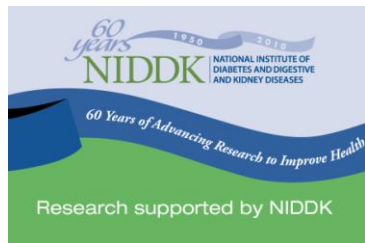
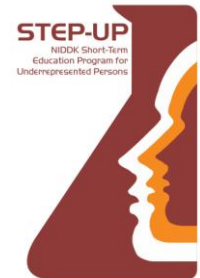


# *Over-Activation of Hypoxia-Inducible Transcription Factor 1 alpha (HIF)-1 $\alpha$ by Chronic Hypoxia Mediates Chronic Ischemic Renal Injury*



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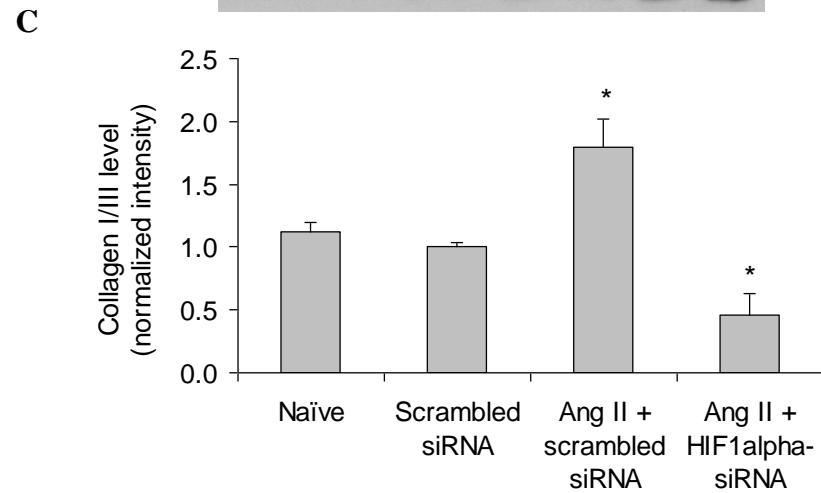
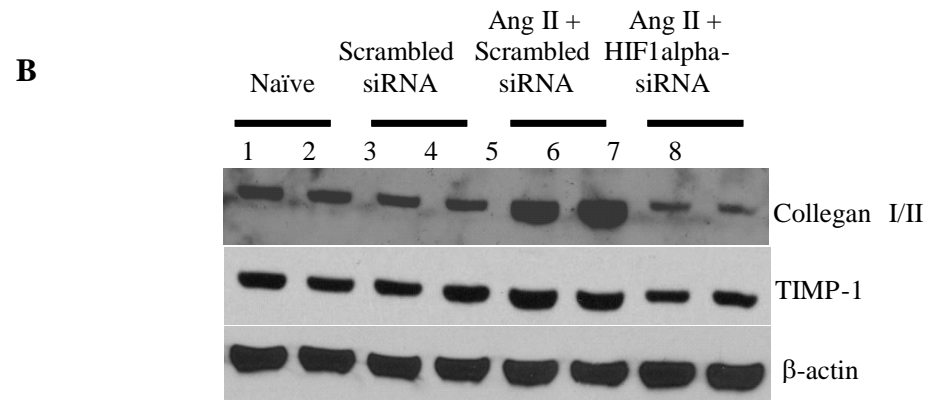
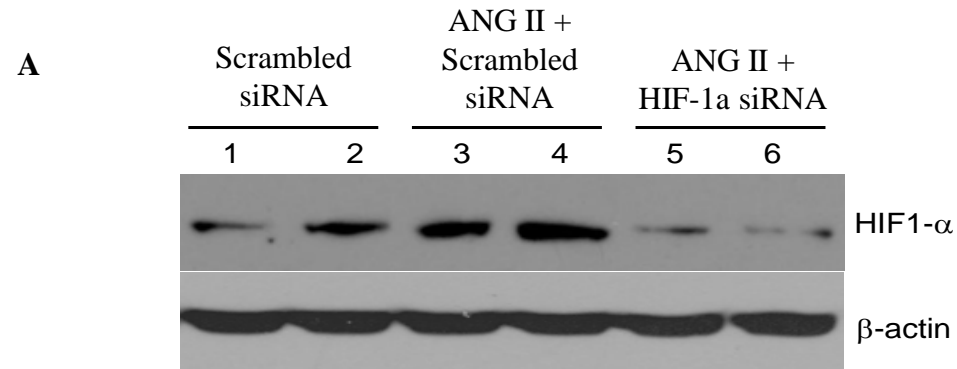
Short-term Educator Program for Underrepresented Persons (STEP-UP)  
Mentors: Dr. Pin-Lan Li and Dr. Ningjun Li

# Background

- Once the renal damage reaches a certain threshold, the progression of chronic renal disease is consistent and irreversible.
  - Ultimately leads to fibrosis.
  - Mechanisms are not yet known.
- According to the United States Renal Data System:
  - Total Medicare spending in 2006 - nearly \$355 billion
  - End Stage Renal Disease (ESRD) cost \$23 billion.
- Need efficient therapeutic strategies to reverse or prevent the progress of chronic renal injury.

# Background

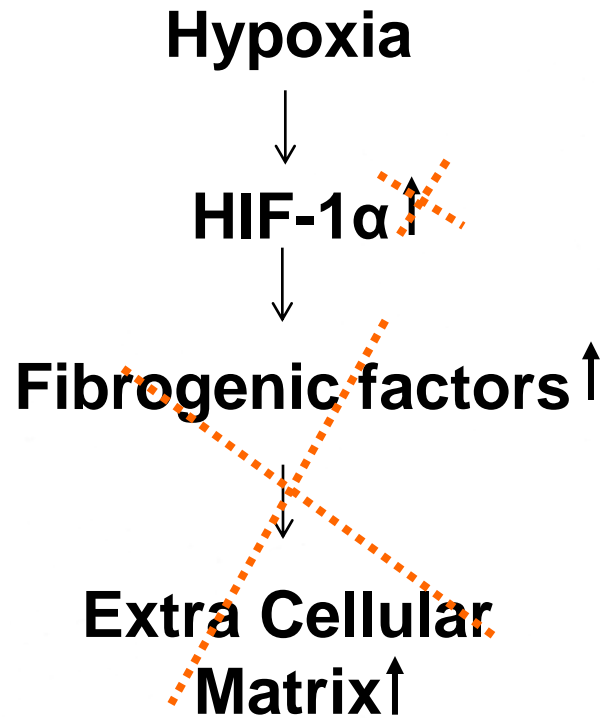
- **Hypoxia-inducible transcription factor 1 alpha (HIF-1 $\alpha$ ).**
  - Transcription factor.
  - Extremely prevalent in the kidney.
  - Hypoxia detected in all kinds of chronic renal diseases.
  - HIF-1 $\alpha$  is up-regulated in different chronic renal diseases.
  - Activation of HIF-1 $\alpha$  stimulates the fibrotic factors.



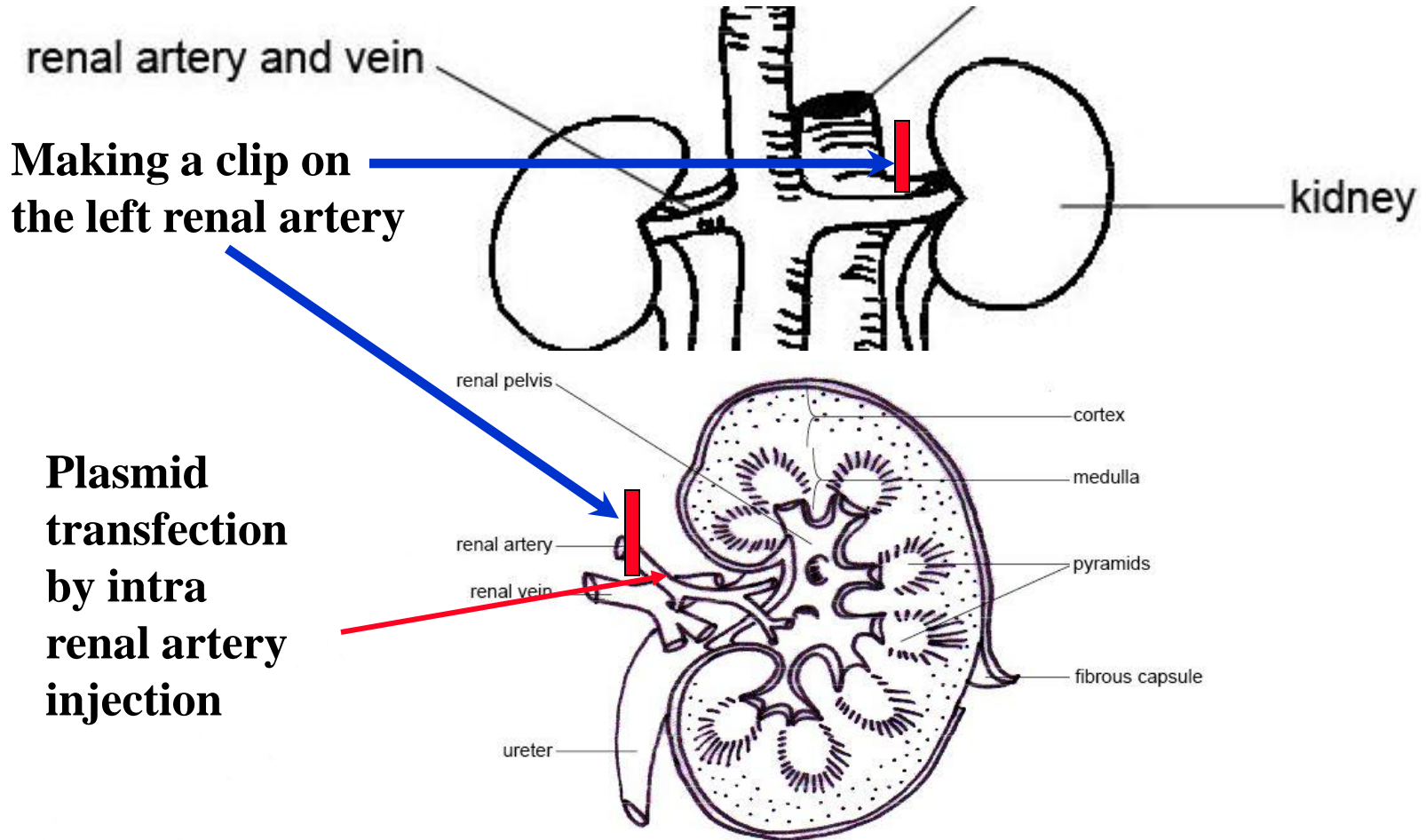
# Background

- Chronic hypoxia is possibly responsible for the over-activation of HIF-1 $\alpha$  in chronic kidney diseases.
- HIF-1 $\alpha$  may be a pathogenic factor that mediates chronic renal injury.
- At present, no direct evidence showing the contributing role of HIF-1 $\alpha$  in this process.
- Therefore, in the present study we use 2 kidneys 1-clip rat as a chronic renal ischemia model to test our hypothesis, which is whether HIF-1 $\alpha$  is increased in clipped kidneys and whether HIF-1 $\alpha$  shRNA blocks renal injury .

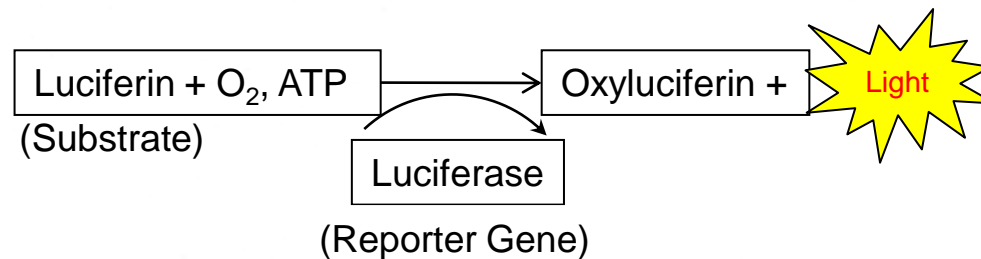
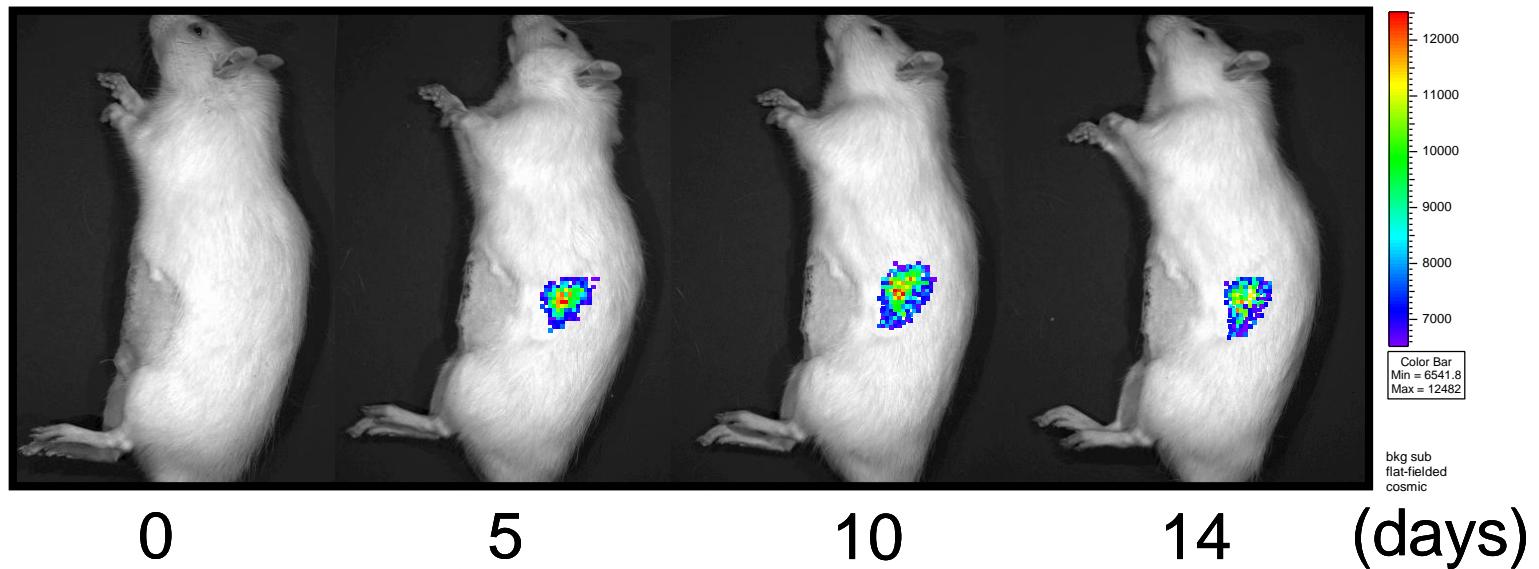
# Hypothesis



# Animal Model

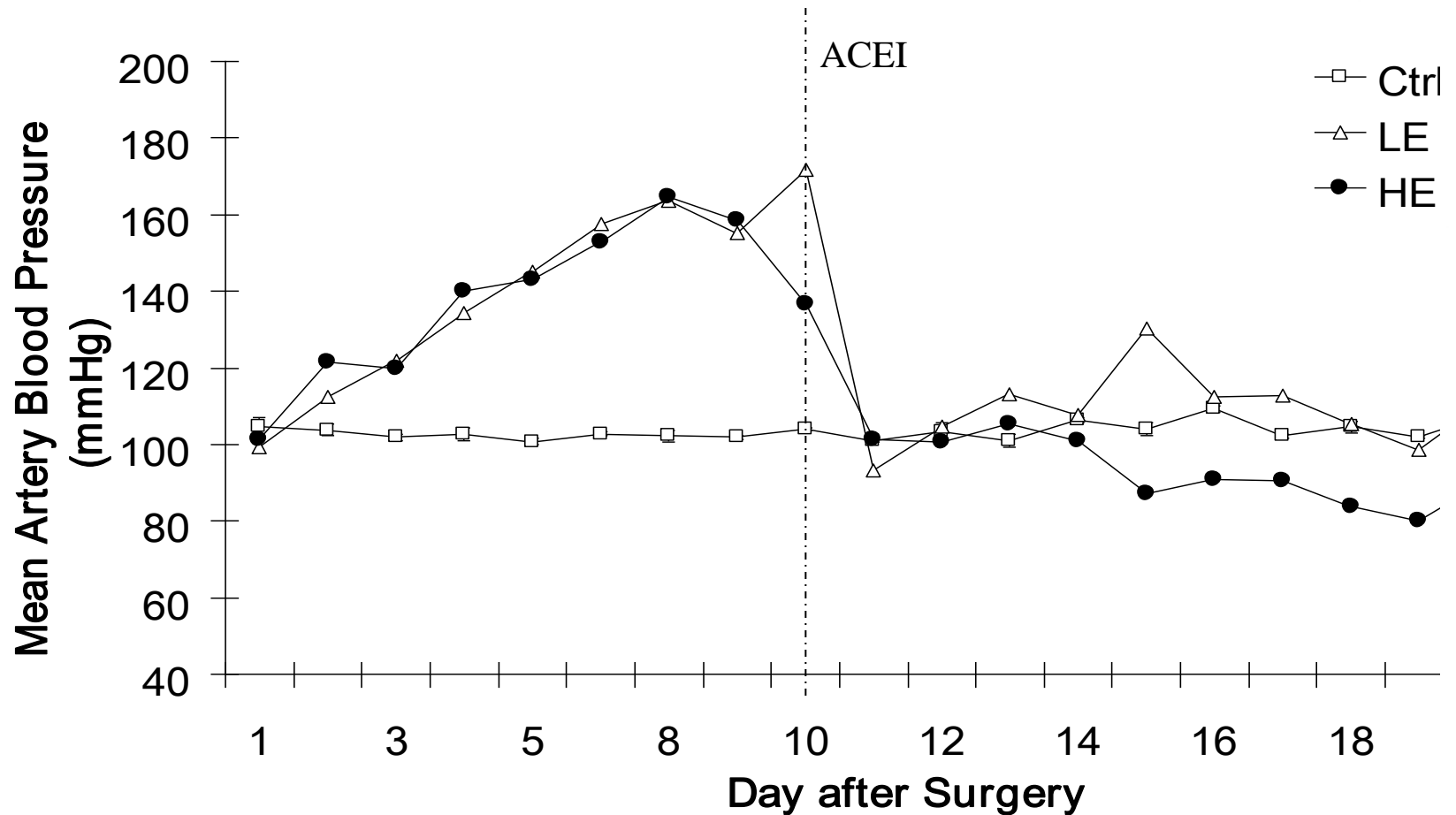


# Bioluminescent Signal After Transfection of Luciferase Plasmids as Reporter genes.

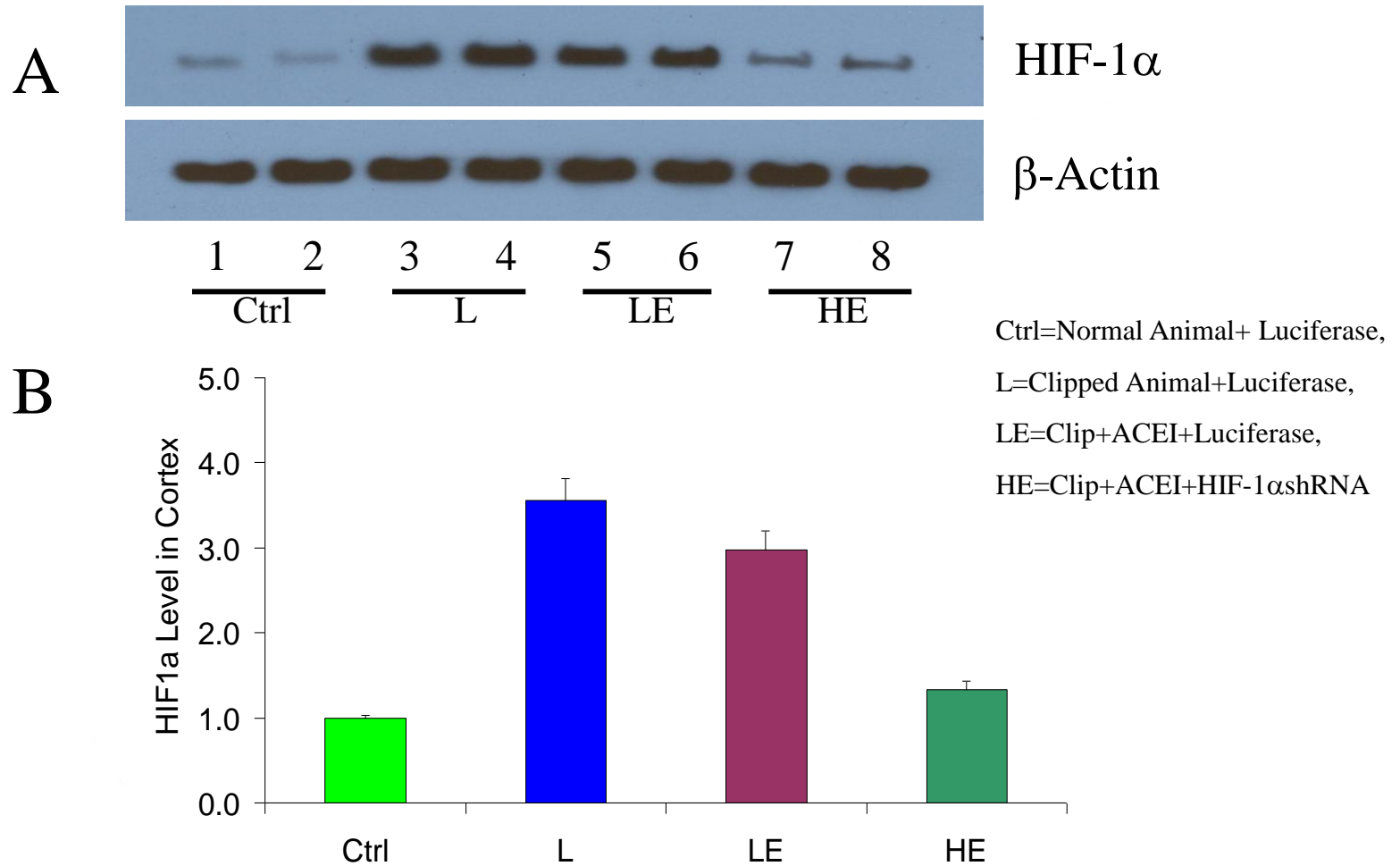




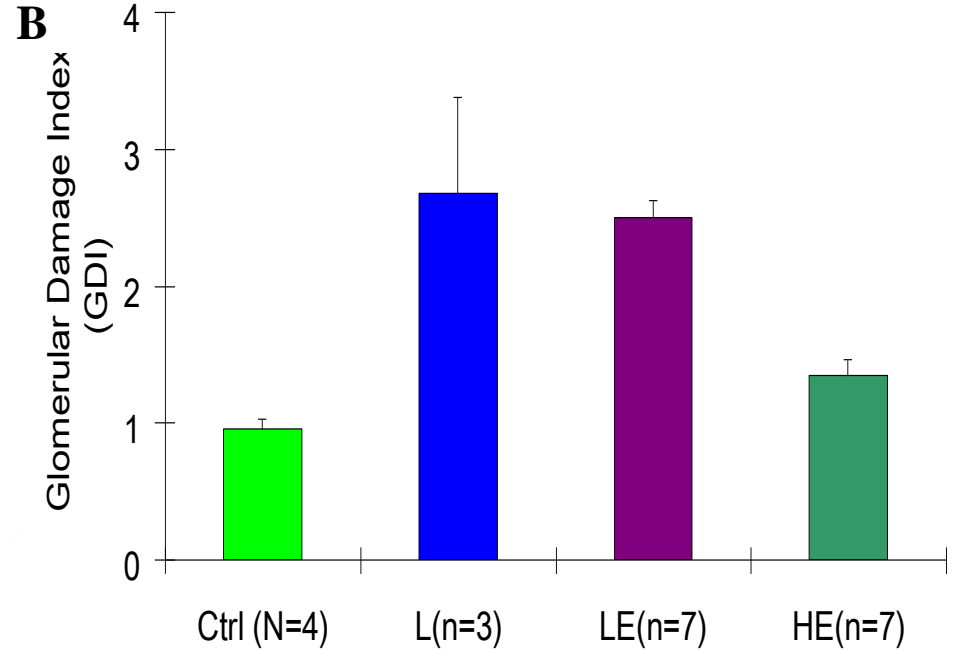
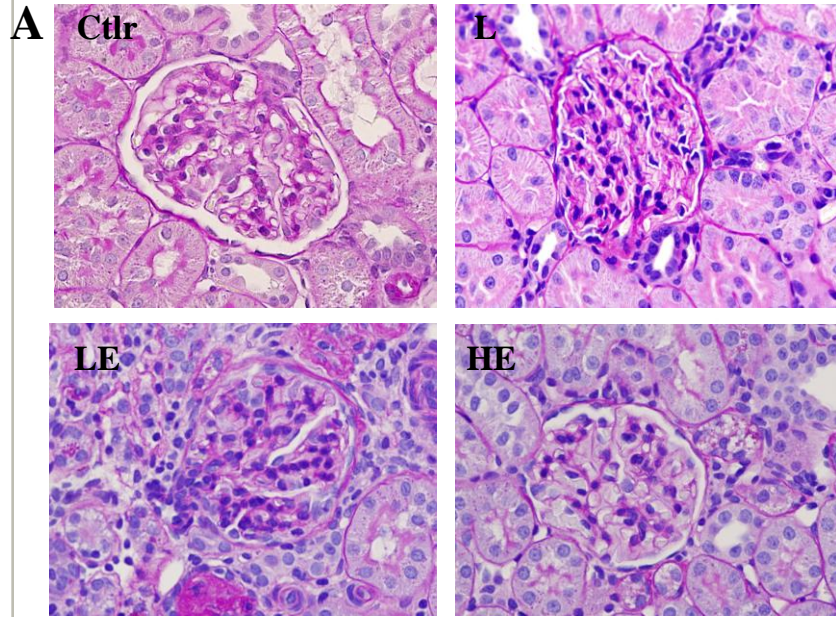
# Blood Pressure Changes



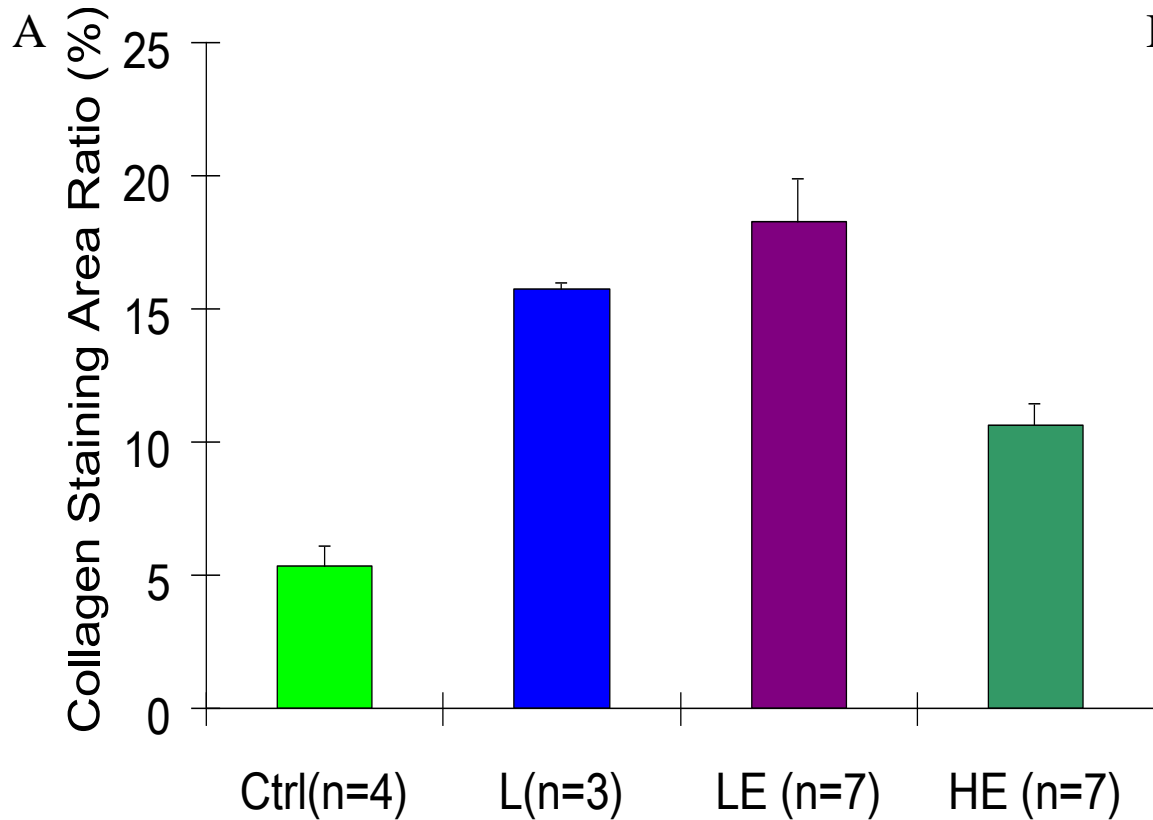
# HIF-1 $\alpha$ Expression in Each Group



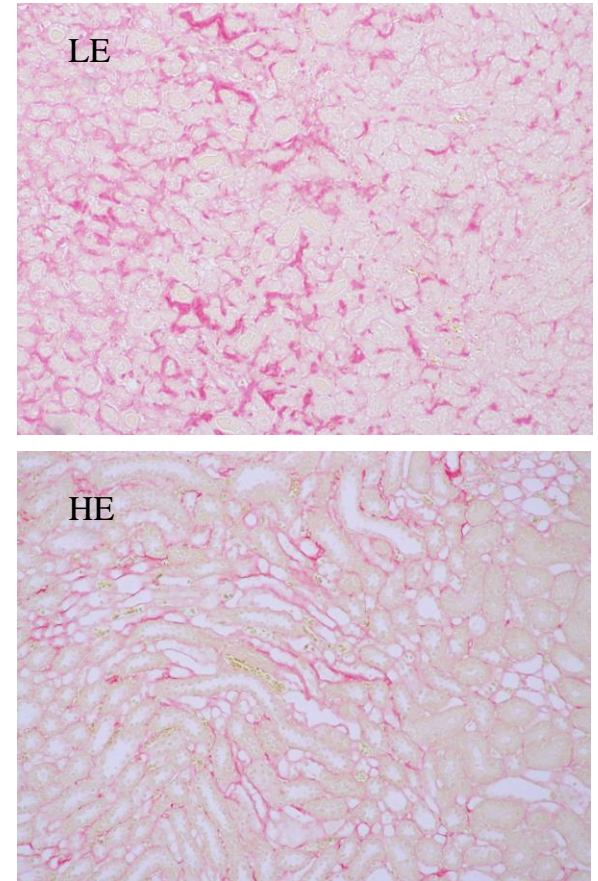
# Glomerular Damage in Each Group



# Effect of Silencing HIF-1 $\alpha$ on Collagen Distribution

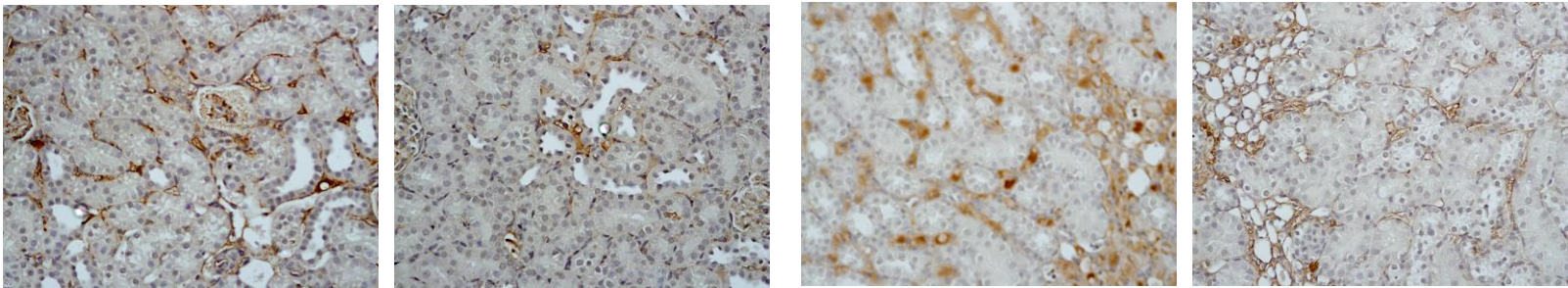


**B**

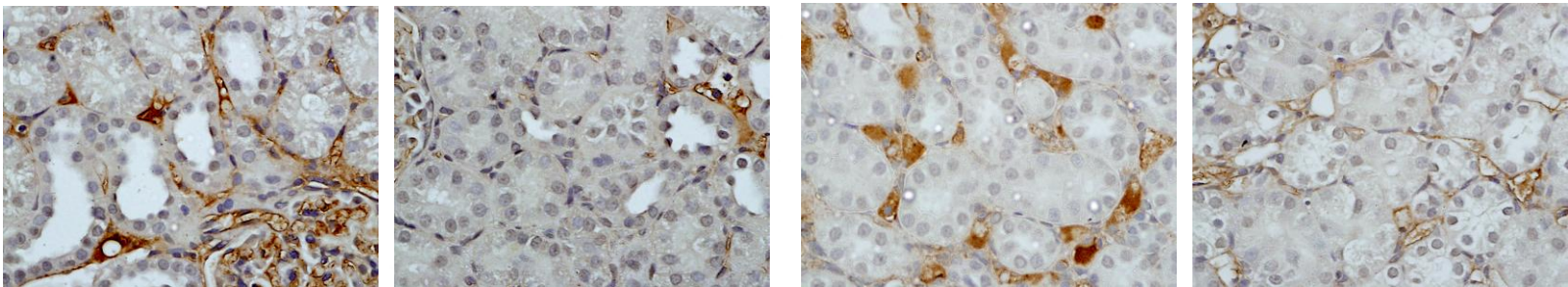


Effect of Silencing HIF-1 $\alpha$  on CD5, B Cell Marker

100X



200X



Clip+ACEI+Luciferase Clip+ACEI+HIF-1 $\alpha$  shRNA

Clip+ACEI+Luciferase Clip+ACEI+HIF-1 $\alpha$  shRNA

Cortex

Medulla

# Conculsion

- Clip over-activates hypoxia-inducible transcription factor – 1 alpha (HIF-1 $\alpha$ ) expression by chronic hypoxia.
- Over-activation of HIF-1 $\alpha$  contributes to chronic ischemic renal injury.
- Inflammation is involved in this renal injury.
- Silencing HIF-1 $\alpha$  can protect chronic ischemic renal injury.

# Future Directions

- Use disease models such as diabetic nephropathy, hypertensive nephropathy and see whether silencing HIF-1 $\alpha$  can protect against chronic ischemic renal injury.
- HIF prolyl hydroxylase (PHD):
  - Oxygen sensor that regulate HIF-1a levels in response to changes of oxygen concentrations
  - In normoxia, targets HIF-1 $\alpha$  for destruction.
- To determine whether PHD will also be involved in CKD via regulation of HIF-1alpha.

# Acknowledgements

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- Dr. Zhengchao Wang and Dr. Qing Zhu;
- Lori P. Payne;
- All other staff in the lab;
- This work is supported by NIH and STEP-UP.

