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The migratory switch – investigating mesenchymal-amoeboid transition (MAT) in high grade gliomas

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One of the most devastating hallmarks of cancer is cell migration/invasion, a prerequisite for tumour metastasis. Targeting this cellular phenomenon offers an opportunity to improve the treatment of invasive and highly migratory tumours such as Glioblastoma multiforme, and to better understand the cellular mechanisms controlling cell migration. Previous work, using a range of migration assays and inhibitors targeting the actin polymerisation pathway, identified a compound, CCG-1423, that distinctively failed to halt migration in 3D invasion assays. We suggest that mesenchymal-amoeboid transition (MAT) is induced by CCG-1423 allowing the switch from one migratory modality to another. It is reported that CCG-1423 reduces the expression of CCN1; a key adhesion protein in mesenchymal migration, by blocking nuclear import of the transcriptional co-activator, MKL1. ELISA assays also confirm significantly reduced CCN1 levels following treatment with CCG-1423 in the established cell lines U251 and U87 compared to untreated controls. In addition, preliminary data using immunofluorescence and western blotting techniques, suggest an increase in MKL1 levels in the cytosol of CCG-1423 treated cells, which is consistent with the absence of MKL1 nuclear import, as previously reported. Phenotypically, CCG-1423 has been shown to induce MAT, visualised using Instant Structured Illuminated Microscopy (iSIM), a super-resolution microscope built and housed at Leeds University. With 150nm resolution and rapid acquisition of Z-stacks, this technology has allowed us to observe in detail a change in morphology from elongated to rounded in treated versus untreated cells detached from the core of U251 spheroids embedded in collagen. Detailed analysis of the iSIM images will allow us to understand the effect of CCG-1423 on MAT and the signalling pathways involved. This will facilitate pharmacological intervention by the development of combination treatments to target both mesenchymal and amoeboid cell migration and to fully prevent glioma cell migration and invasion.