Evaluation of Metastatic Pathway Inhibition by Novel Ruthenium-Based Metallodrugs Using the Zebrafish Model

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Cancer progression into metastasis is an incredibly complex, multistep process that is the major cause of cancer-related deaths. Targeting this cancer phenotype would result in decreased mortality. However, therapeutic efficacy is difficult to evaluate *in vitro* due to the complex nature of metastasis. The widely accepted model of testing metastasis is immunosuppressed nude mice, but the field agrees there are limitations and drawbacks to this model. Additionally, small quantities of new drugs make statistical power in mice difficult. Although new potentially therapeutic metallodrugs are being synthesized at high rates, there is currently no robust method for evaluation of toxicity or efficacy in mice or other model organisms. In fact, New Anti-Tumor Metastasis Inhibitor (NAMI-A), a ruthenium (Ru)-based complex, showed antimetastatic properties *in vitro* and in the nude mouse model, but failed clinical trials. As such, there is a need for an alternative method of evaluating therapeutic efficacy, to prioritize the most promising of candidate compounds**.** We investigated two novel Ru-based compounds, LCR134 and PMC79, for metallodrug evaluation in zebrafish. A structure-activity relationship between these compounds and NAMI-A, made antimetastatic activity promising. To evaluate antimetastatic potential, we conducted morphometric anti-angiogenic assays, gene expression analysis and wound repair. LCR134 showed no significant fold changes of six genes involved in metastatic progression. However, the majority of these genes were down-regulated after treatment of with PMC79. In addition, angiogenesis is a critical component of anticancer research. New blood vessels formed at tumor sites are required for tumor survival and growth. Blood vessel growth inhibition was measured after treatment with compounds using live-animal imaging. PMC79 exposure demonstrated larger blood vessel lengths at lower doses and significantly less branching at higher doses. Additionally, preliminary data for wound repair indicated that cisplatin and PMC79 exposure resulted in significantly less tissue regeneration and cisplatin caused significant upregulation of proliferating cellular nuclear assay. Together, these zebrafish-based assays could offer an alternative model for assessing anti-metastatic pathways. *Supported by: NJAES-Rutgers NJ01201, NIH-MIEHS P30 ES005022, and Training Grant T32-ES 007148, FCT (project UID/QUI/00100/2013), FCT2013 Initiative project IF/01302/2013 FCT, POPH and FSE - European Social Fund. Ph.D. Grant (SFRH/BD/100515/2014).*