Targeting Axl: a potential therapy for glioblastoma

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INTRODUCTION

Brain cancer is one of the cancer types with the poorest survival rates, which has barely changed in spite of continuous improvements in anti-cancer therapies. Glioblastoma (GBM) is the most common and malignant form of adult brain cancers. One of the reasons for this poor survival is the highly infiltrative nature of GBM cells. Targeting GBM invasion is therefore key to successful treatment for GBM patients.

Targeted therapies such as the epidermal growth factor receptor (EGFR) inhibitor erlotinib are currently under pre-clinical evaluation for treatment against GBM. The mechanisms of action for these types of therapies is to inhibit key signalling pathways that mediate the invasive phenotype of GBM. While the EGFR is commonly overexpressed in GBM and is therefore a potential target, both pre-clinical and clinical evidence suggests that EGFR inhibitors are ineffective. The Axl tyrosine kinase regulates cellular invasion and has the potential to mediate resistance to EGFR-targeted therapies.

AIM

We wish to investigate targeting the Axl tyrosine kinase as a potential target for GBM therapy, in particular as an inhibitor of GBM invasion.

NZ BRAIN CANCER CELL LINES

One of the largest collections of brain cancer cell lines in the southern hemisphere, the NZB lines were developed from a decade-long partnership between the Auckland Cancer Society Research Centre and the Department of Neurosurgery, Auckland City Hospital. All cell lines were developed and maintained in a 5% O_2 atmosphere that mimics the physiological levels found in patients.

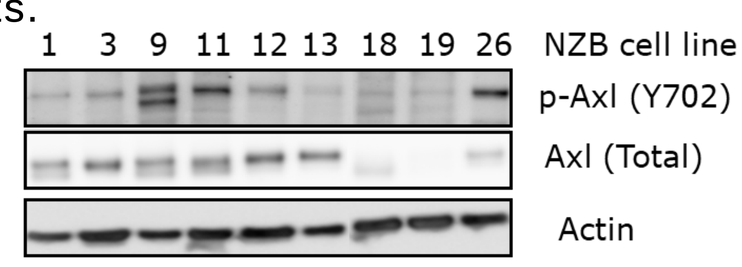

Figure 1. NZ GBM cell lines express Axl and its phosphorylated form at various levels.

TARGETING THE AXL PATHWAY

The AXL receptor tyrosine kinase is a master regulator of cell plasticity, proliferation, migration, metastasis and immune response. BGB324, an AXL kinase inhibitor is currently under clinical evaluation against a number of cancer types but not GBM.

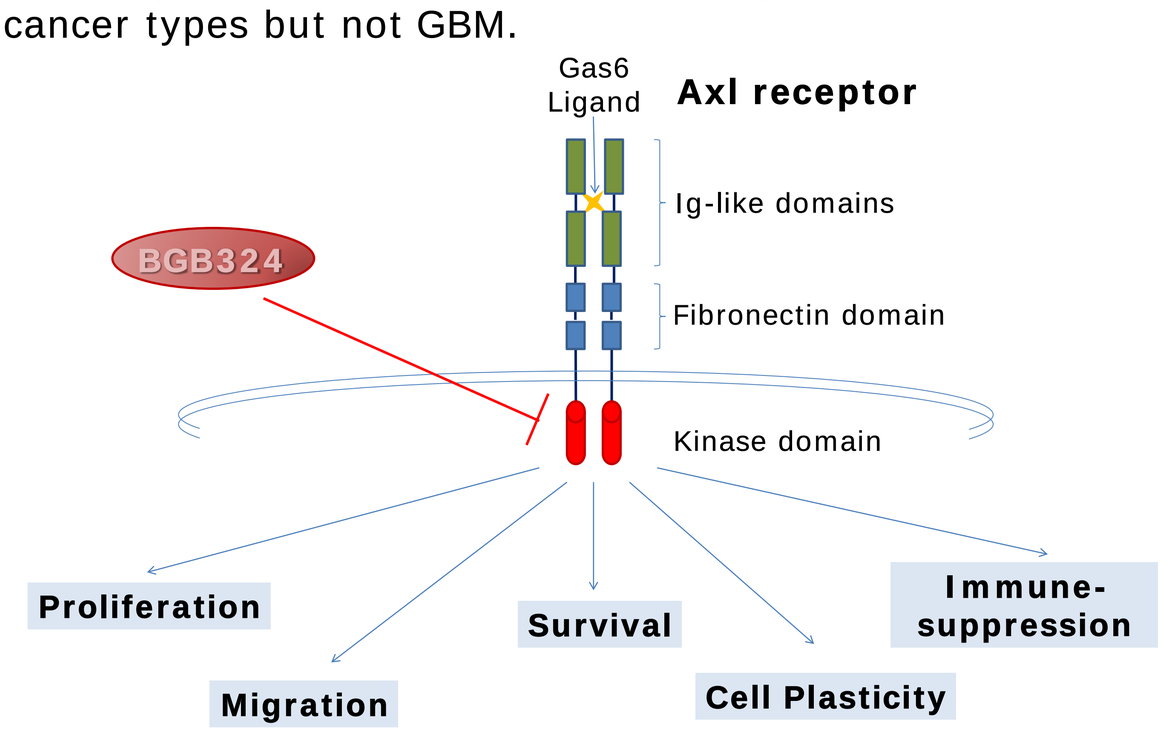

Figure 2. The Axl receptor tyrosine kinase regulates multiple downstream signalling pathways associated with cancer.

TARGETING GLIOBLASTOMA INVASION

METHOD: The 3-dimensional collagen invasion assay

A 3-dimensional collagen invasion assay was used to investigate the anti-invasive effect of BGB324 on 10 NZ GBM cell lines.

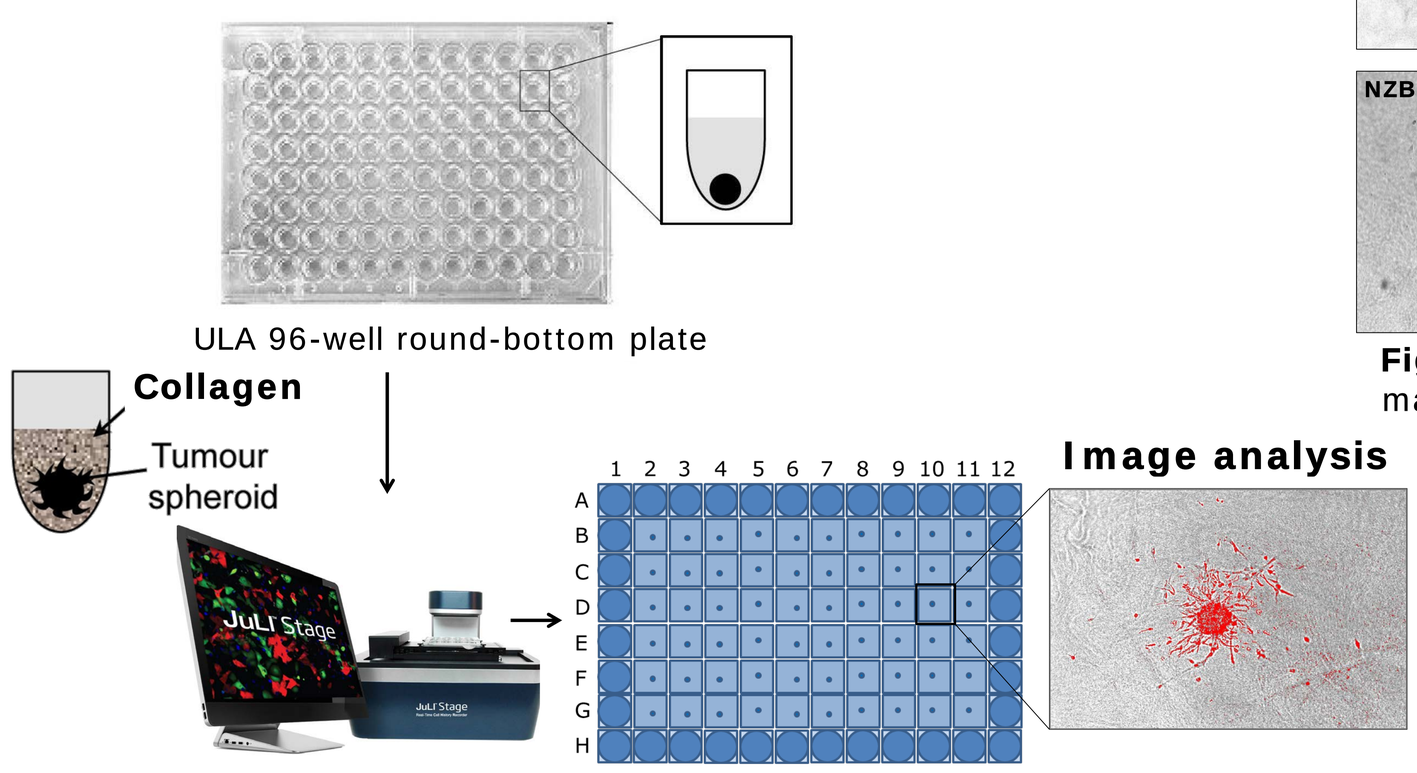

Figure 3. 3-dimensional collagen invasion assay. GBM neurospheres were cultured in ULA 96-well round-bottom plates and embedded in rats-tail collagen I. Invasion through the collagen matrix was imaged by the JuLI Stage imaging system and the relative invasion area was quantified using the ImageJ software.

The invasive phenotype of NZ brain cancer cell lines

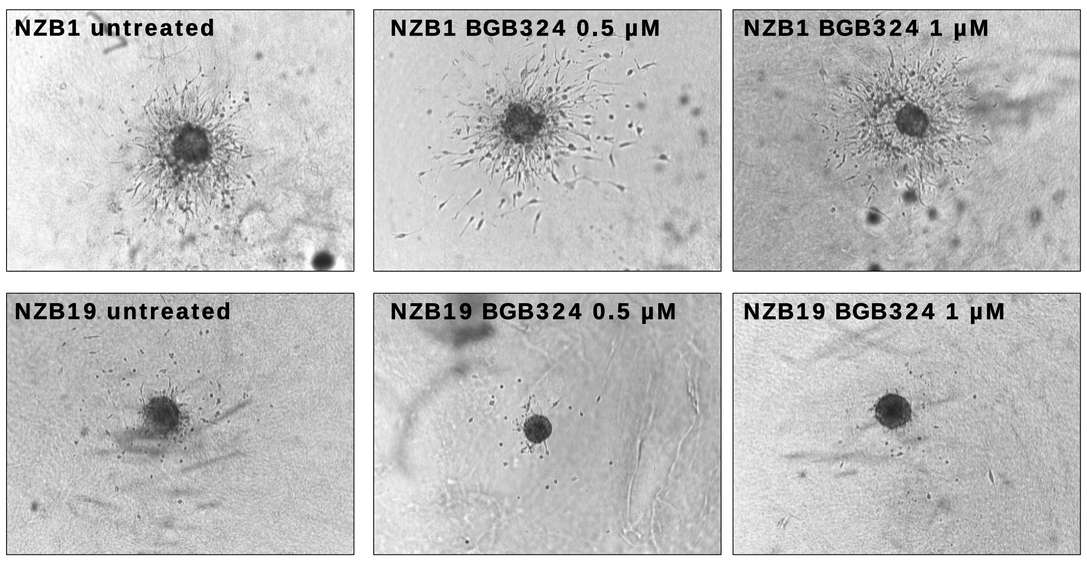

Figure 4. NZ GBM neurospheres invading into the collagen matrix and their response to BGB324.

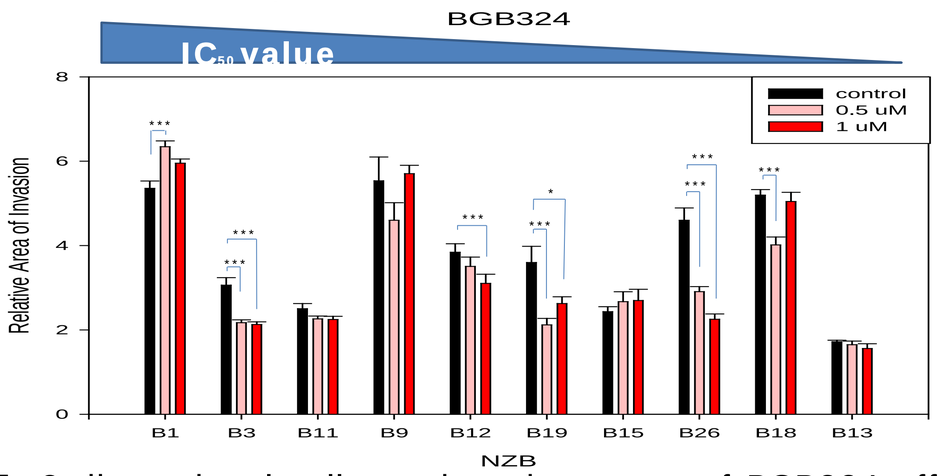

Figure 5. 3-dimensional collagen invasion assay of BGB324 effect on GBM cell lines. Significant effects are indicated by *P < 0.05; **P < 0.01; ***P < 0.001.

CONCLUSIONS

- GBM cell lines readily invade collagen matrix and some, but not all cell lines responds to BGB324-Axl inhibition.
- There is no correlation between the anti-invasive and anti-proliferative effect of BGB324, and also between the basal expression of Axl and its phosphorylated form in the NZB cell lines, and their response to BGB324.

Targeting Axl using the BGB324 compound may be an effective treatment for some GBM patients. However, as not all GBM cell lines responded to BGB324, we should investigate the potential contribution of other pathways to the invasive phenotype of GBMs.

ACKNOWLEDGEMENTS

This study was made possible due to the generous tissue donations made by patients at the Auckland City Hospital, financial support from a Lottery Health Translational Research Grant, and collaborative support from Professor Lorens (University of Bergen, Norway), and BerGenBio (Norway).