Title: Identification of new, efficacious inhibitors of DNA-PK and their hypoxia activated pro-drugs

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Introduction: DNA-PK is a crucial component of the non-homologous end joining (NHEJ) repair mechanism of radiation-induced DNA damage. As such, DNA-PK represents a validated therapeutic target for the treatment of cancer as a stand-alone agent or in combination with radiotherapy and chemotherapy. We have synthesised compounds (effectors) capable of inhibiting the phosphorylation of DNA-PK and converted them into pro-drugs that are only activated (converted to effector) in hypoxic tumour cells.

Methods: We set up a cellular assay targeting the inhibition of the phosphorylation of DNA-PK in normoxic conditions, using compounds created in-house. This allowed us to screen and identify potent inhibitors of DNA-PK and evaluate their pro-drugs. The best compounds were then tested in 3D spheroid tumour model for activity against normoxic and hypoxic cancer cells.

Results: Several effector-pro-drugs pairs were identified, having cellular potency. Several pro-drugs are as efficacious in hypoxic cells as their effectors

Conclusion: Efficacious pro-drugs of inhibitors of DNA-PK have been identified through their actions in hypoxic cells, and these are being further evaluated.