Development and preclinical assessment of a first-in-class small molecule inhibitor of the major cell death regulator protein FLIP

Ray Booth1, Catherine Higgins1, Joanna Majkut1, Jennifer Fox1, Margarita Espona-Fiedler1, Jamie Roberts2, Luke Humphreys1, Peter Blunt2, Trevor R. Perrior2, Timothy Harrison2, Daniel B. Longley1
1Centre for Cancer Research and Cell Biology, Queen’s University Belfast, BT7 1NN
2Domainex Ltd, Chesterford Research Park, Little Chesterford, Saffron Walden, CB10 1XL

Introduction: FLIP, the DISC and Drug Resistance

Model of DISC Assembly

Differential affinity of FLIP and procaspase-8 for FADD

Confirmation of On-target Activity

In Vivo efficacy and Tolerability

Clinical Positioning

Combination with EGFR intrinsic mutant NSCLC

PD Readouts

Summary

FLP is a frequently overexpressed, key regulator of cell death and drug resistance in many cancers. A medicinal chemistry programme has identified first-in-class drug-like compounds capable of: - Binding to FLIP with low sub-nanomolar activity and disrupting FLIP recruitment to the DISC in cancer cells - Inducing apoptosis as a single agent and potentiating TRAIL- and TNF-mediated apoptosis - Retarding growth of NSCLC xenografts as a single agent and in combination with a multi-valent TRAIL agonist - Enhancing standard-of-care chemotherapy in KRAS mutant CRC and NSCLC - Demonstrating anti-proliferative activity against key immunosuppressive T regulatory cells - Ablating colony formation and suppressing tumour growth following Osimertinib treatment in EGFR mutant NSCLC

References

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Domainex welcomes interest from any potential collaborators, industrial or academic. If you would like to learn more about applying our drug-discovery platform to other targets, please contact: ray.booth@domainex.co.uk (www.domainex.co.uk)