Stabilised peptides that specifically inhibit activity of the Grb7 adaptor protein, a potential oncology drug target for tumours driven by epidermal growth factor receptor and/or ephrin receptors. The target and peptides offer a basis for developing novel, safe and effective anti-cancer drug compositions.

- Potential for ‘First in Class’ anti-cancer drugs targeting Grb7 adaptor protein in epidermal growth factor receptor (EGFR) and/or ephrin receptor driven tumours
- Differentiated Mechanism of Action that inhibits the direct intra-cellular link to the Ras/proto-oncogene pathway
- In vitro ‘Proof of mechanism’ with efficacy for stabilised peptide molecule inhibitors
- Potential as a single agent and in combination therapies

THE CHALLENGE

Growth factor receptor-bound protein 7 (Grb7) is a signaling protein with critical roles in tumor cell proliferation and migration and is an established cancer therapeutic target. It belongs to a small family of SH2-domain adaptor proteins that interact with a number of receptor tyrosine kinases and signalling molecules.

Grb7 interacts with EGFR and ephrin receptors, providing a direct intra-cellular link to the Ras proto-oncogene. This links the function to proliferation of EGFR or ephrin driven tumours. Grb7 also plays a role in the integrin signalling pathway by binding with focal adhesion kinase (FAK), and support its role in cell migration/tumour metastasis.

Grb7 is validated as a prognostic marker of HER2+ve breast cancers and was identified as a therapeutic target in this and other cancers, including triple negative breast cancers for which there are no current effective treatments.

THE TECHNOLOGY

Monash researchers led by A/Prof. Jackie Wilce are developing novel bicyclic peptide-based Grb7 inhibitors.

The researchers have created a library of stabilised peptides that specifically inhibit the activity of Grb7 in vitro with Kd in the nM range, having 140x improvement over first generation monocyclic inhibitors.

Members from this new series have been demonstrated to enhance activity of other anticancer agents, reduce breast cancer cell migration in vitro and reduce tumour size as a single agent in a mouse model of pancreatic cancer. We have also demonstrated that cell permeable analogues successfully block Grb7-mediated interactions in a breast cell cancer line.

While first generation inhibitors lacked stability, our new generation Grb7 inhibitors are potent and highly stable as well as having high selectivity against other SH2 domain proteins.

THE OPPORTUNITY

Monash University seeks a partner to advance this series through lead optimisation to develop potent and specific Grb7 targeting drugs. The Monash team has extensive experience in the structure-activity of Grb7 inhibitors, peptide chemistry, structural biology and cellular biology with in vitro analysis and in vivo integrative function.

This knowledge forms the basis for creating novel, safe and effective anti-cancer drug compositions based on small molecules or stabilised peptides.

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