SELECTED OPPORTUNITIES IN NEPHROLOGY

NGAL AS A NOVEL TARGET FOR THE TREATMENT OF CHRONIC KIDNEY DISEASE (BIO10870)

BIO 10870 – NGAL AS A NOVEL TARGET FOR THE TREATMENT OF CHRONIC KIDNEY DISEASE

Product factsheet

In vivo PoC

- **Target:**
  - NGAL (lipocalin2,Lnc2)
- **Product:**
  - NGAL (Lipocalin 2, Lnc2) could be potentially targeted with an antibody or antisens
- **Application:**
  - Treatment of Chronic Kidney Disease (CKD)
- **Technology:**
  - Antisens (currently in development) or blocking antibody
- **Rational / POC:**
  - The severity of renal lesions after nephron reduction varied substantially among mouse strains and required activation of EGFR.
  - Lipocalin 2 (Lcn2, also known as neutrophil gelatinase–associated lipocalin [NGAL]), the most highly upregulated gene in a mouse strain which develop severe renal lesions, is not simply a marker of renal lesions, but also an active player in disease progression.
  - The severity of renal lesions was dramatically reduced in Lcn2–/– mice.
  - Lcn2 expression increases upon EGFR activation and Lcn2 mediates its mitogenic effect during renal deterioration.
  - EGFR inhibition prevented Lcn2 upregulation and lesion development in mice expressing a dominant negative EGFR isoform. Cell proliferation was dramatically reduced in Lcn2–/– mice.
  - LCN2 is increased particularly in patients who rapidly progressed to end-stage renal failure.
- **Patent and publication:**
  - Viau A. et al., J Clin Invest. 2010 Nov;120(11):4065-76. doi: 10.1172/JCI42004.
  - Priority date: EP10306077.8 filed on October 1st, 2010 for “METHODS FOR PREDICTING THE PROGRESSION AND TREATING A CHRONIC KIDNEY DISEASE IN A PATIENT”

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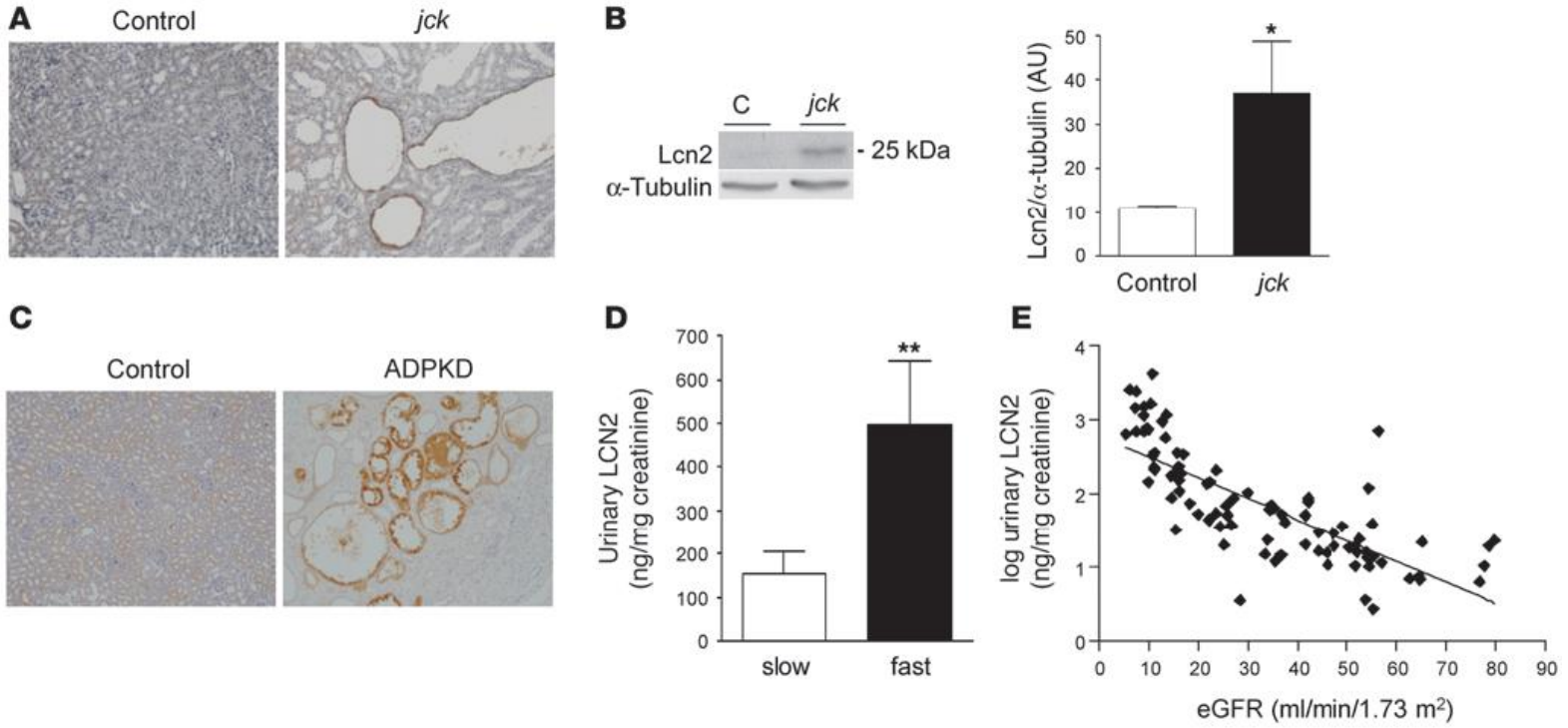
Proof of Concept

Lcn2 is overexpressed in polycystic kidney disease in mice and humans and correlates with CKD progression



(A and B) Lcn2 expression evaluated by (A) immunohistochemistry and (B) Western blot in kidneys from wild-type (control) and jck mice, 3 weeks after birth. (C) LCN2 staining in kidneys from controls (n = 9) and patients with ADPKD (n = 9). (D) Urinary LCN2 excretion in patients with slow progression as compared with fast progressors toward ESRF. (E) Urinary LCN2 excretion inversely correlates with eGFR in patients with ADPKD (n = 87 for ADPKD patients).

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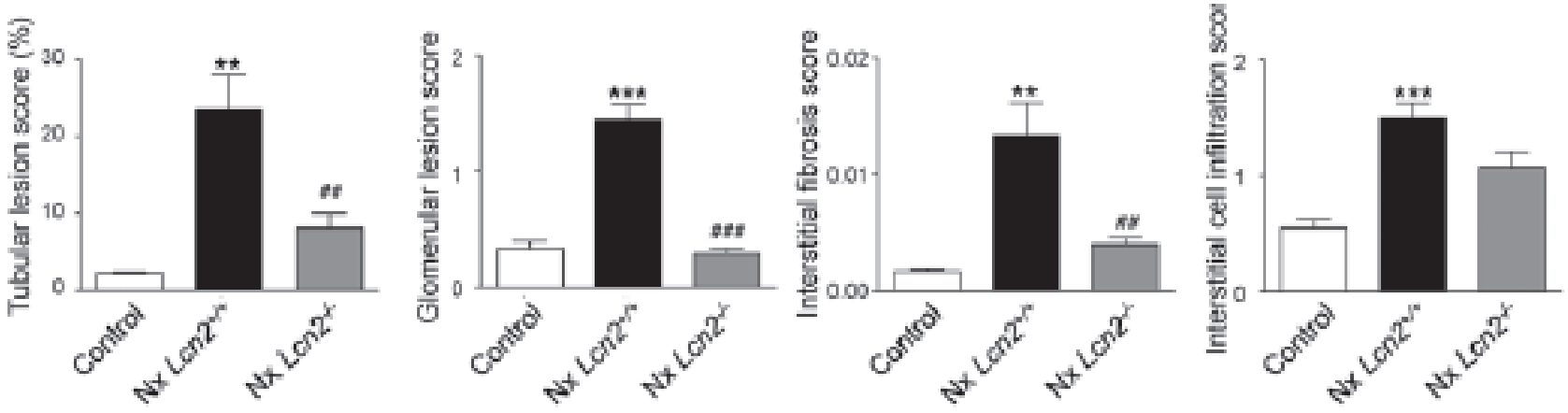
Proof of Concept

Lcn2 deficiency protects from the development of renal lesions



Lesion scores of kidneys from control, 75% Nx Lcn2+/+, and Lcn2–/– FVB/N mice, 2 months after nephron reduction.

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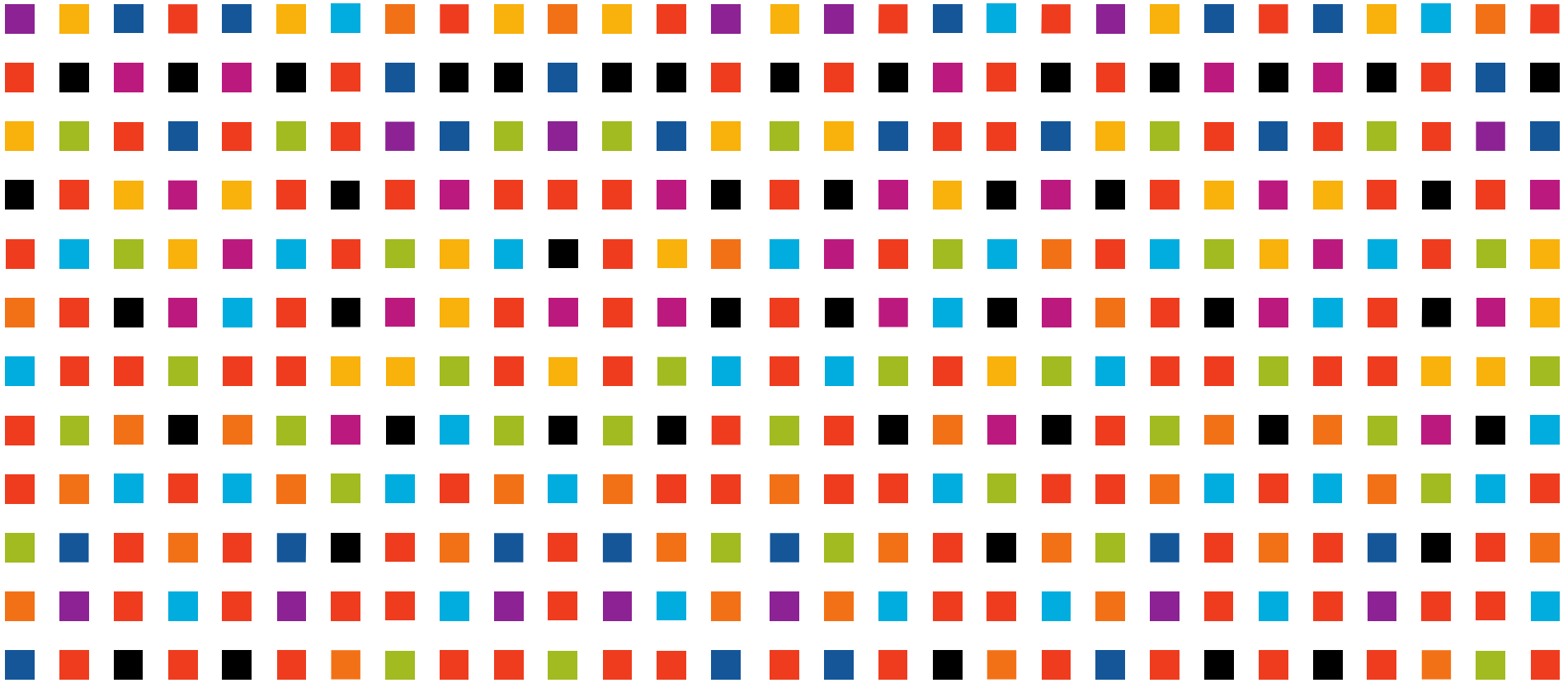

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