SELECTED OPPORTUNITIES IN ONCOLOGY – SOLID TUMOR

Title (BIO xxx)

DIAGNOSIS OF GIST (BIO13315)

Product factsheet

Stage:
Pre-Analytic
Validation

- **Biomarker:**
  - LIX1
- **Technology:**
  - RT-PCR
- **Sample:**
  - Biopsy
- **Information:**
  - Diagnostic
  - Risk Predisposition
  - Prognosis

- **Scientific and Clinical Rationale:**
  - Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of gastrointestinal tract. It has recently been shown that genes involved in the development and plasticity of Smooth Muscle Cells (SMCs) demonstrate abnormal expression in GISTs. Genes with higher expression at the earliest stages of stomach development were identified. This approach allowed to identify Limb Expression 1 (LIX1), a gene coding for a 281-amino acid protein with no cellular function described yet.
  - LIX1 function was investigated during digestive smooth muscle development. LIX1 is a novel marker of stomach mesenchymal progenitors and that its expression is strong and highly dynamic. LIX1 positively regulates cell proliferation and SMC determination.
- **POC:**
  - In a chick model, LIX1 expression is transient and defines Mesenchymal Progenitors, which give rise to SMCs and is required for cell differentiation and proliferation.
  - High LIX1 expression is associated with poor prognosis in patients with GIST (n=60) but not in non-GIST patients (n=255).
- **Selling points:**
  - **Priority:**
    - EP16 305 159.2 on 2016/02/11
    - PCT/EP2017/052979 on 2017/02/10
  - **Scientific Publication(s):**
    - BMC Biol, 2016 Apr 28, *McKey J. et al.*, doi: 10.1186/s12915-016-0257-2

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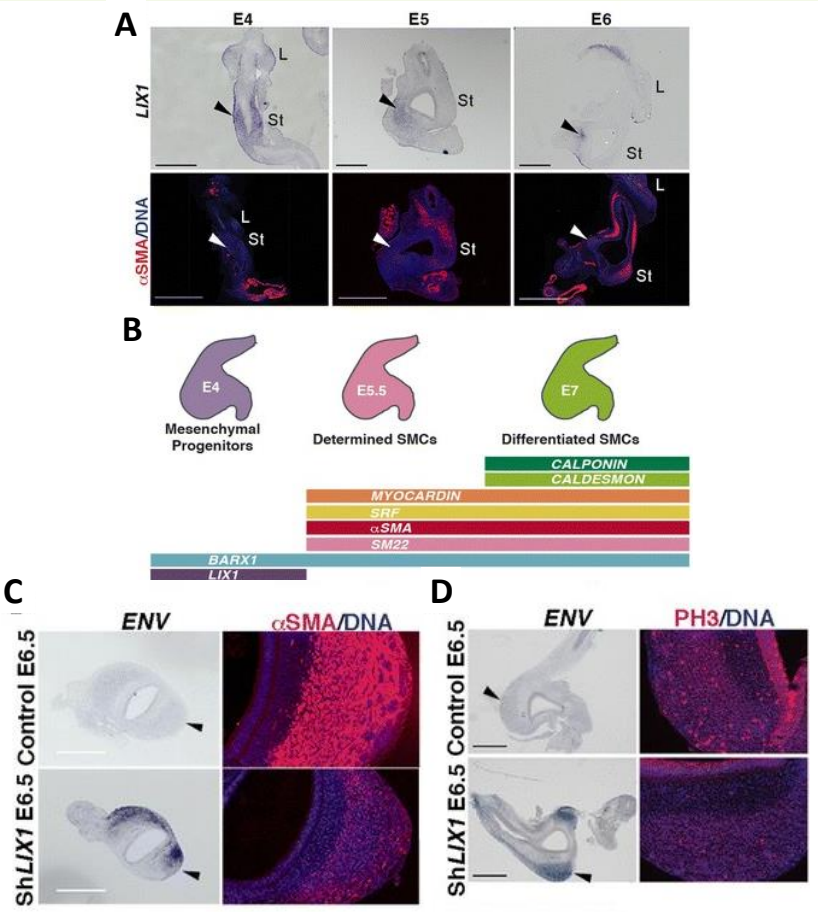
Proof of concept

LIX1 expression in the development of Smooth Muscle Cells

- **<u>Biomarker discovery:</u> LIX1 is expressed in Mesenchymal Progenitors and is required for cell differentiation and proliferation.**
  - (A) Serial longitudinal sections of E4 to E6 stomachs analysed by ISH using the LIX1 riboprobe and by immunofluorescence with anti-αSMA antibodies. Black arrowheads show the mesenchymal expression of LIX1 at these stages. White arrowheads show the absence of αSMA in the LIX1-expressing domains. L, Lung; St, Stomach.
  - (B) Cartoon illustrating the steps of stomach mesenchyme development
  - (C-D) Serial transverse sections of stomachs (with control or expressing shLIX1) analysed either by ISH using the retroviral *Envelop* (*ENV*) riboprobe, (C) by immunofluorescence with anti-αSMA antibodies or (D) anti-PH3 antibodies. Black arrowheads in the *ENV* panels indicate the area that is imaged at high power in the αSMA or PH3 panels.
  - Scale bars, 500 µm. Nuclei are visualized with Hoechst in (A), (C) and (D).



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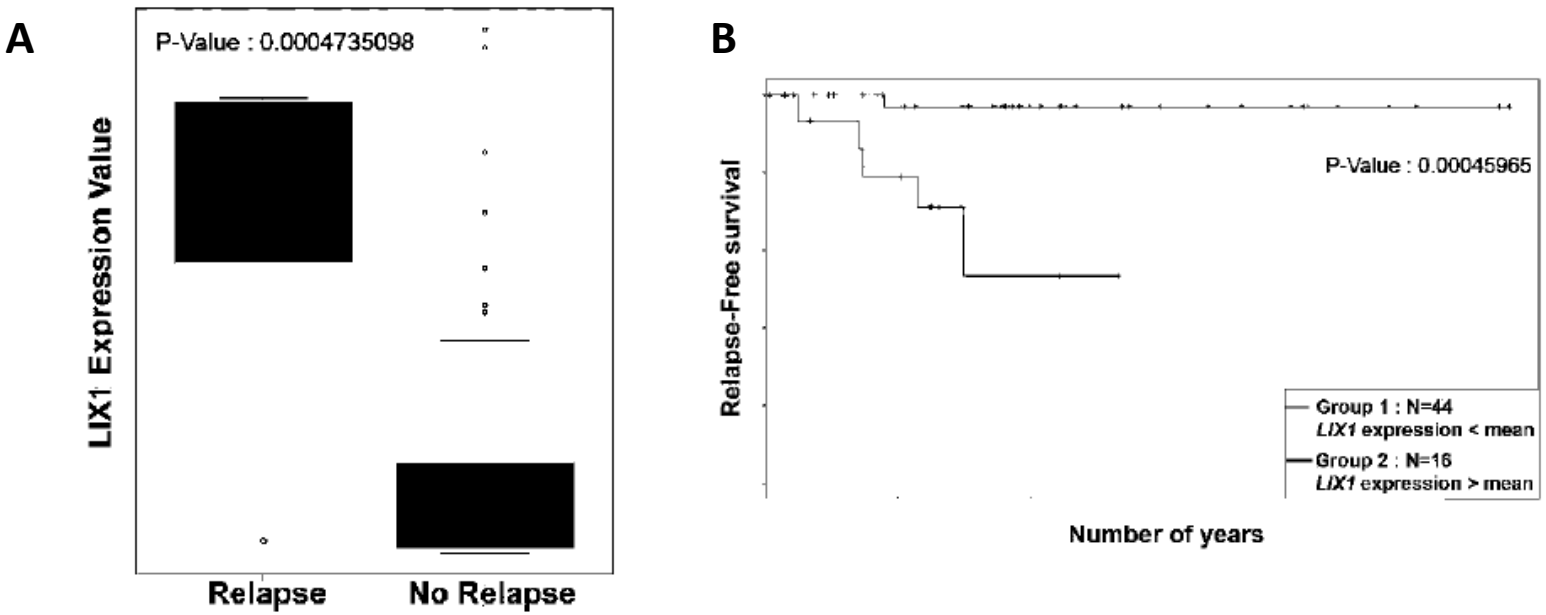
Proof of concept

- **<u>Pre-Analytic Validation:</u> High LIX1 expression is associated with poor patient prognosis in patients with GIST.**

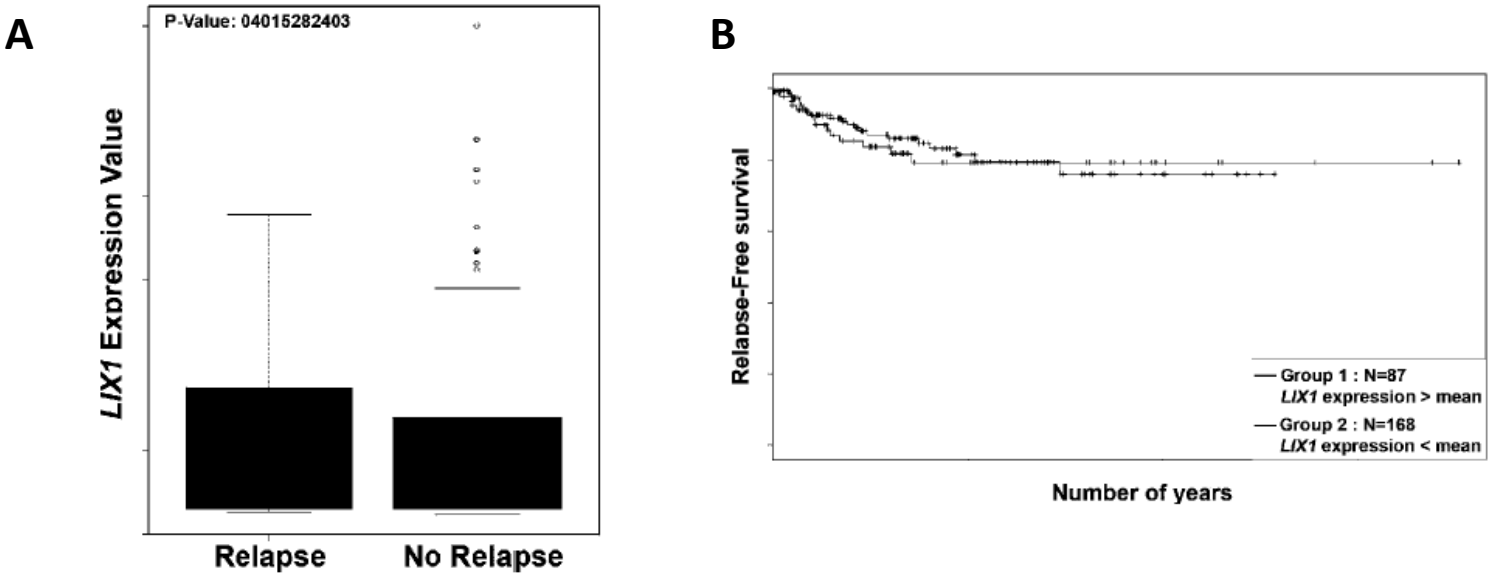


- (A) Analysis of the correlation between LIX1 expression level and relapse rates.
- (B) Relapse-free survival from initial imatinib mesylate treatment in group 1 presenting low level of LIX1 compared with group 2 presenting high level of LIX1 individuals with GIST, assessed in a univariate analysis using the Kaplan-Meier method. The log-rank test was used. SubM, submucosa; CSM, circular smooth muscle; LSM, longitudinal smooth muscle.

DIAGNOSIS OF GIST (BIO13315)

Proof of concept

- **<u>Pre-Analytic Validation:</u> High LIX1 expression is not associated with poor patient prognosis in non-GIST sarcomas.**



- (A) Correlation between LIX1 expression level in primary sarcomas with or without relapse after treatment.
- (B) Relapse-free post-treatment survival in group 1 presenting low level of LIX1 (n = 168) compared with group 2 presenting high level of LIX1 (n = 87) individuals with sarcomas, assessed in univariate analysis using the Kaplan-Meier method. The log-rank test was used.