SELECTED OPPORTUNITIES IN TRANSPLANTATION

ANTAGONISTS OF IL-33 FOR USE IN METHODS FOR PREVENTING ISCHEMIA REPERFUSION INJURY IN AN ORGAN (BIO 17218)

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Product factsheet

PoC in vivo

- **Target:**
  - IL-33
- **Product:**
  - IL-33 antagonist
- **Application:**
  - Ischemia reperfusion injury (main indication: renal transplantation)
- **Technology:**
  - Antibody
- **Rational / POC:**
  - Inflammation is a prominent feature of ischemia-reperfusion injury (IRI) characterized by leukocyte infiltration and renal tubular injury.
  - The nuclear alarmin interleukin (IL)-33 is constitutively expressed throughout the healthy kidney and concentrated in peritubular and periglomerular spaces, mainly by microvascular endothelial cells. IL-33 is released immediately from kidney tissue during IRI.
  - IL-33 is an important and early mediator of innate immune response after experimental kidney ischemia-reperfusion in mice.
  - In mice lacking IL-33 ($IL\text{-}33^{Gt/Gt}$), ischemia-reperfusion-induced renal injury is reduced.
- **Patent and publication:**
  - PCT/EP2019/051738: ANTAGONISTS OF IL-33 FOR USE IN METHODS FOR PREVENTING ISCHEMIA REPERFUSION INJURY IN AN ORGAN
  - *Endogenous IL-33 Contributes to Kidney Ischemia-Reperfusion Injury as an Alarmin*. Ferhat M et al., J Am Soc Nephrol. 2018

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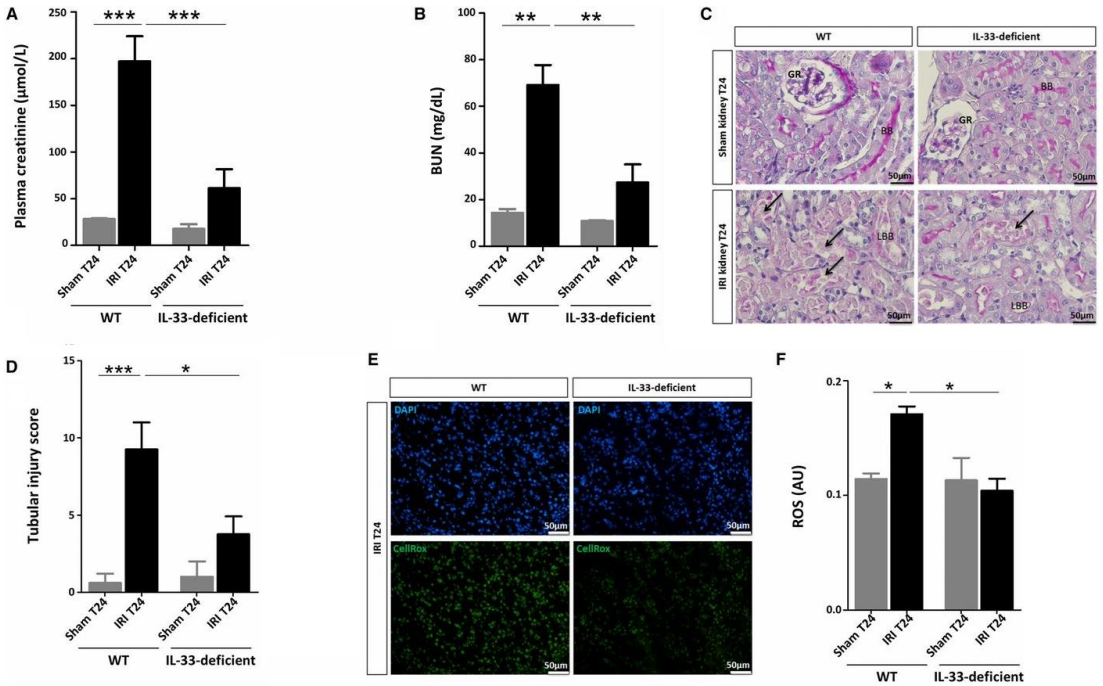
Proof of concept

Mice Lacking IL-33 or Its Specific Receptor ST2 Are Protected against IRI



WT and IL-33Gt/Gt (IL-33–deficient) mice were subjected to sham surgery (Sham) or 32 minutes of unilateral ischemia (IRI) after contralateral nephrectomy (Ctr). After 24 hours (T24) of reperfusion, kidneys and peripheral blood were obtained (five to eight animals per group). (A–D) AKI changes are attenuated in IL-33–deficient mice. IL-33–deficient mice exhibited decreased (A) blood creatinine and(B) BUN levels. (C and D) Tubulointerstitial damage was attenuated in IL-33–deficient mice compared with WT mice. (C) Representative tissue samples for tubular injury assessed with periodic acid–Schiff staining. Sham-operated WT and IL-33–deficient mice exhibited normal tubular structure with intact brush borders (BBs). After IRI, kidneys from WT mice displayed extensive tubular necrosis and loss of brush border (LBB). Arrows indicate extensive tubular necrosis and cast formation. These changes were markedly reduced in IL-33–deficient mice. Arrows indicate ATN. GR, glomerular. (D) Tubular injury scores (five to eight mice per group). (E and F) IRI-induced oxidative stress generation is attenuated in IL-33–deficient mice. ROS production in renal tissue from WT and IL-33–deficient mice was measured using the fluorogenic probe called CellROX Green Reagent. (E) Images are representative of three animals for each group. CellROX Green Reagent was weakly fluorescent in Sham kidneys (not shown) and exhibited green fluorescence T24 post-IRI in WT mice but not in IL-33–deficient mice. (F) Quantification of CellROX fluorescence intensity (three animals per group).

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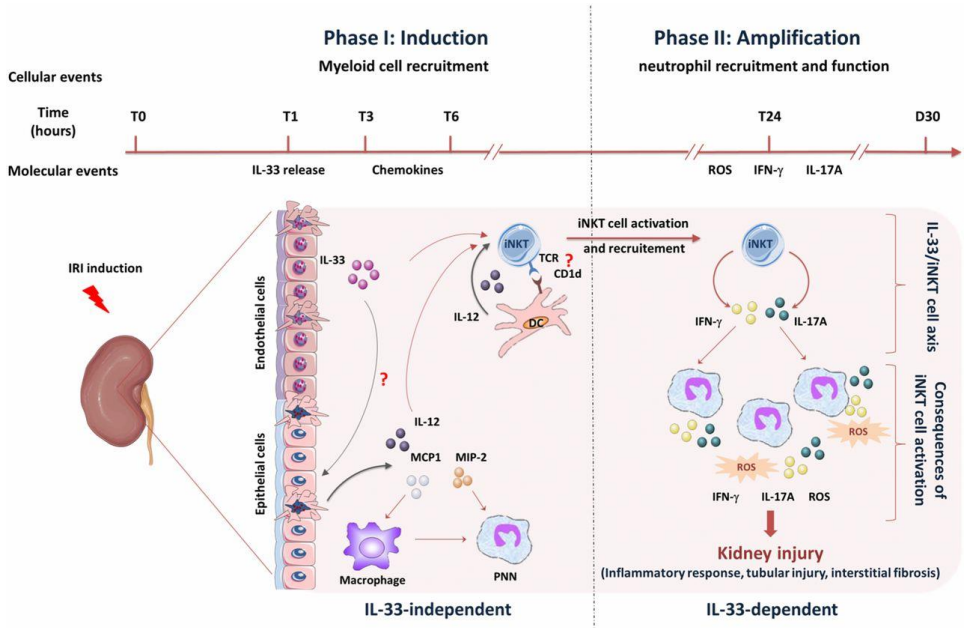
Proof of concept

Endogenous IL-33 contributes to kidney ischemia-reperfusion injury as an alarmin by promoting ST2-expressing cell recruitment.



Within 3–6 hours post-IRI induction, monocyte/macrophage and neutrophil kidney infiltration occurs. Despite the concomitant IL-33 release by injured microvascular endothelial cells, this early phase of innate inflammatory response is IL-33 independent (left side) and may result from chemokine release and action, We postulate that, in this early phase, the production of proinflammatory mediators (cytokines and chemokines) by damaged kidney cells and resident immune cells is sufficient to initiate the recruitment of neutrophils and monocytes/macrophages. Within 6–24 hours post-IRI induction, iNKT cell recruitment and activation occur in an IL-33–dependent (right side) manner. Mechanistically, this phenomenon could involve IL-1247,49–51 and CD1d-dependent presentation of self-ligands31 by myeloid DC, of which of the recruitment depends on IL-33. We postulate that TCR engagement and IL-12 do not provide sufficient stimulation during IRI for effective activation and recruitment of iNKT cells and that IL-33 acts as a requisite coplayer leading to complete activation and recruitment of these cells. During this late phase, IFN-γ/IL-17A–expressing iNKT cells amplify monocyte/macrophage and neutrophil recruitment and promote their proinflammatory cytokine production. Despite discordant results in earlier studies, it is now generally accepted that neutrophils play a direct and deleterious role in kidney IRI,44–46 supporting the view that their IL-33/iNKT cell–dependent recruitment results in severe acute tubular injury and ultimately, interstitial fibrosis. Lastly, IL-33, other than its immune-dependent actions, can also target proximal tubule epithelial cells to produce inflammatory mediators. PNN, polynuclear neutrophil.

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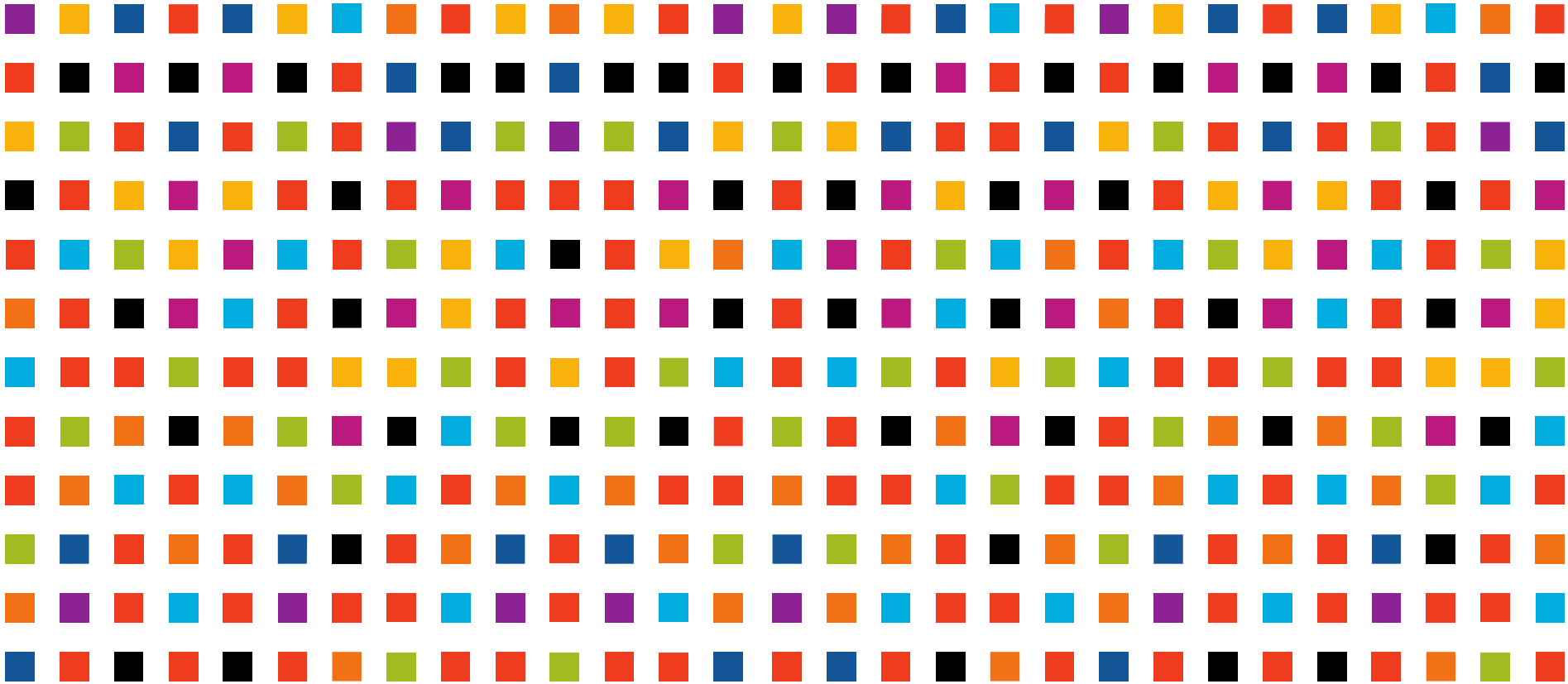
Business Opportunity

- **Collaboration/Licensing**:
  - Collaborate with an INSERM team specialized in your therapeutic area.
  - Develop your Renal Transplantation Drug Pipeline.
- **Team:**
  - Work with Herbelin team, part of IRTOMIT lab("Ischémie Reperfusion en Transplantation d'Organes: Mécanismes et Innovations Thérapeutiques").
  - http://irtomit.labo.univ-poitiers.fr/



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