glucose metabolism by exploiting its unique spectral fingerprint in the cell silent region. I now aim to investigate the impact of ZAG protein on metabolic processes, namely lipolysis. So far, ZAG appears to be interacting with 3T3-L1 adipocytes in such a way consistent with the literature. I also believe effects may be species specific between mice & humans.

Kirsty Weighill, University of Strathclyde

Title: Investigating the response of patient derived glioblastoma cells to mechanical stimulation induced by nanovibration.

Glioblastoma is a malignant primary brain tumour containing stem cells that are resistant to chemotherapy and radiotherapy. Nanovibration is a novel, potential, therapy that mechanically stimulates cells, influencing cell behaviour .e.g. mesenchymal stem cell differentiation, that could potentially target resistant glioblastoma stem cells. Patient-derived glioblastoma cells were cultured in stem-cell enriched conditions (STEM), media containing foetal bovine serum promoting differentiation (DIFF) and STEM conditions plus nanovibration (NANO) at 1 kHz, ±30 nm amplitude and 20 kHz, ±40 nm amplitude. Glioblastoma cell response to nanovibration has been extensively investigated. Mechanical stimulation via nanovibration at 1 kHz and 20 kHz has no effect on the differentiation, stemness, radiosensitivity, chemosensitivity, cell and nuclear area and cytoskeleton protein intensities of E2 and G7 cells. Ongoing work will investigate other mechansensitive proteins and pathways including vinculin expression, YAP localization and Piezo1 activity and the potential reasons for the lack of mechanosensitivity in these cells.

Savvas Iannou, University of Glasgow

Title: Remodelling the bone marrow niche: A 2.5D in vitro platform for discovery

The bone marrow (BM) niche integrates biochemical and mechanical cues to regulate hematopoietic stem cell (HSC) maintenance, yet recreating these interactions remains difficult. HSCs rapidly differentiate under standard culture conditions. Mechanically relevant systems that preserve stromal function are needed to interrogate niche-driven regulation in healthy and malignant haematopoiesis. We established a 2.5D BM-niche model using soft, fibronectin-functionalised, degradable PEG-maleimide hydrogels overlaid onto mesenchymal stromal cells (MSCs), introducing mechanical confinement while retaining 2D imaging access and intact MSC paracrine signalling. MSCs overlaid with the hydrogel upregulated niche-associated markers (NESTIN, SCF, CXCL12, ALCAM, LepR), showed reduced size, reinforced focal adhesions, and maintained YAP1 under ROCK inhibition, indicating cytoskeletal stabilisation. MSCs remained quiescent in low serum and re-entered the cycle upon proliferative stimulation. Functionally, mechanically primed MSCs supported greater primitive HSC maintenance and clonogenicity than 2D controls. Accessible 2.5D systems offer a mechanistically relevant platform for studying stromal mechanobiology and human-relevant HSC culture.

Carsten Schulte, University of Strathclyde

Title: A mechanobiological perspective on primary brain cancers

In recent years, it became increasingly evident that genetics alone cannot explain the intricate complexity of aggressive primary brain cancers, such as glio- (GB) and medulloblastoma (MB), but that mechanobiological aspects heavily contribute to their pathophysiology. Understanding how the extracellular matrix (ECM) nanoarchitecture affects cancer cells is thus of significant relevance to identify new levers for therapeutic approaches. In this context, we are developing biomaterials that we optimised for advanced bioimaging and experimental throughput harnessing electrospinning and e-beam lithography. We use these substrates that mimic primary brain ECM as faithfully as possible to dissect the impact of mechanotransductive processes on

GB and MB cell pathophysiological capabilities and therapeutic resistance. Mechanobiological characterisations comprise techniques, such as deformability cytometry, Brillouin spectroscopy, and super-resolution microscopy. These experiments are integrated with the study of the role of potential mechanotransductive key regulators informed by deep analyses of patient genomic data (e.g., TCGA and IvyGAP) to ensure clinical relevance.

Jaijeet Singh, University of Dundee
Title: LRRK2-Mediated Rab8A Phosphorylation Drives TBC1D2 Recruitment
Parkinson's disease is a progressive neurodegenerative disorder affecting approximately 1.5 per 1,000 people worldwide. While most cases are sporadic, 10–15% are familial, with mutations in the LRRK2 kinase gene representing the most common known genetic cause. Pathogenic LRRK2 mutations drive disease through hyperphosphorylation of a subset of Rab GTPases, key regulators of vesicle trafficking and endolysosomal homeostasis, yet the downstream effectors that transduce these aberrant phospho-Rab signals into cellular dysfunction remain poorly characterised. Here, we identify TBC1D2, a proposed Rab7 GTPase-activating protein, as a novel and selective phosphorylation-dependent interactor of LRRK2-phosphorylated Rab8A (pRab8A). Using immunoprecipitation–mass spectrometry, co-immunoprecipitation, and AlphaFold3 structural modelling, we demonstrate that TBC1D2 engages pRab8A through coiled-coil lysine residues K410 and K414, establishing a direct phospho-dependent binding interface. Proteomic characterisation of the endogenous pRab8A–TBC1D2 complex reveals selective co-recruitment of functionally distinct protein classes, including lysosomal components (V-ATPase subunits), lipid transfer proteins (BLTP3A and VPS13 family members), and 14-3-3 adaptor proteins. Focusing on the 14-3-3 interaction, phosphoproteomic analysis identified threonine 290 (T290) as a critical regulatory site; mutational analysis confirms that T290 phosphorylation is required for 14-3-3 association. Ongoing work aims to determine how pRab8A binding and 14-3-3 recruitment alter TBC1D2 GAP activity and downstream lysosomal function. This study provides mechanistic insight into a previously uncharacterised node of LRRK2-dependent signalling and identifies TBC1D2 as a novel effector regulated by pathogenic LRRK2 activity.

Nelson Ankamah, University of Glasgow
Title: Investigating ISGylation in Radiotherapy Resistant Colorectal Cancers
Background Colorectal cancers (CRC) are the second cause of cancer related mortality globally, a third of which are rectal cancers (RC). Radiotherapy (RT) is a standard treatment for locally advanced rectal cancer (LARC), but resistance limits its effectiveness. Although type I interferons contribute to RT responses, the role of Interferon-Stimulated Gene 15 (ISG15), their downstream effector, remains unclear in RT resistance. Methods Mouse models, patient-derived CRC datasets, and an orthotopic LARC model were used to investigate ISG15 expression, signalling, and responses to RT and poly(I:C), assessed by RNA sequencing and western blotting. Results ISG15 expression strongly correlated with WNT/YAP-high tumour cell states in mouse models and CRC patients. RT and poly(I:C) significantly increased ISG15 protein levels in organoids, while in vivo RT induced progressive ISG15 upregulation. Conclusions Altogether, our findings identify ISG15 is an RT-responsive factor and highlights a potential mechanistic link between ISGylation and WNT/YAP pathways in CRC progression.

Flavia Constantinescu, University of Edinburgh
Title: Selective interaction of SMCHD1 with chromatin is governed by LRIF1 and SMCHD1 ATPase activity
The chromosomal protein SMCHD1 is a GHKL ATPase with important roles in epigenetic silencing, including on the inactive X chromosome (Xi). Mutations of SMCHD1 have been linked

to facioscapulohumeral muscular dystrophy (FSHD) and Bosma arrhinia microphthalmia syndrome (BAMS). We use live-cell and single-molecule imaging to investigate SMCHD1 interactions with chromatin and its function in epigenetic silencing. We show that chromatin binding of SMCHD1 genome-wide, including on the Xi, is critically dependent on the protein LRIF1 that mediates interaction with H3K9me2/3-modified nucleosomes. Engineered mutations in the GHKL ATPase domain demonstrate that ATP hydrolysis is required for selective enrichment of SMCHD1 at specific chromatin regions, which is critical for X-linked gene silencing. Conversely, gain-of-function BAMS-associated mutations are linked to accelerated Xi recruitment and gene silencing, or increased Xi compaction. Together, our findings advance understanding of SMCHD1 recruitment and function on the Xi and at other target sites in the genome.

Nerea Caro, University of Strathclyde
Title: Mechanically Defined Microenvironments Regulate Neurovascular Organisation in Blood–Brain Barrier Organoids
Extracellular matrix (ECM) remodelling contributes to blood–brain barrier (BBB) dysfunction in ageing and vascular dementia, where altered stiffness and viscoelasticity may disrupt neurovascular organisation. However, most in vitro BBB models lack defined mechanical microenvironments. Here, we developed tri-culture BBB organoids composed of human brain endothelial cells (hCMEC/D3), pericytes, and astrocytes within ECM-functionalised sodium alginate hydrogels with tunable mechanical properties. Alginate formulations were ionically crosslinked to model compliant brain-like and stiffness-elevated microenvironments associated with ageing-related ECM remodelling. Mechanical properties were characterised using oscillatory rheology and stress relaxation analyses. Multicellular spheroids were embedded within laminin- or fibronectin-functionalised matrices to investigate how biochemical and mechanical cues regulate neurovascular organisation. Preliminary observations indicate that increased matrix stiffness alters spheroid compactness and F-actin organisation. This work establishes a mechanically defined BBB organoid platform to investigate mechanobiological drivers of barrier dysfunction in vascular dementia.

Nikolai Gajic, University of Glasgow
Title: OxPhos-DLBCL Exploit Thioredoxin-Mediated Cystine Reduction to Promote CSF Survival and Secondary CNS Relapse
Diffuse large B-cell lymphoma (DLBCL) exhibits distinct metabolic phenotypes - oxidative phosphorylation (OxPhos) versus BCR-glycolytic - but how these programs dictate central nervous system (CNS) relapse risk and cell death vulnerabilities remains unknown. Using tail-vein-injected murine models, cerebrospinal fluid (CSF) in vitro, clinical databases, and CSF single-cell RNA sequencing, we demonstrate that OxPhos-DLBCL possess leptomeningeal tropism that mirrors clinical relapse patterns. Mechanistically, while the cystine-scarce CSF microenvironment triggers ferroptosis in BCR-DLBCL by restricting glutathione synthesis, OxPhos cells uniquely bypass this System XC- dependency. We show that OxPhos-DLBCL tumours have an enriched thioredoxin system, utilising the rate-limiting cystine reductase TXNDC17 and its obligate upstream reductase TXNRD1 to reduce extracellular cystine and survive CSF-induced starvation. Consequently, pharmacological inhibition of this pathway using the clinically available TXNRD1 inhibitor Auranofin re-sensitises OxPhos cells to ferroptotic stress and markedly reduces in vivo CNS tumour burden, offering a readily translatable therapeutic strategy to prevent CNS relapse.

Emilie Hollville, University of Aberdeen

Title: Control of neuronal arborization and dopaminergic signalling by the ubiquitin ligase CUL9, a schizophrenia risk factor

Ubiquitin ligases regulate neuronal morphogenesis and connectivity, and their function is increasingly found disrupted in neurodevelopmental and neuropsychiatric conditions. However, the precise mechanisms by which they modulate neuronal development remain poorly understood. Our work investigates CUL9, a Cullin-RING ubiquitin ligase recently identified as a high-confidence schizophrenia risk gene in the most recent genome-wide association study. Despite this association, the role of CUL9 in the nervous system remains largely uncharacterized. Our work aims to elucidate whether CUL9 contributes to the regulation of neuronal structure and function. Using mice carrying a deletion of the Cul9 gene, we recently found that CUL9 is required for dopamine-associated signalling, connectivity, and behaviours. We also identified CUL9 as an essential regulator of neuronal dendrite development. Our results have implications for understanding the dopaminergic dysfunction observed in schizophrenia and raise the question of the molecular networks controlled by CUL9-mediated ubiquitination in neurons.

Sara Gohar, CRUK Scotland Institute

Title: Mitochondrial nucleotide salvage in hepatocellular carcinoma (HCC)

Introduction: Nucleotides (d)NTPs are building blocks of DNA and RNA, in addition to being essential to most cellular processes. Mitochondrial gene expression and metabolism depend on a constant and balanced supply of (d)NTPs, which are synthesised de novo in the cytosol or salvaged from precursor nucleotides in the matrix. Our previous work identified the mitochondrial nucleoside diphosphate kinase, NME6, to be required for the supply of pyrimidine (d)NTPs and mitochondrial gene expression in proliferating cancer cells. However, to what extent mitochondrial nucleotide salvage in tumours is required for sustained and balanced mitochondrial nucleotide supply, and its potential as a targetable metabolic vulnerability, is unclear. Comparison between tumour vs healthy tissue from HCC patients shows elevated expression of NME6 in tumours, which correlated with lower survival. NME6 knockout (KO) limits mitochondrial gene expression, OXPHOS and cell proliferation in HCC cell lines. Simultaneous inhibition of the de novo pyrimidine synthesis pathway via DHODH inhibition, exacerbates mitochondrial pyrimidine depletion and further depletes mitochondrial RNA and OXPHOS protein subunits. While loss of NME6 is well tolerated by the healthy liver, the absence of NME6 in intrahepatic transplanted HCC cells limits tumour growth and extends animal survival. These data suggest that perturbed mitochondrial nucleotide supply is a metabolic vulnerability in liver cancer. Ongoing work will explore the broad roles for mitochondrial pyrimidine nucleotide salvage in HCC development and progression.