

# CRT Licensing Opportunity



## Lamin A/C: Prognostic marker in colorectal cancer

- Urgent unmet medical need for improved stratification of CRC patients
- Proprietary antibodies and validated immunoassay available
- Expression of Lamin A/C is a highly significant risk marker for CRC mortality
- Validated by immunohistochemistry in 656 independent patient samples

DIAGNOSTICS | Validation

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### Introduction

Studies in the laboratory of Professor Chris Hutchison at the University of Durham have demonstrated that the presence of the proteins lamin A/C in early stage colorectal cancer (CRC) sensitively predicts increased risk of tumour recurrence and likelihood of cancer-related death. As such, lamin A/C is a biomarker useful for guiding therapeutic strategy and disease follow-up.

### Background

Colorectal cancer is the third most common form of cancer, and accounts for the greatest proportion of cancer deaths in the Western world. Currently, colorectal cancers are graded pathologically by the Dukes scale (A - D) according to the size, invasiveness and spread of the tumour. The long-term outlook for Dukes C and D patients is poor, although adjuvant chemotherapy has been shown to reduce the rate of recurrence after surgery by 40-50% and overall deaths by 16%. In contrast, greater than 85% of Dukes A patients are treated successfully by surgery alone.

The effects of adjuvant chemotherapy for the Dukes B subset of patients have been harder to prove, though small survival benefits have been demonstrated. As such the majority of Dukes B cases are currently treated by surgical resection alone, though greater than 30% of these suffer tumour recurrence and cancer-related death. There is an urgent medical need to develop diagnostic tests that can identify this high-risk group of Dukes B patients that may benefit from a more aggressive treatment regime after diagnosis.

A-type lamins are type V intermediate filament proteins, which are major components of the nuclear lamina. Mutations in the lamin A gene give rise to diverse degenerative diseases related to premature ageing. A-type lamins also influence the activity of retinoblastoma protein (Rb) and oncogenes such as a  $\beta$ -catenin. As a result, it has been suggested that their expression may also influence tumour progression.

### The Technology

The inventors have found that lamin A is expressed in colonic cells located within the putative stem cell niche, a population currently receiving significant attention in the field of colorectal tumorigenesis. *In vitro* studies suggest that lamin A is an upstream regulator of a pathway linking actin dynamics to loss of cell adhesion, leading to enhanced cell motility and increased invasive potential. Consistent with this, positive nuclear expression of lamin A/C in colorectal tumours is significantly correlated with poor prognosis.

Proprietary antibodies were used to determine nuclear lamin A/C expression by double blind scoring of IHC staining of >650 randomly-selected independent CRC patient samples from the Netherlands Cohort Study on Diet and Cancer. The samples were derived from a large number of centres and associated with 5-year follow-up data. Cox hazard ratio scoring indicated that patients expressing lamin A/C are twice as likely to suffer CRC-related death compared to patients lacking the biomarker ( $p=0.001$ ).

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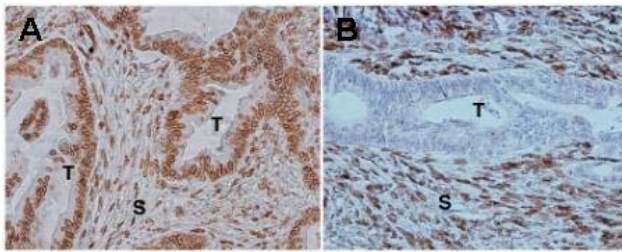


Figure 1. Staining of CRC tissue with anti-lamin A/C monoclonal antibody JoL2. JoL2 was either strongly positive (A) or negative (B) in the tumour (T). Surrounding stromal tissue (S) was always positive giving an internal positive control and demonstrating that a negative stain corresponds to absence of the antigen rather than poor staining.

Notably, based upon previous studies on this cohort, lamin A/C was the only highly significant prognostic indicator amongst other known potential indicators also assessed (including APC promoter methylation, APC truncations, lack of p53 expression and Ras activating mutations). Of 515 samples assessed in the Dukes A, B and C patient groups, the presence of lamin A/C predicted CRC-related death with 81% sensitivity.

Taken together, these data indicate that lamin A/C is a highly sensitive independent marker of a high-risk CRC population that could be used in conjunction with other markers to establish a biomarker panel to guide therapeutic strategy for CRC patients.

## Intellectual Property

CRT holds the rights to the patent family WO2007/148095, which is available for licensing together with antibody clones JoL2 and JoL4 and associated data. CRT is seeking partners for licensing or collaborative development.

## References

Willis, N.D *et al.* Lamin A/C is a risk biomarker in colorectal cancer. *PLoS One.* 2008 **3**(8):e2988

Humphries, A. & Wright, N.A. Colonic crypt organisation and tumorigenesis. *Nature Reviews Cancer.* 2008. **8**:415-424

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Mortality Hazard Plot

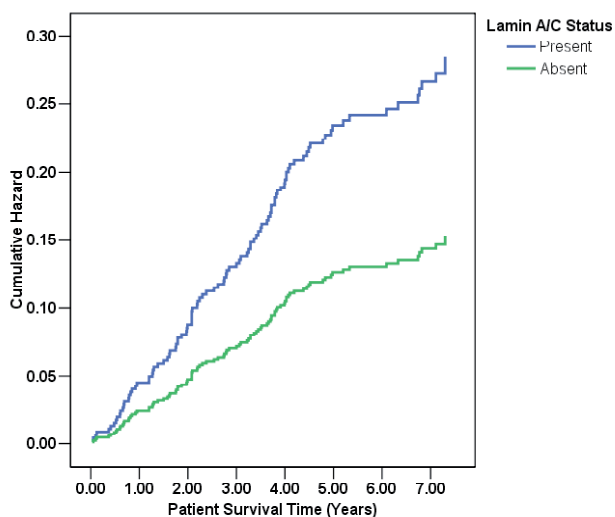


Figure 2. Kaplan-Meier plot of cumulative hazard for colorectal cancer patients in relation to lamin A/C expression