CRT Licensing Opportunity

SNAIL: A Prognostic Marker for Epithelial Cancers

- Expression of SNAIL in tumour cells is a significant prognostic marker for recurrence and mortality
- Opportunity to develop an independent prognostic marker for breast and other epithelial tumours
- Granted US and EP patents protecting detection of SNAIL for diagnostic/prognostic applications
- Proprietary antibodies that detect nuclear SNAIL in human carcinoma cells

Introduction

Studies in a variety of different cancers have suggested a role for SNAIL as a prognostic marker. In particular, SNAIL expression has been associated with breast, ovarian, colon, prostate, thyroid, adrenocortical, squamous cell and hepatocarcinoma (see Table 1). SNAIL expression can predict the risk of cancer progression and lymph node metastasis and has been associated with an increased risk of tumour recurrence and decreased survival. As such, SNAIL is a biomarker useful for guiding therapeutic strategy and disease monitoring.

A strong patent portfolio covering the use of SNAIL as a diagnostic and/or prognostic marker is available for licensing from CRT to further develop this promising biomarker. In addition, proprietary antibodies that detect nuclear SNAIL are available for licensing.

Background

Epithelial-mesenchymal transition (EMT) is a crucial process in tumour progression. One of the hallmarks of EMT is the functional loss of E-cadherin caused by transcriptional repression by members of the SNAIL, ZEB and bHLH families. SNAIL (SNAI1) has been associated with invasion, metastasis and poor clinical outcome [1] and has therefore been suggested as a prognostic marker for several different indications.

Active phosphorylated SNAIL localises to the nucleus and correlates with poor clinical outcome. Several recent publications [2-9] point towards a significant association of nuclear SNAIL staining of primary tumours and an increased risk of cancer progression, lymph node metastasis and decreased survival.

The ability to identify groups at high risk of tumour relapse is critically important to identify patients who will benefit from frequent monitoring and adjuvant therapy in relevant cancer indications. SNAIL has the potential to stratify the risk of cancer progression independent of, but adding power to standard clinical prognostic factors and existing gene expression predictors. As such, SNAIL is useful for guiding therapeutic strategy and disease monitoring in a broad class of tumours.

Study Data

SNAIL expression has been extensively studied by RT-PCR and immunohistochemistry in a wide range of clinical samples. In particular, there is significant support within the literature for the association of EMT with breast cancer progression [reviewed by 1, 10]. The expression of SNAIL in breast carcinomas has been associated with E-cadherin repression and metastasis [2, 8, 11-13], and with tumour recurrence and poor prognosis [14, 15].

Moody et al. [15] identified SNAIL as an independent predictive marker of recurrence in breast cancer. Microarray analysis of 464 human breast cancer samples correlated elevated SNAIL expression with decreased relapse-free survival. Significant association between SNAIL expression and the rate of relapse was observed for both locally advanced and node-negative breast cancers as well as among ER-positive and -negative breast cancers. This suggests that SNAIL expression might

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be an important prognostic indicator for breast cancer in a variety of clinical contexts, with the prognostic significance being independent of the most robust currently recognised molecular and cellular markers.

In an independent study Côme *et al.* [2] found that SNAIL was significantly overexpressed in tumours associated with lymph node metastasis (n=128). Elloul et al. [14] analysed mRNA expression of SNAIL in malignant effusions from patients with breast carcinomas (n=23). SNAIL was differentially expressed and was suggested to predict poor outcome in patients with breast carcinoma with metastatic effusions. Imanishi *et al.* [8] analysed 185 primary human breast cancer specimens that included 97 tumours with lymph node and/or distant metastasis and found a significant correlation between the expression of angiopoietin-2 and E-cadherin, SNAIL, metastatic potential, tumour grade, and lymph-vascular invasion during breast cancer progression.

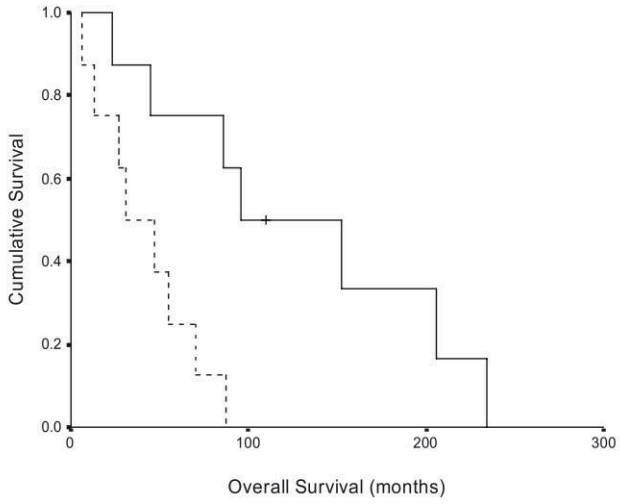

Figure 1. Kaplan-Meier survival curve for overall survival of patients with low SNAIL expression (n=8; solid line) or high SNAIL expression (n=33, p=0.008; dashed line) in breast carcinoma cells in effusions (personal communication).

SNAIL has also been associated with a range of clinico-pathological factors in other cancers (see Table 1) and may therefore be developed as a prognostic marker for several different indications.

Commercial Opportunity

CRT holds the rights to granted patents (US, EP) and a provisional CA patent application covering the use of SNAIL as a diagnostic/prognostic marker for cancer. Proprietary antibodies have been generated. CRT is seeking a commercial partner for non-exclusive licensing and/or collaborative development.

Table 1: Expression of SNAIL in Human Tumours

Cancer Type	Associated clinico-pathological factors
Breast carcinoma	Lymph node metastasis [2, 12, 13], effusion [14, 16], distant metastasis [2, 11], tumour recurrence and rate of relapse [15], metastatic potential, tumour grade and lymph-vascular invasion [8], decreased relapse-free/overall survival [14, 15]
Ovarian carcinoma	Hypoxia [17], distant metastasis [14], decreased overall survival [9]
Colon carcinoma	VDR downregulation [18, 19], distant metastasis [20]
Squamous cell carcinoma	Increased MMP expression [21], expression at the tumour-stroma interface [22], lymph node metastasis [3, 23], invasion and metastasis [3, 24], local recurrence and decreased overall survival [6], poor clinical outcome [23]
Hepatocarcinoma	Invasion [25], early recurrence and poor prognosis [26]
Prostate cancer	Dedifferentiation [27]
Thyroid carcinoma	Lymph node metastases and invasive front [5]
Adrenocortical carcinoma	Distant metastases and decreased survival [4]

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