

47th meeting of European
Pancreatic Club
Toledo, Spain, June 24-26, 2015

**Hypoexpression of Galectin-4 Inhibits Invasive
Behavior of Primary Pancreatic Adenocarcinoma Cells
And Is Associated With Modulation of Wnt/ β -catenin
Signalling And Reduced Lymph Node Metastasis**

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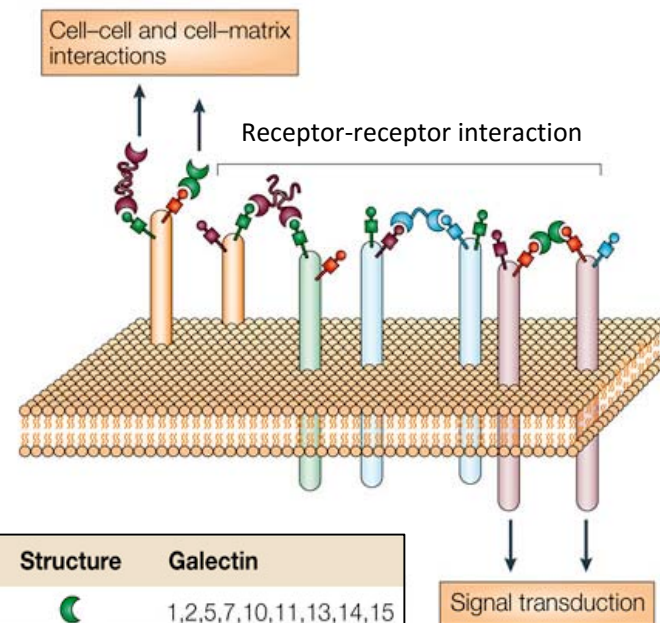
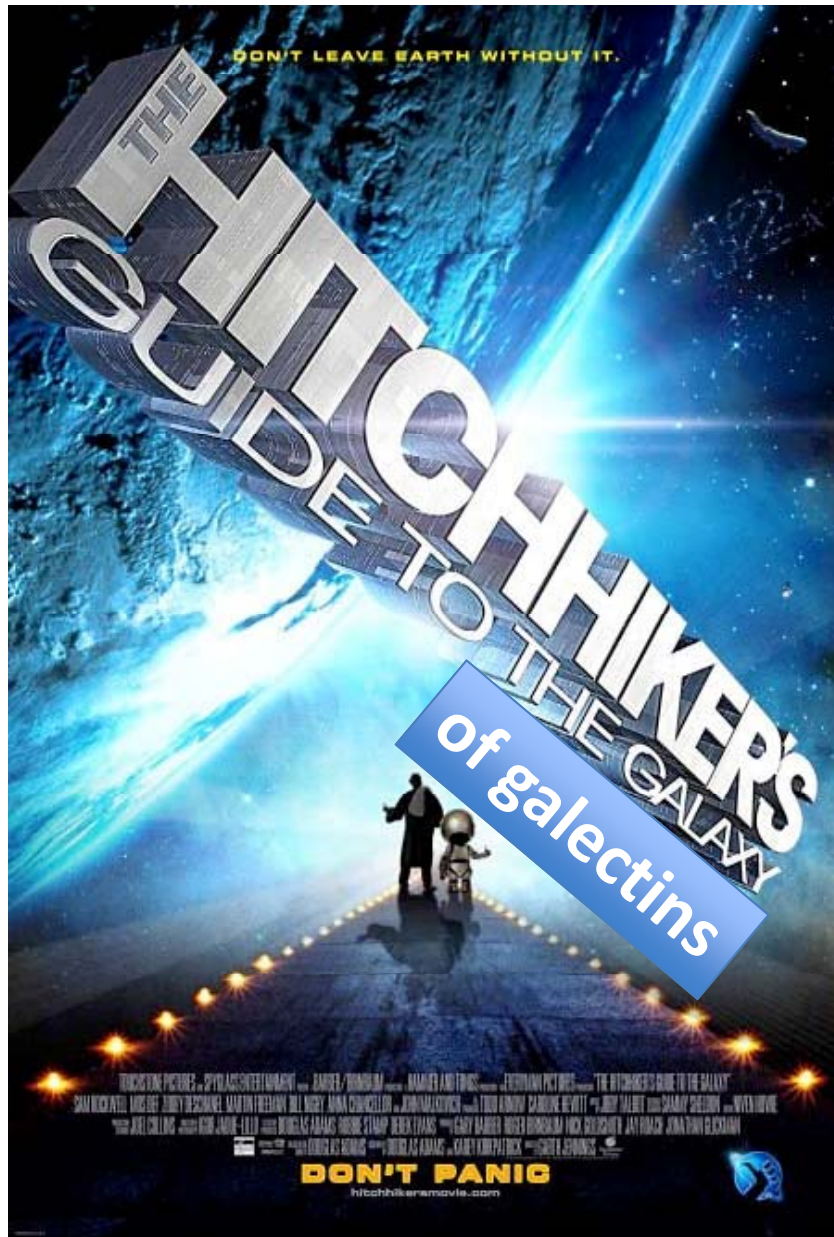
Maftouh M, Belo AI, Avan A, Funel N, et al.

Oncotarget. 2014;5(14):5335-49

Galectins

➤ carbohydrate-binding proteins that can recognize carbohydrates attached to proteins/lipids — known as glycoconjugates — on cell surfaces and extracellular matrices

➤ have many functions, including mediation of cell adhesion, cell-cell interactions, and modulation of cellular communication



Type	Structure	Galectin
One CRD		1,2,5,7,10,11,13,14,15
		3
Two-CRD		4,6,8,9,12

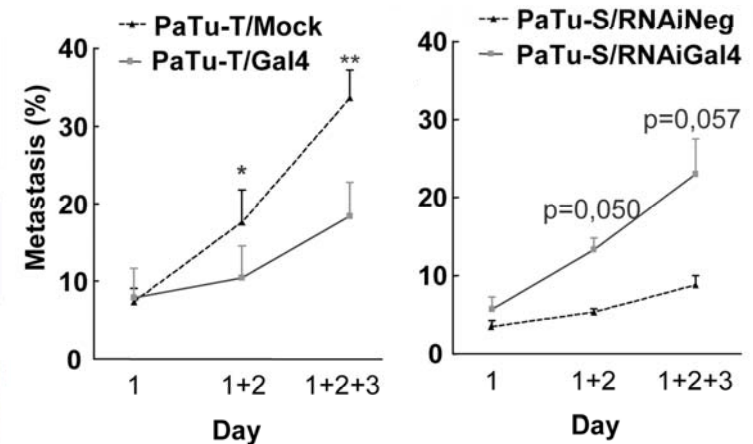
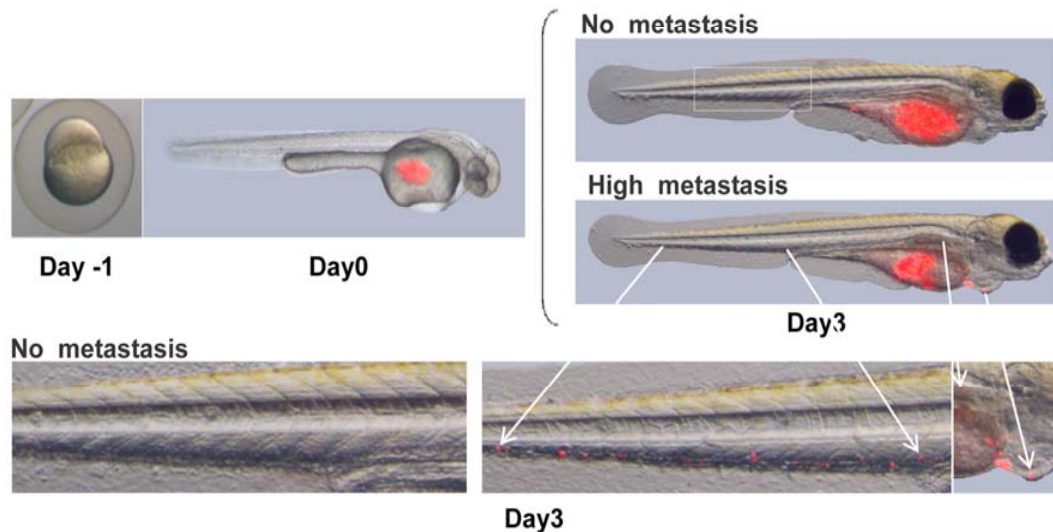
Galectin-4

➤ Gal-4 is a 323-amino acid (36 kDa) protein predominantly expressed in the luminal epithelia of the gastrointestinal tract, from the tongue to the large intestine

➤ Gal-4 shows a significantly higher expression in IPMN and in PDAC compared to normal pancreas [Bauer A et al., Pancreatology 2009]

BUT...

➤ Gal-4 expression is high in PaTu-S, which shows poor migratory properties, whereas much lower Gal-4 levels are observed in the highly metastatic cells PaTu-T



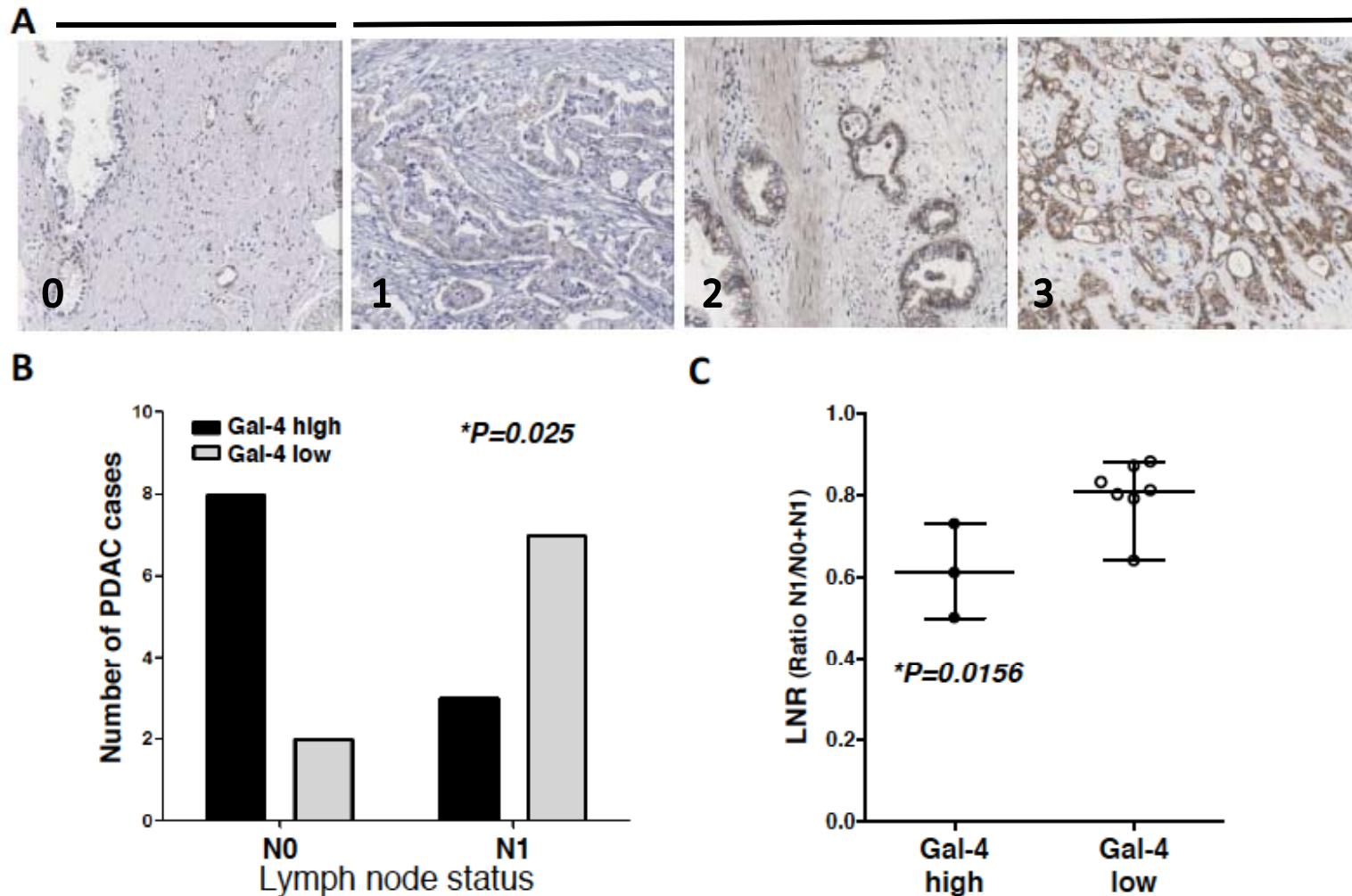
Belo et al., PLoS ONE 2013

AIMS

This study was aimed at

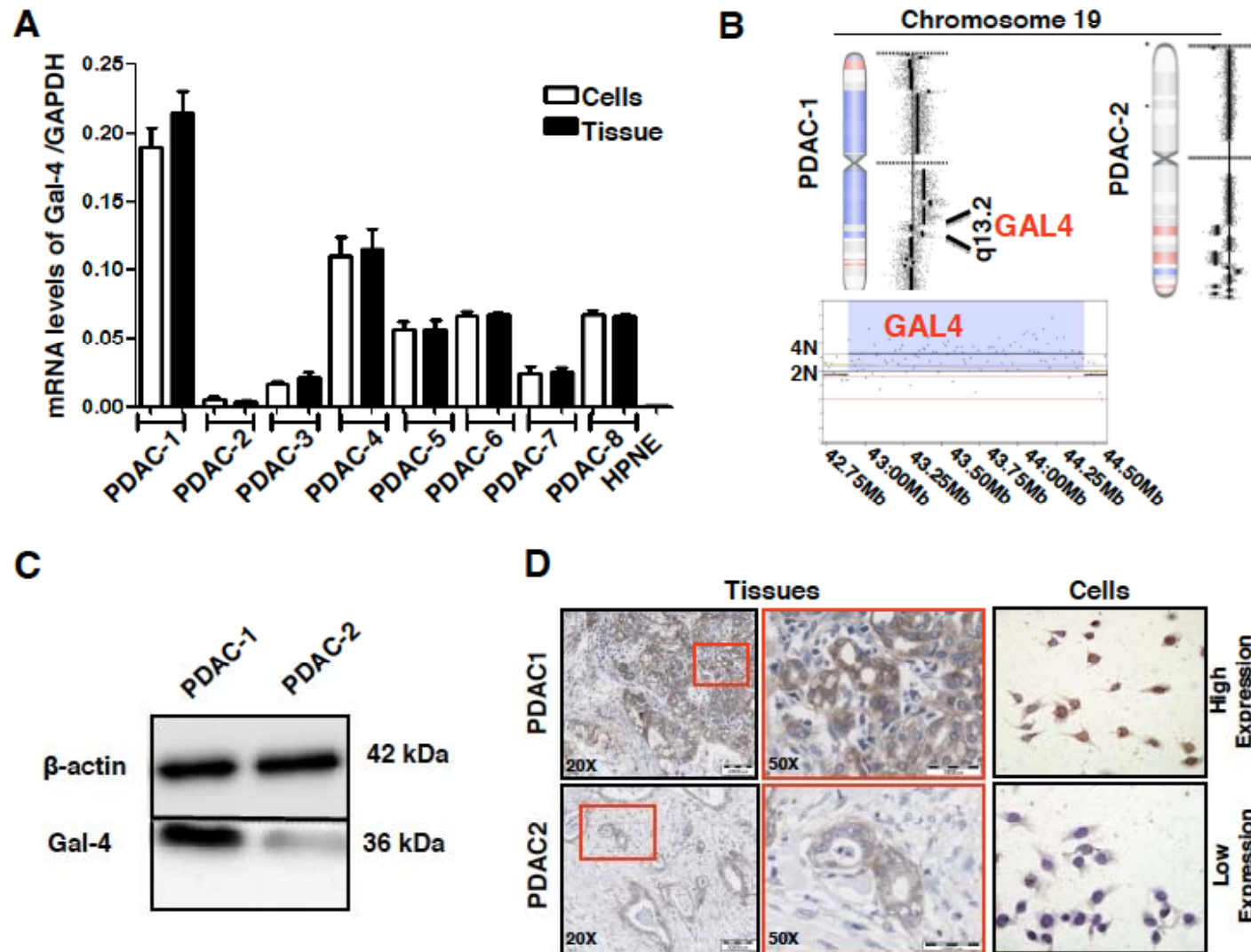
- 1) Evaluating the expression of Gal-4 in PDAC tissues selected according to their lymph node metastatic status (N0 vs. N1)**
- 2) Evaluating the role of Gal-4 in the metastatic potential of primary PDAC cells and orthotopic models**
- 1) Investigating the therapeutic potential of targeting the cross-link with the Wnt signaling pathway**

Gal-4 expression in PDAC patients



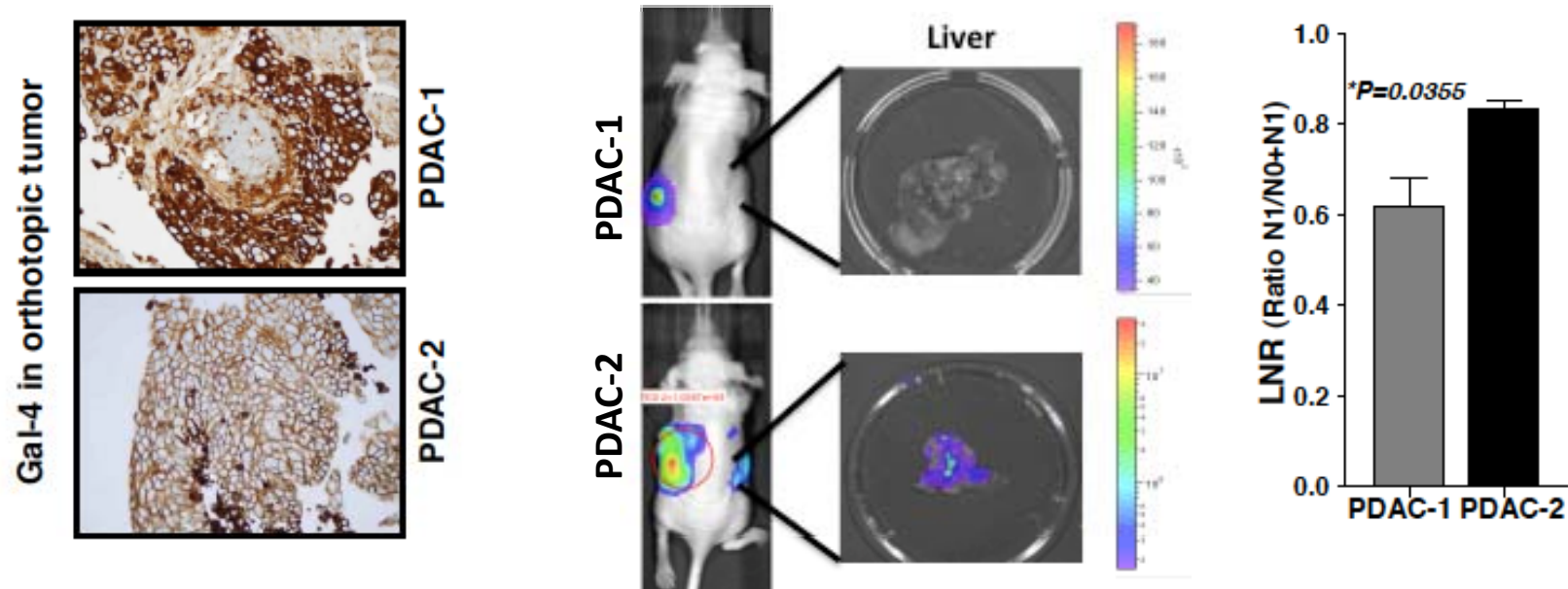
- Gal-4 expression is associated with lack of tumor invasion in the lymph nodes
- Patients with low Gal-4 expression had a significantly higher LNR than patients with high Gal-4 expression

Gal-4 expression in PDAC primary cells



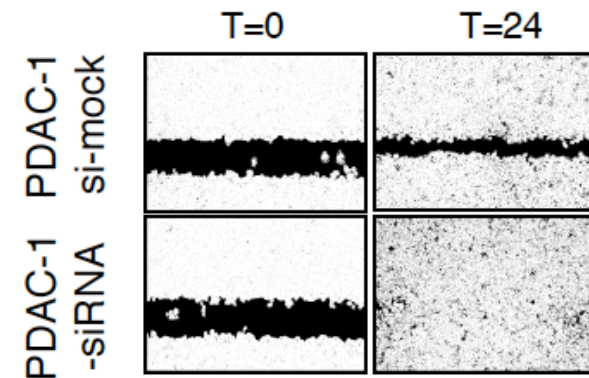
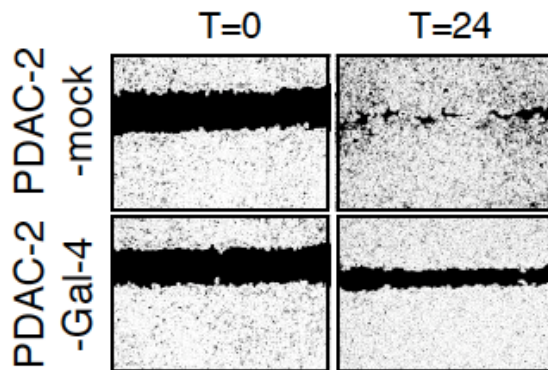
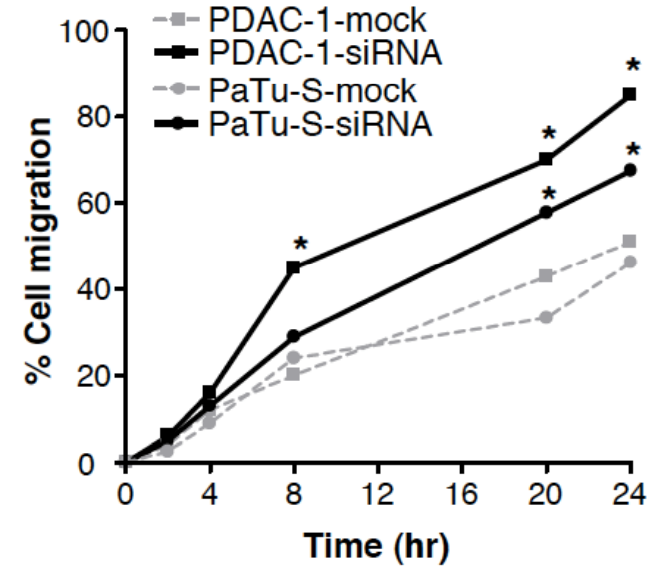
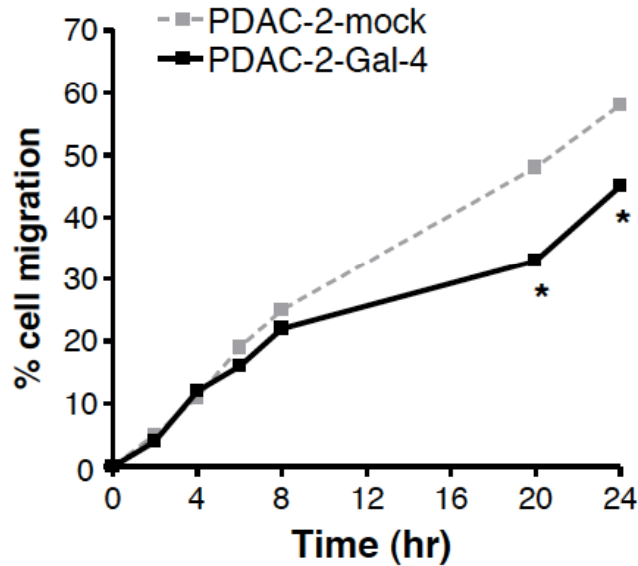
- Gal-4 is differentially expressed in primary PDAC cells, as well as in their originator tissues
- PDAC-1 had markedly higher expression of Gal-4 protein with respect to PDAC-2

Gal-4 expression in PDAC orthotopic models with differential metastatic potential



- PDAC-1 tumors showed a strong staining for Gal-4, while the PDAC-2 tumors had only a weak staining
- Macroscopic metastases were observed in all the livers of the PDAC-2 mice, while no liver metastases were detected in 33% of the mice of the PDAC-1 group
- LNR ratio in the PDAC-2 models was 1.4-fold higher than in PDAC-1

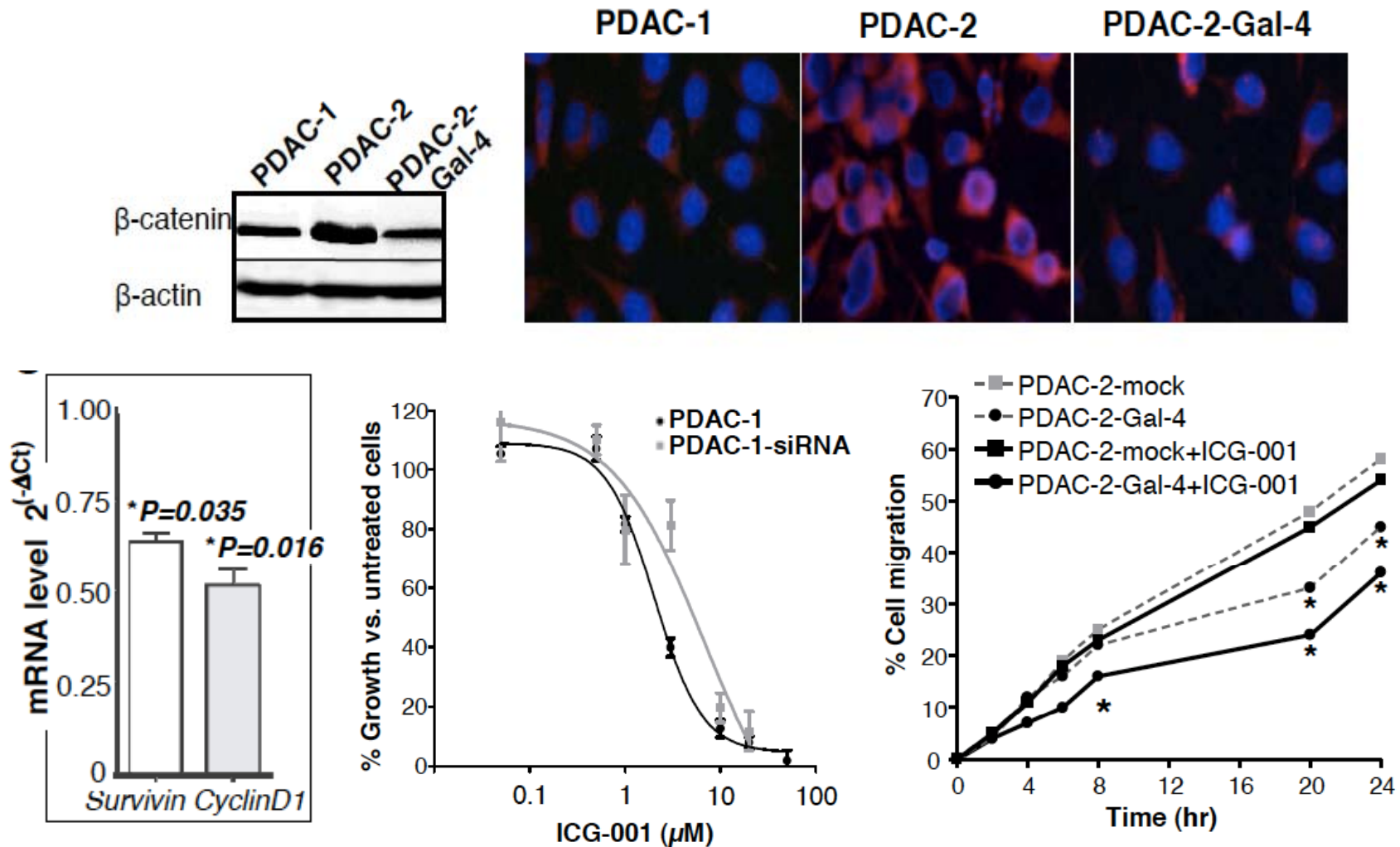
Modulation of Gal-4 expression alters the migratory and invasive behavior of PDAC cells



➤ Modulation of Gal-4 in our gain- and loss-of-function models support the role of Gal-4 in the inhibition of migration and invasion

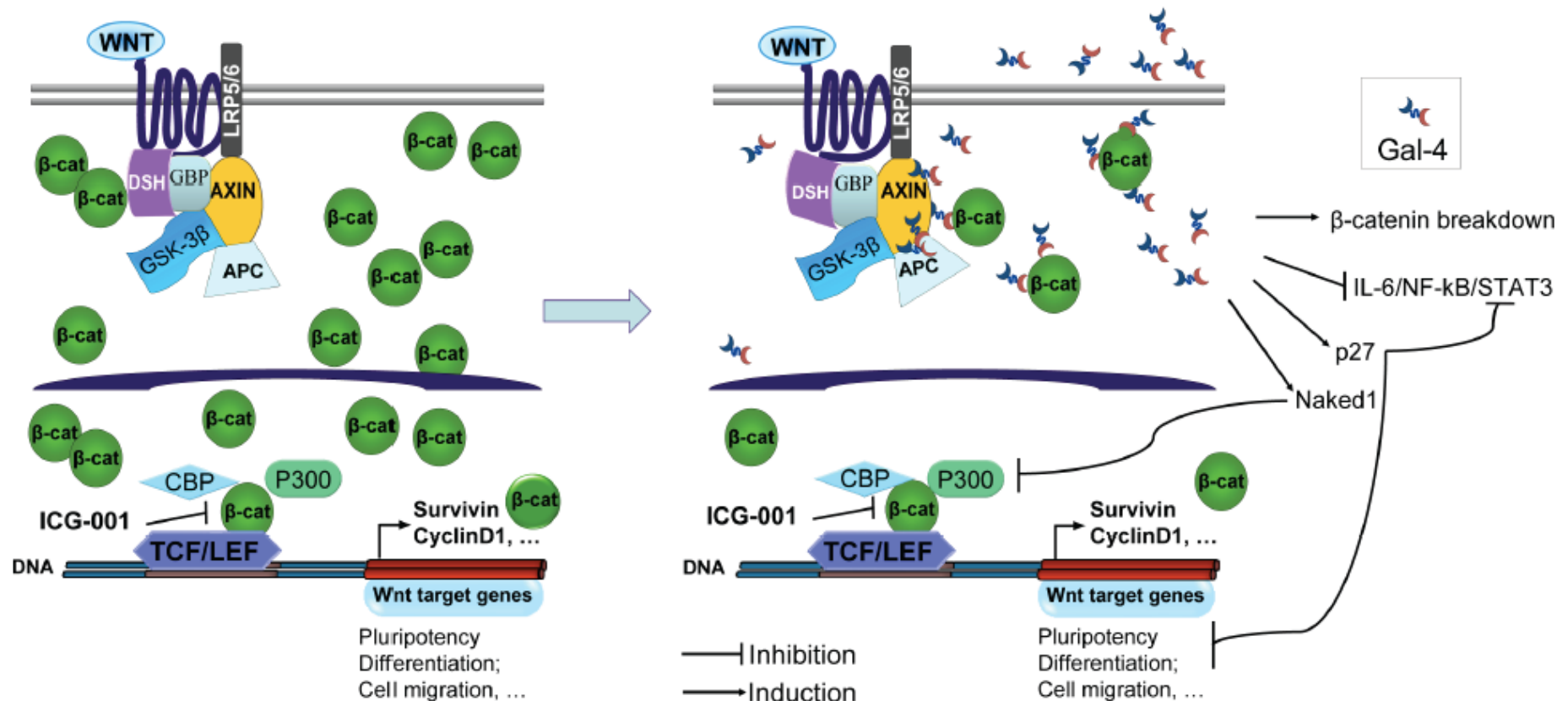
Gal-4 reduced β -catenin levels and sensitizes PDAC cells to the Wnt inhibitor ICG-001

➤ Gal-4 inhibits metastasis by down-regulation of β -catenin and Wnt signaling target genes, in colon rectal cancer [Satelli et al., Int J Cancer 2011]



Conclusions 1

- Gal-4 emerged as a novel tumor suppressor in PDAC, since elevated Gal-4 levels correlated with reduced lymph node metastasis, *in vitro* migratory/invasive behavior and *in vivo* metastasis
- Possibly, Gal-4 cross-links axin, β -cat and APC, thereby enhancing degradation of β -cat. Furthermore, Gal-4 is shown to inhibit the IL-6/NF- κ B/STAT3 pathway and to induce expression of the Wnt signaling inhibitor Naked1. Collectively, these effects of Gal-4 might contribute to reduced cell migration and sensitization to ICG-001 activity



Acknowledgements

