LGI1 mimetic peptide as a directed therapeutic strategy for endocrine related tumour metastasis

Introduction

Endocrine therapy is the treatment of choice for estrogen receptor (ER) positive breast cancer. Approximately 30% of patients eventually relapse and many develop distant metastatic disease. Metastasis is the prime cause of breast cancer patient mortality. There is currently no specific therapeutic for the treatment of endocrine resistant breast cancer. ADAM22 is a novel therapeutic target for metastatic disease, with a peptide drug based on its natural ligand, LGI1.

The Technology

The technology compromises of a clinically validated and commercially ready immunohistochemical assay for the detection of ADAM22 in breast cancer tissue to be utilised as (i) as a biomarker for predicting the metastatic potential of breast tumours in endocrine treated breast cancer patients and (ii) as a companion diagnostic for a novel therapeutic (LGI1) to treat metastatic ER positive breast cancer.

The technology further comprises of a peptide mimetic of leucine-rich, glioma inactivated 1 (LGI1) which is a potential therapy for the treatment of endocrine related metastatic breast cancer in combination with a companion immunohistochemistry diagnostic ADAM22, providing directed personalised treatment for patients with recurrent disease.

Background and Invention

The transmembrane glycoprotein ADAM22 was identified in discovery studies as a transcriptional target of the metastatic oncogene SRC-1, specific to the endocrine resistant phenotype. Work from RCSI has established a role for ADAM22 in cancer cell adhesion, dedifferentiation and migration *in vitro* and *in vivo*, processes which are critical to the metastatic phenotype. Mechanistic studies suggest that ADAM22 mediates these effects, at least in part, through activation of tyrosine-kinase receptors and inhibition of apoptosis. These data firmly implicate ADAM22 in the development of metastatic breast disease and suggest ADAM22 as a viable drug target for the treatment of endocrine resistant breast cancer.

ADAM22 as a biomarker of resistance in endocrine treated patients

An immunohistochemical assay for the detection of ADAM22 in primary breast cancer patient tissue has been developed to CLIA/Industry standards. The ability of ADAM22 to predict response to endocrine treatment was assessed in a retrospective clinical trial (ICORG 07/09) in conjunction with the All Ireland Cooperative Clinical Research Group (www.icorg.ie). ADAM22 expression significantly associated with reduced disease free survival in endocrine treated breast cancer patients.

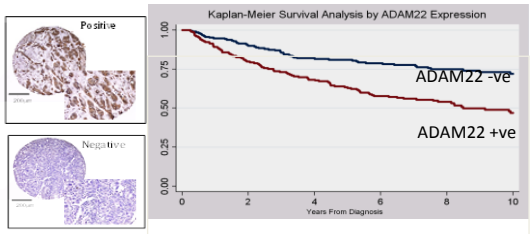

Figure 1: *ADAM22 positive expression in primary tumours predicts poor disease free survival in ER positive breast cancer, (p<0.0001).*

LGI1 as a therapeutic for metastatic disease

The neuronal protein, LGI1 serves as a specific extracellular ligand for ADAM22. It functions as a tumour suppressor of glioblastoma and neuroblastoma. The RCSI group have developed and synthesised several LGI1 peptide mimetics with simple hairpin structures against the active binding domain of ADAM22. The lead peptide can reduce metastatic potential of endocrine resistant cells. In *in vivo* studies, treatment of endocrine resistant xenografts with the LGI1 mimetic reduces local disease recurrence and eliminates distant metastatic disease. These data support the LGI1 mimetic as a directed therapy to treat endocrine related tumour metastasis with its receptor ADAM22 acting as a companion diagnostic.

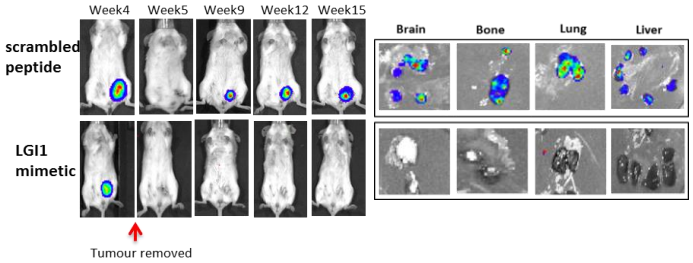

Figure 2: *Treatment of endocrine resistant xenografts with LGI1 reduces primary tumour burden and eliminates metastatic disease.*

Conclusion

LGI1 mimetics are new directed therapies which have the potential to treat endocrine resistant tumour metastasis with the receptor ADAM22 acting as a companion diagnostic.

References

McCartanD et al. Global characterization of the SRC-1 transcriptome identifies ADAM22 as an ER-independent mediator of endocrine-resistant breast cancer. Cancer Res. 2012 Jan 1;72(1):220-9.

Bolger JC, Young LS. ADAM22 as a prognostic and therapeutic drug target in the treatment of endocrine-resistant breast cancer. Vitam Horm. 2013;93:307-21. doi: 10.1016/B978-0-12-416673-8.00014-9

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