SELECTED OPPORTUNITIES IN RARE KIDNEY DISEASES

METHODS FOR THE PREVENTION AND THE TREATMENT OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (BIO 13363)

BIO13363 - METHODS FOR THE PREVENTION AND THE TREATMENT OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

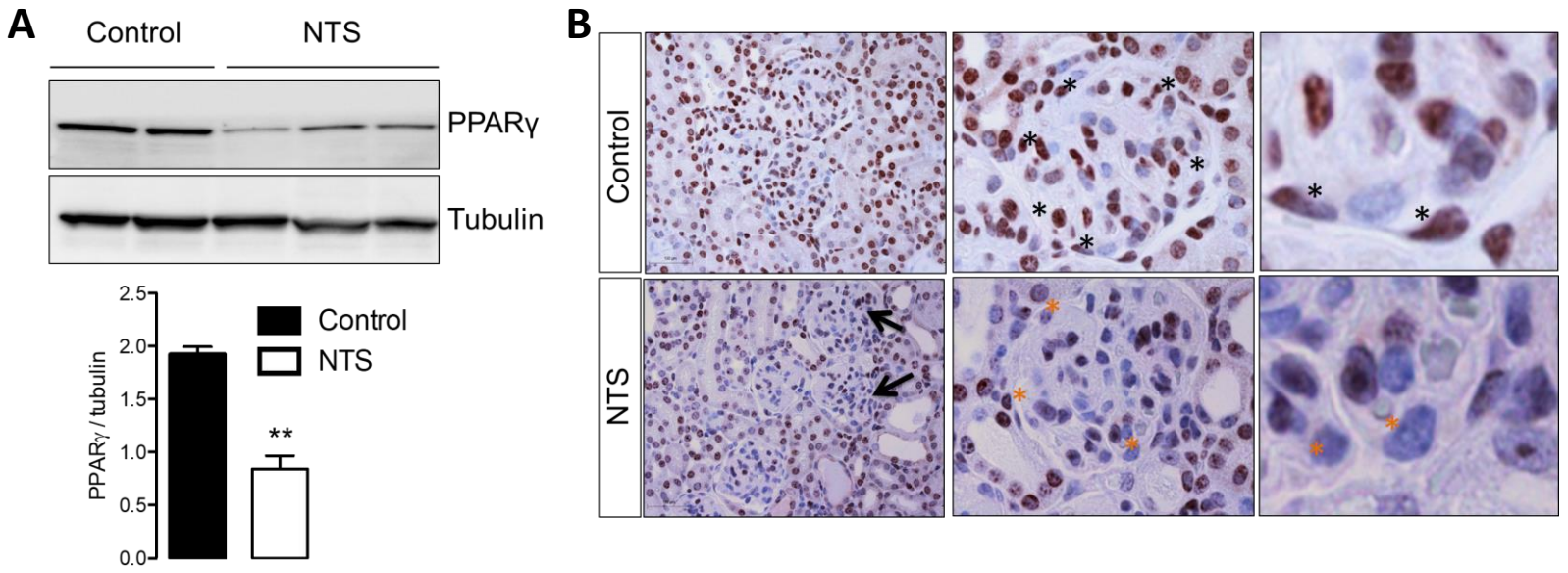
Product factsheet

PoC in vivo

- **Target:**
  - Peroxisome proliferator-activated receptor γ (PPARγ)
- **Product:**
  - PPARγ agonist (Pioglitazone)
- **Application:**
  - Necrotizing and Crescentic Rapidly Progressive GlomeruloNephritis (RPGN)
- **Technology:**
  - Small molecule
- **Rational / POC:**
  - RPGN is a life-threatening syndrome characterized by a rapid loss of renal function. Evidence suggests that podocyte expression of the transcription factor PPARγ may prevent podocyte injury;
  - There is a loss in PPARγ abundance and transcriptional activity in glomerular podocytes in experimental RPGN. Blunted expression of PPARγ in podocyte nuclei was also found in kidneys from patients diagnosed with crescentic GN;
  - Podocyte-specific Pparγ gene targeting accentuated glomerular damage, with increased urinary loss of albumin and severe kidney failure;
  - PPARγ gain of function approach with pioglitazone treatment improves glomerular structure and function in experimental RPGN.
- **Patent and publication:**
  - WO2016071727: Methods for the prevention and the treatment of rapidly progressive glomerulonephritis
  - Nuclear Factor Erythroid 2-Related Factor 2 Drives Podocyte-Specific Expression of Peroxisome Proliferator-Activated Receptor γ Essential for Resistance to Crescentic GN. Henrique et al., J Am Soc Nephrol. 2016 Jan;27(1):172-88

Proof of concept

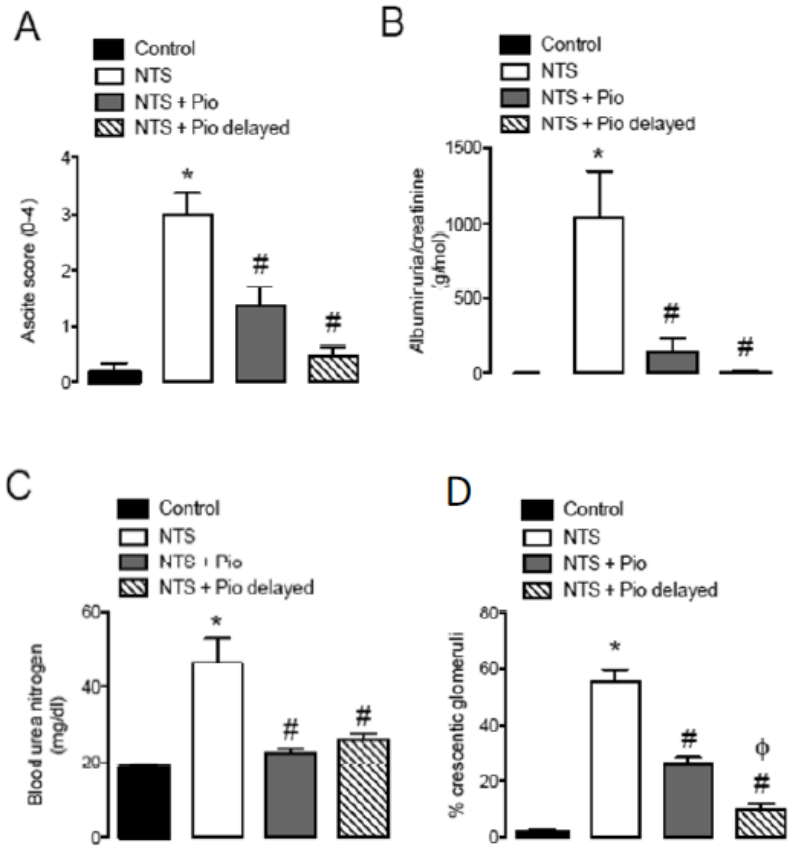
Decrease in glomerular PPARγ expression during experimental RPGN



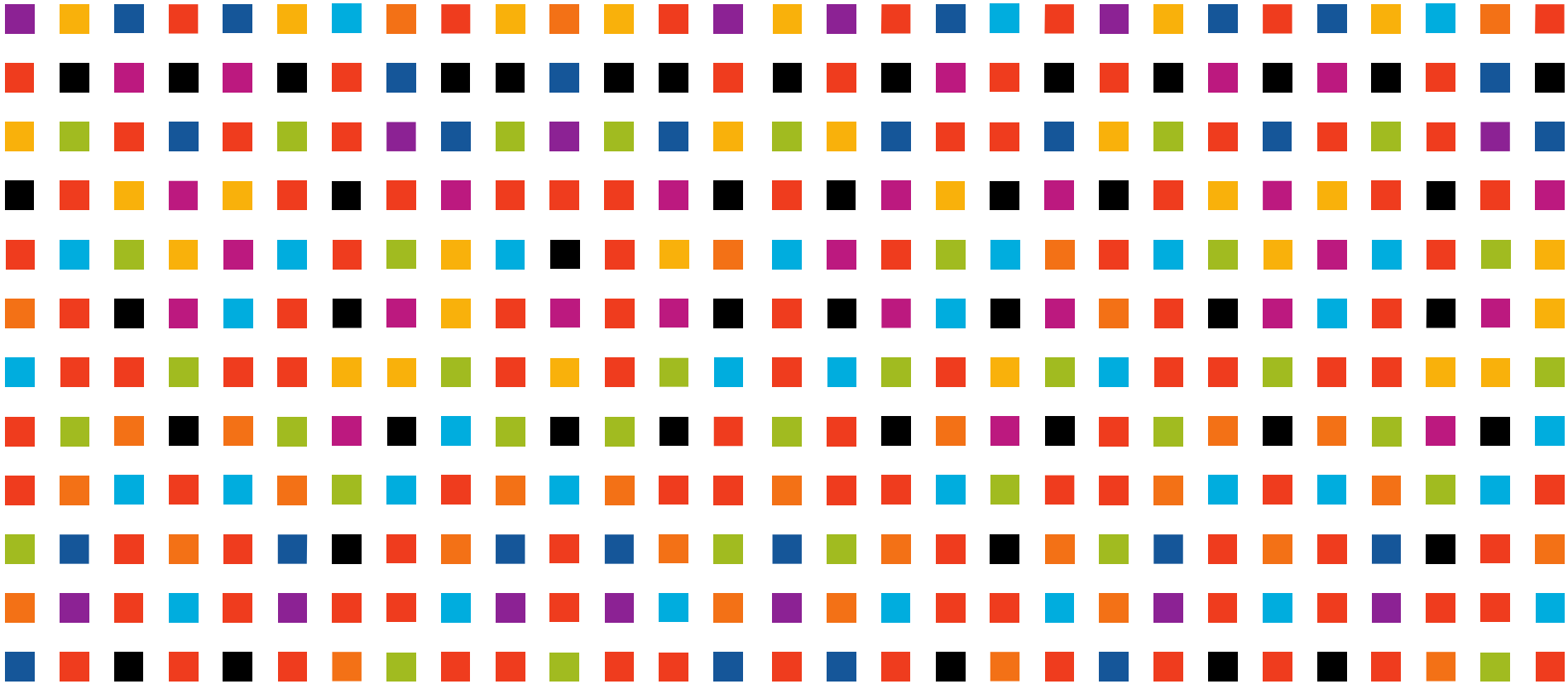
A *Western blot analysis of PPARγ expression in isolated glomeruli from control or NTS-challenged mice (NTS) mice. At day 10 after NTS injection, we show a decrease in glomerular PPARγ expression.* ***B*** *Immunostaining of PPARγ in kidney sections from control or or NTS-challenged mice (NTS) mice. Cresecent formations are indicated by black arrows. The black star (*) show positive staining and orange star (*) negative staining. Data demonstrates a decrease in PPARγ expression in podocytes during experimental RPGN.*

Proof of concept

Pioglitazone treatment improves glomerular structure and function in crescentic glomerulonephritis



(A) *Ascites score as index of albumin plasma loss and water and sodium retention. Ascites were quantified with a five-point scale (0-4) on the day mice were killed.* ***(B)*** *Urinary albumin excretion rates* ***(C)*** *and blood urea nitrogen concentration at day 10 after NTS injection in non-injected mice (control), NTSchallenged mice (NTS) or NTS-challenged mice treated with pioglitazone started in same time of NTS (NTS + Pio) or in a delayed manner (NTS + Pio delayed).* ***(D)*** *Proportion of crescentic glomeruli in groups of mice as in B. Values are means ± sem of 8-12 mice per group, of two independent experiments. * P<0.05 vs. control mice, # P<0.05 vs. NTS-challenged mice (NTS), Φ P<0.05 vs. NTS + Pio.*



AYMERIC.EMPEREUR@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr