Targeting RSK4 prevents both chemoresistance and metastasis in lung and bladder cancer: potential of re-purposed floxacins as novel therapeutic agents

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Lung and bladder cancers are mostly incurable due to early development of drug resistance and metastatic dissemination. Hence, novel therapies that tackle these two processes are urgently needed to improve clinical outcome. We have identified RSK4 as a promoter of drug resistance and metastasis in lung and bladder cancer cells and silencing this kinase sensitises to therapy and hinders metastasis in vitro and in vivo. This is mediated through inhibition of the NFkB pathway and of the transcription of anti-apoptotic proteins such as BCL2, cIAP1 and cIAP2. Drug screening revealed several floxacin antibiotics as potent RSK4 activation inhibitors and trovafloxacin reproduces all effects of RSK4 silencing in vitro and in vivo. Through crystallography, Markov transient analysis and biophysical assays, we propose a mechanism for the action of this compound. Finally, we show that patients undergoing chemotherapy and adhering to prophylactic levofloxacin in the large placebo-controlled randomised phase3 SIGNIFICANT Trial had significantly increased long-term overall survival times. Hence, we suggest that RSK4 inhibition represents a novel therapeutic strategy for treating lung and bladder cancer.

Biography:

Olivier E Pardo graduated from the Faculty of Pharmacy Paris-V, France where he was awarded a Doctorate in Industrial Pharmacy (1997). He completed his PhD at Imperial College-London (2002), UK and subsequently joined the laboratory of Prof. Julian Downward at the CRUK-LRI as a post-doctoral fellow. In 2006, he became team leader at Imperial College-London, Department of Surgery and Cancer where he created the Cellular Regulatory Networks lab. His team focuses on understanding the molecular mechanisms underlying chemo-resistance and metastasis in lung and other cancers. This involves multidisciplinary collaborations with other labs in the UK, France, the US, Canada and China bringing in biochemistry, molecular biology, physics and bioinformatics expertise. The data generated by his lab led to the initiation of several clinical trials in lung and breast cancer patients.