Tumours must overcome numerous metabolic challenges in order to thrive in nutrient-deprived microenvironments and evade therapeutics. Mitochondria are dynamic organelles that provide the metabolic flexibility and plasticity demanded by cancer cells. Our overall objectives are to understand how mitochondria are reprogrammed at different stages of tumorigenesis and to reveal metabolic vulnerabilities in cancer by targeting mitochondrial metabolite transporters.

The transport and metabolism of mitochondrial nucleotides
One group of metabolites that we have been particularly interested in this year are nucleotides. Mitochondria contain their own genome, packaged into mitochondrial DNA (mtDNA) but lack the ability to synthesise their own mitochondrial nucleotides. Therefore, they must therefore be imported into mitochondria for the replication and subsequent expression of mtDNA. In addition to providing the building blocks of DNA and RNA, regulated nucleotide transport is required for the exchange of mitochondrial ADP/ATP and GTP for metabolic enzymes to identify genes that regulate mtDNA synthesis. Recent research indicates that perturbing the transport and metabolism influences tumour immunogenicity and responses to pyrimidine analogue chemotherapies such as 5-fluorouracil and gemcitabine.

Blocking nucleotide supply to suppress mitochondrial activity
We tested what happens to proliferating cells when their mitochondrial pyrimidine import routes are blocked. We were surprised to find that depletion of the two described pyrimidine transporters, SLC25A33 and SLC25A36, had little effect on cell division or mtDNA. One challenge of studying mitochondrial metabolism in mammalian cells is an apparent redundancy in metabolic transporters. Together with the Beatson Advanced Imaging Resource and the High-Content Analysis team, we performed a CRISPR–SpCas9 screen of mitochondrial transporters and nucleotide metabolism enzymes to identify genes that regulate mtDNA content when pyrimidine nucleotide import is impaired. Our screen and subsequent experiments revealed that a poorly characterised nucleoside diphosphate kinase, NME6, could preserve mtDNA in pyrimidine-depleted conditions (Figure 2). Further work, in collaboration with Prof Thomas Langer (MPI Biology of Ageing, Cologne), revealed that NME6 is constitutively required for the supply of pyrimidines for mitochondrial RNA synthesis. Cells lacking NME6 were deficient in oxidative phosphorylation and could not proliferate in respiration-dependent conditions. Recent research indicates that perturbing the transcription and translation of mitochondrial genes is a promising strategy to impair tumour proliferation and metastasis. We are therefore excited by our results as NME6 represents a novel node by which we can manipulate mitochondrial gene expression. Our next aim is to target tumours with a particularly high demand on mitochondrial activity and to test if NME6 levels are limiting for tumour progression.