MONASH University

MONASH INNOVATION

STABILISED PEPTIDES TO GRB7 – A NEW ONCOLOGY DRUG CLASS/TARGET

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 to develop '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) 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. A selective Grb7 inhibitor has the potential as a combination therapy, augmenting the efficacy and reducing resistance to first line therapies.

THE TECHNOLOGY

Monash University researchers led by Prof. Jackie Wilce are working to develop compounds that can specifically inhibit Grb7 without inhibiting other SH2 domain proteins.

The researchers have created a library of stabilised bicyclic peptides that specifically inhibit the activity of Grb7 *in vitro* (K_D in the mM to nM range). A first generation of these Grb7 inhibitors 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.

The Grb7 lead series requires optimisation to improve potency and other characteristics to advance a lead candidate for drug development.

THE OPPORTUNITY

Monash University seeks a partner to help us create and test novel compositions (peptide and/or small molecule) against this exciting target. The Monash team has extensive experience in peptide chemistry, structural biology and cellular biology with *in vitro* analysis and *in vivo* integrative function.

The team has gained valuable structure/activity know-how of the target and test compounds. This knowledge forms the basis for creating novel, safe and effective anti-cancer drug compositions based on small molecules or stabilised peptides.

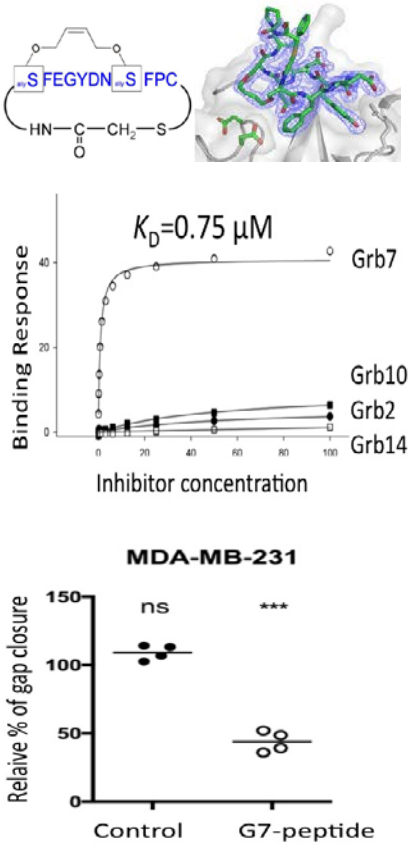

Figure 1: (A) The G7 peptides are constrained in their bound conformation as revealed by structural studies of the inhibitor/target complex. (B) The peptides bind selectively to the Grb7-SH2 domain. (C) Cell permeable versions of G7 peptide inhibit cancer cell migration.

References

1. Watson *et al*., (2015) Cyclic peptides incorporating phosphotyrosine mimetics as potent and specific inhibitors of the Grb7 breast cancer target. *Journal of Medicinal Chemistry.* 58(19): 7707-7718.

2. Gunzburg MJ *et al.,* (2016) Unexpected involvement of staple leads to redesign of selective bicyclic peptide inhibitor of Grb7. *Sci Rep*. 6:27060.

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