Advancing CKD Care and Combating Infectious Diseases: The Taiwan Experience in Kidney Health Policy

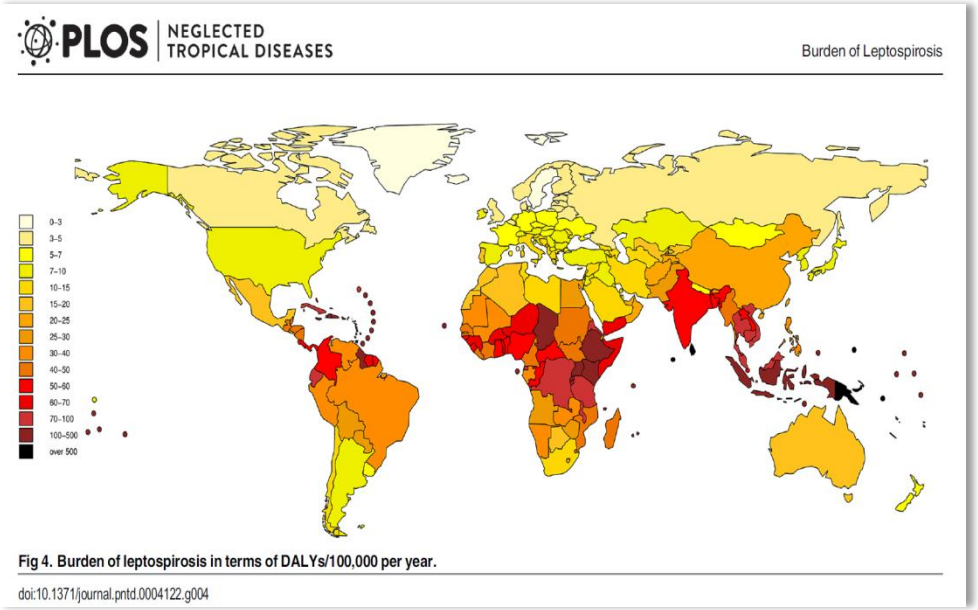
Leptospirosis

Chih-Wei YANG

Kidney Research Center, Chang Gung Memorial Hospital
Chang Gung University
TAIWAN

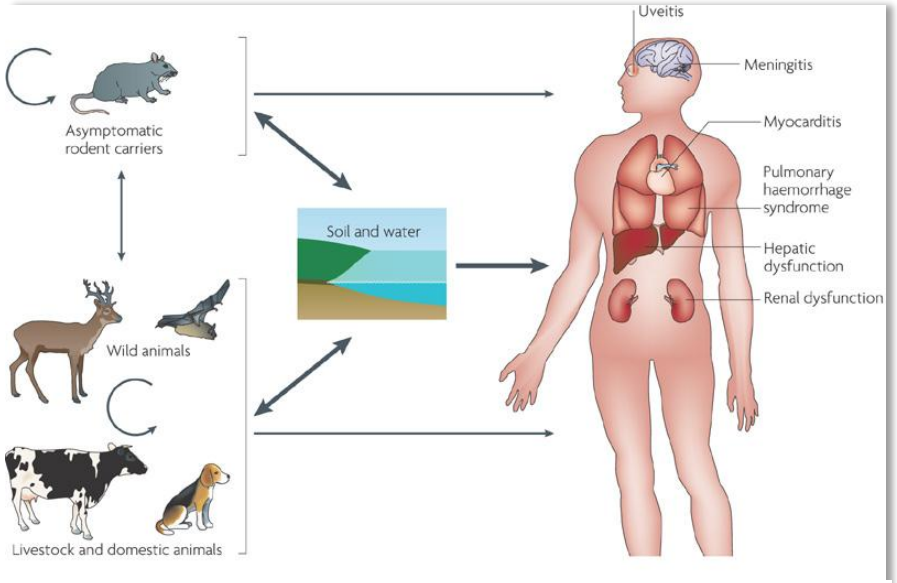
Global Burden of Leptospirosis

The most common zoonosis infecting almost all mammals

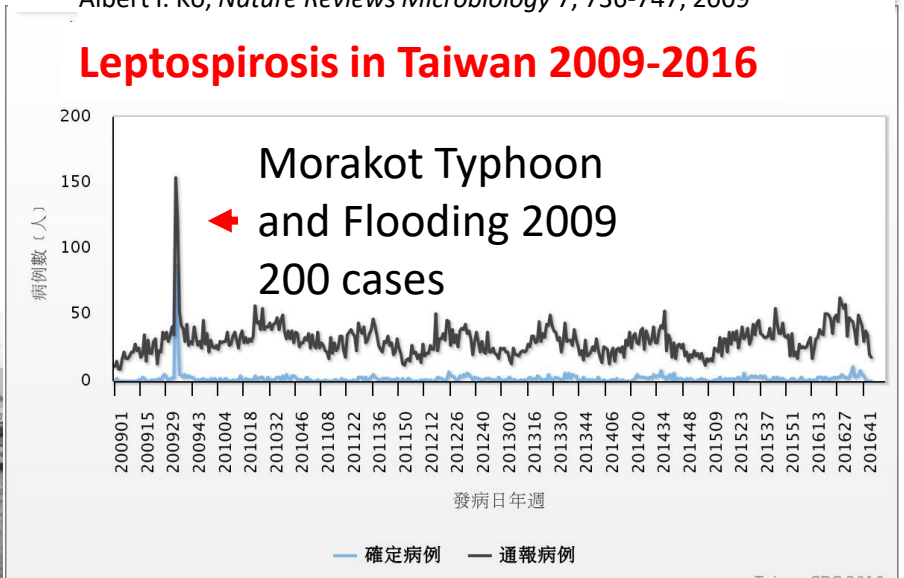


1.03 million cases annually with 59,000 cases fatality globally.

Torgerson PR, *PLoS Negl Trop Dis.* 2015



Albert I. Ko, *Nature Reviews Microbiology* 7, 736-747, 2009



Leptospirosis and Acute Kidney Failure

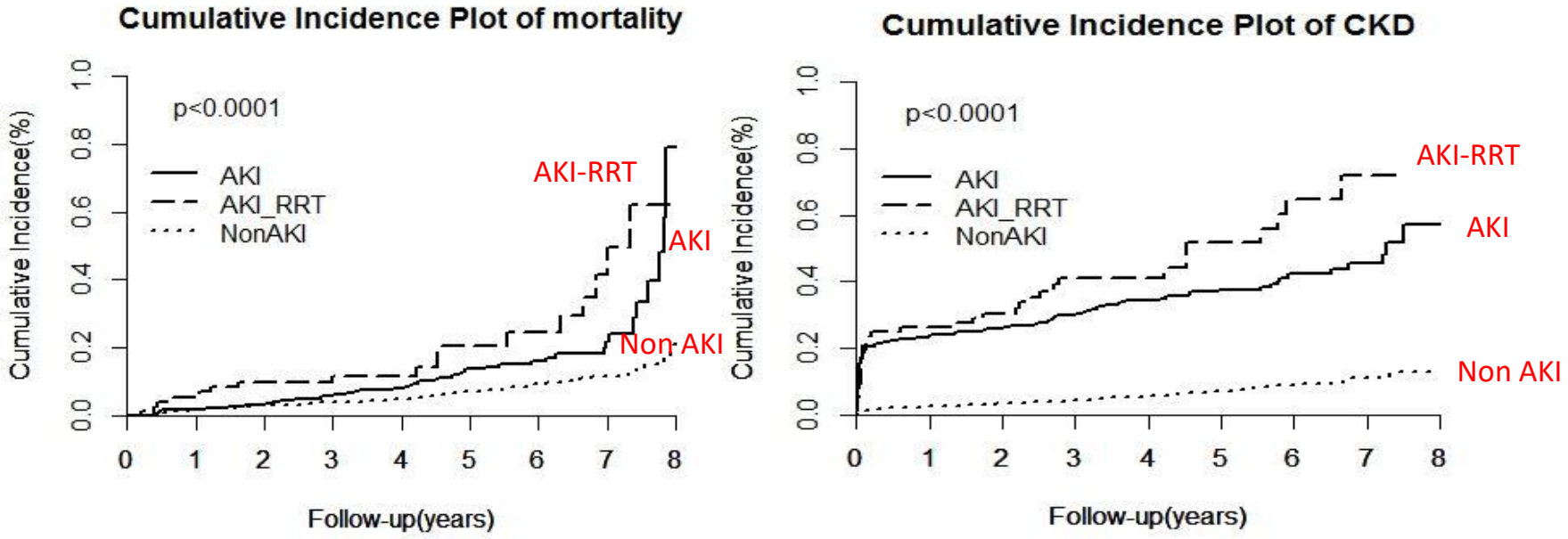
August 2019, Philippines

- **Basketball court** in the National Kidney and Transplant Institute (NKTI) in Quezon City, Philippines turned into an **ICU** for dialysis.
- Rapid increase of acute leptospirosis to 916 leptospirosis cases with 106 deaths nationwide, from January to July, 2019.

AKI to CKD

2145 patients with leptospirosis over 8-year follow-up by National Health Insurance Research Database, TAIWAN

The more severe AKI the more consequent increased incidence of CKD after 8 years

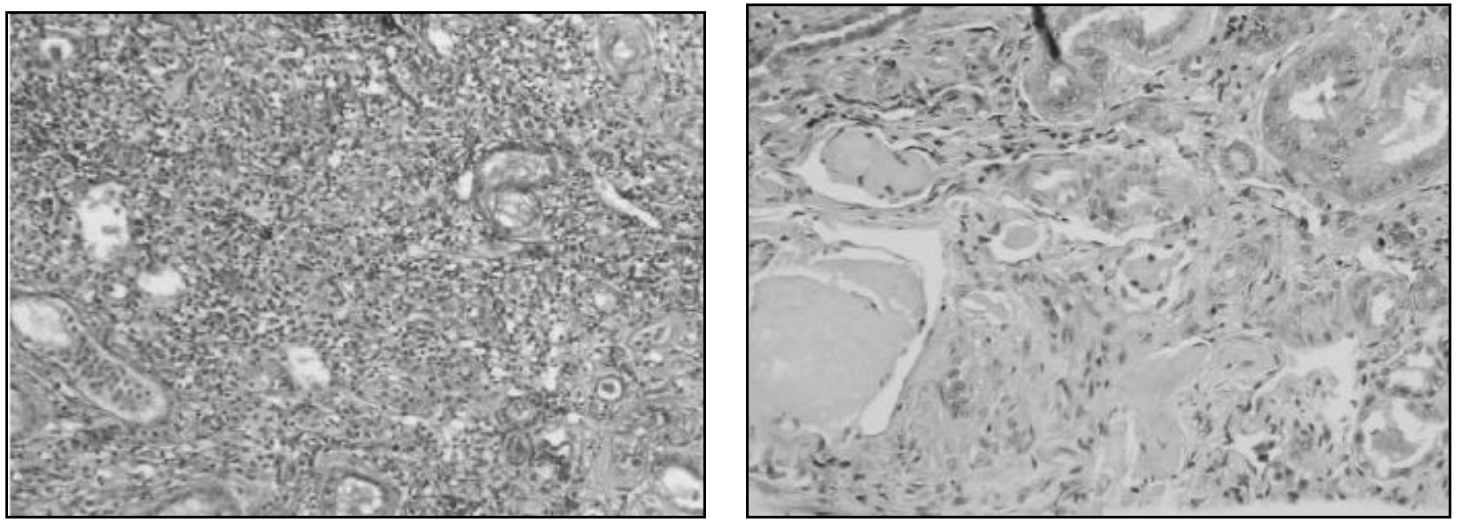


AKI n=443 (20.6%) / AKI-RRT n=77 (3.6%)

Chang CH, Yang CW, *Biomedicine 2022*

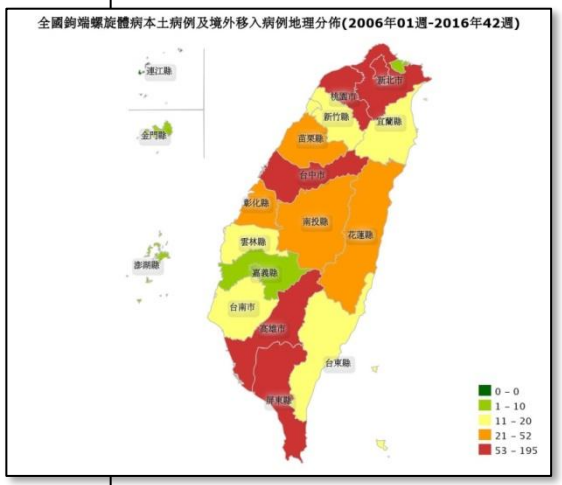
Leptospirosis and renal fibrosis

- A 21 y/o healthy male was diagnosed to have leptospirosis 10 days following admission.
- Irreversible acute renal failure
- On permanent hemodialysis
- Kidney biopsy was performed twice with 3 week interval.



Atasoyu EM, Nephrol Dial Transpl, 2005

PLOS | NEGLECTED TROPICAL DISEASES



RESEARCH ARTICLE

Overlooked Risk for Chronic Kidney Disease after Leptospiral Infection: A Population-Based Survey and Epidemiological Cohort Evidence

Huang-Yu Yang[1,2], Cheng-Chieh Hung[1], Su-Hsun Liu[3], Yi-Gen Guo[1], Yung-Chang Chen[1], Yi-Ching Ko[1], Chiung-Tseng Huang[1], Li-Fang Chou[1], Ya-Chung Tian[1], Ming-Yang Chang[1], Hsiang-Hao Hsu[1], Ming-Yen Lin[4], Shang-Jyh Hwang[4]*, Chih-Wei Yang[1]*

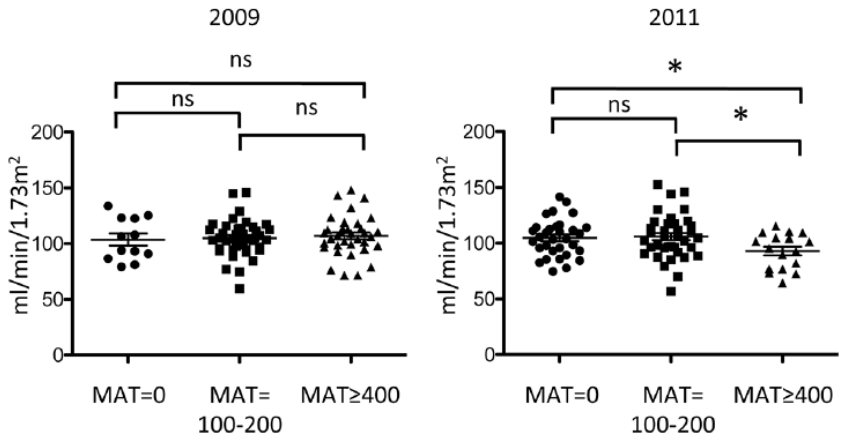
1. Seroprevalence and CKD association

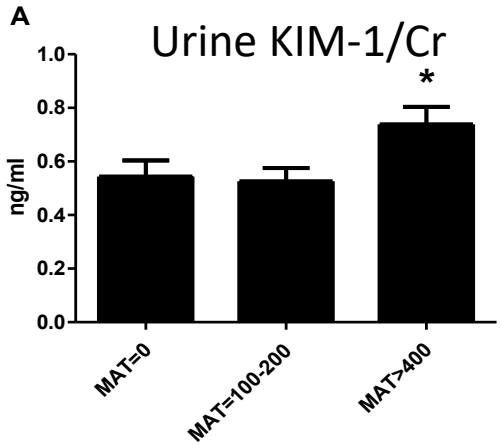
- ***n*=3045 in CKD Screening Program In Kaohsiung County**
- 33.9% seropositive for leptospira antibody
- 2.5% lower eGFR-EPI in seropositive group (P<0.001)

2. Two-Year Cohort after Flooding

- Reduced eGFR in high MAT titer group
- Higher urine KIM-1/Cr
- Leptospira DNA detected in 2 residents (2/88=2.3%), two years after flooding

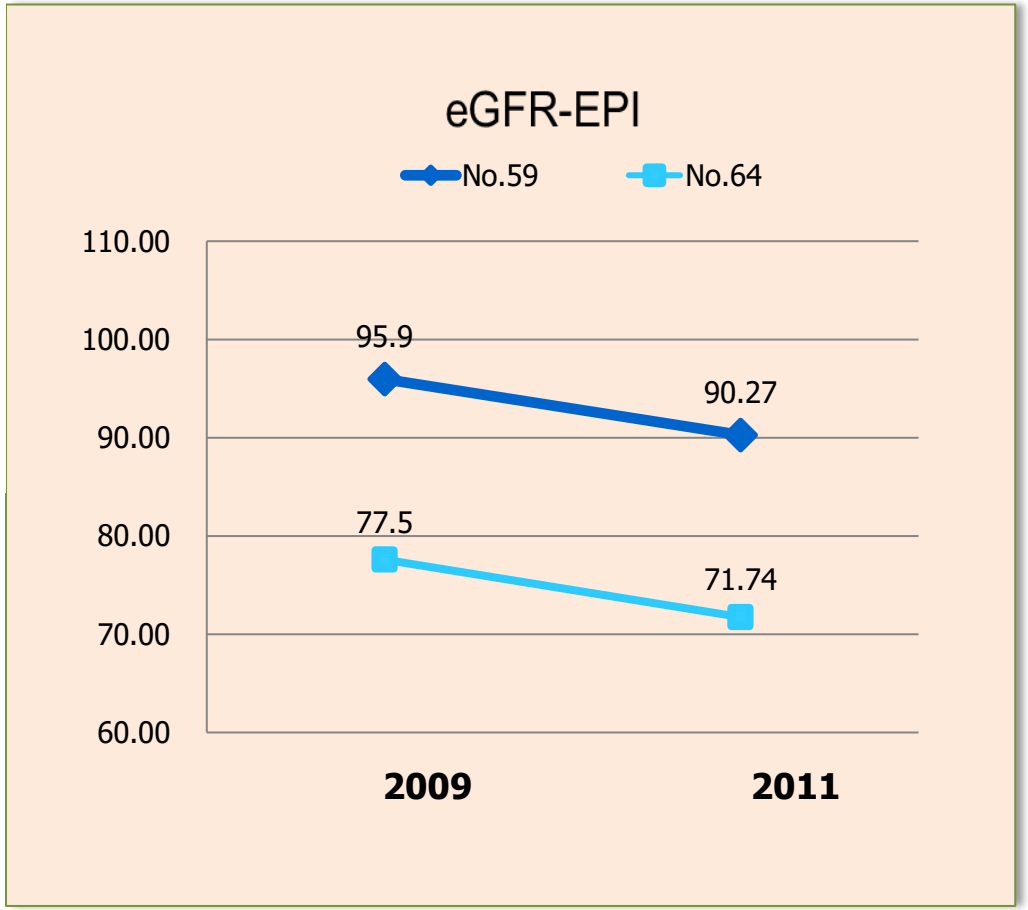
COHORT: Reduced eGFR in High Leptospira Antibody Titer Group (MAT>400)





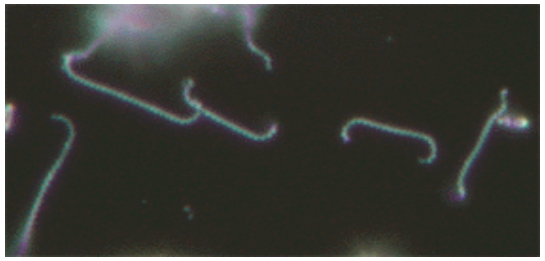
***:P<0.05**

Detectable Leptospira DNA in Urine: Carrier Status

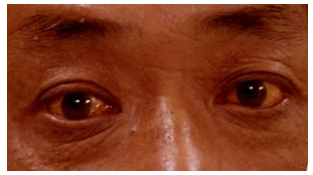


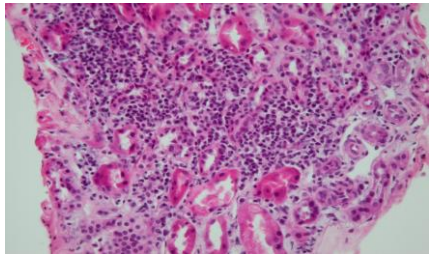
Yang HY, Hwang SJ and Yang CW
PLOS Neglected Tropical Disease 2015

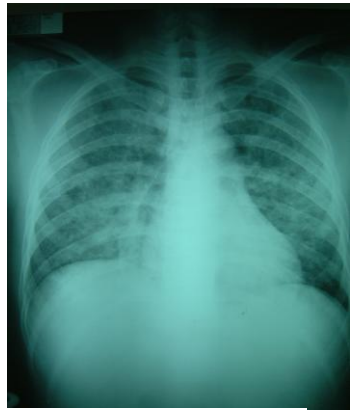
Role of Leptospira Outer Membrane Protein Injury/Inflammation Pathway in Tubulointerstitial Nephritis



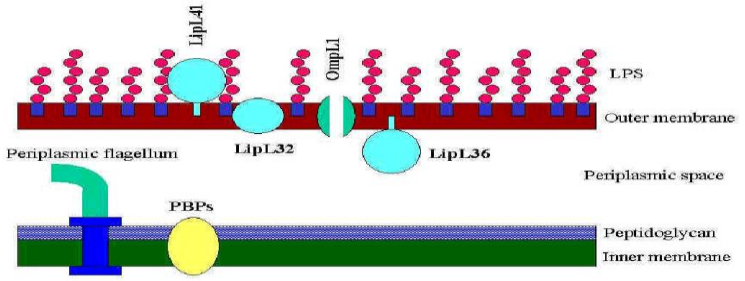
Leptospirosis

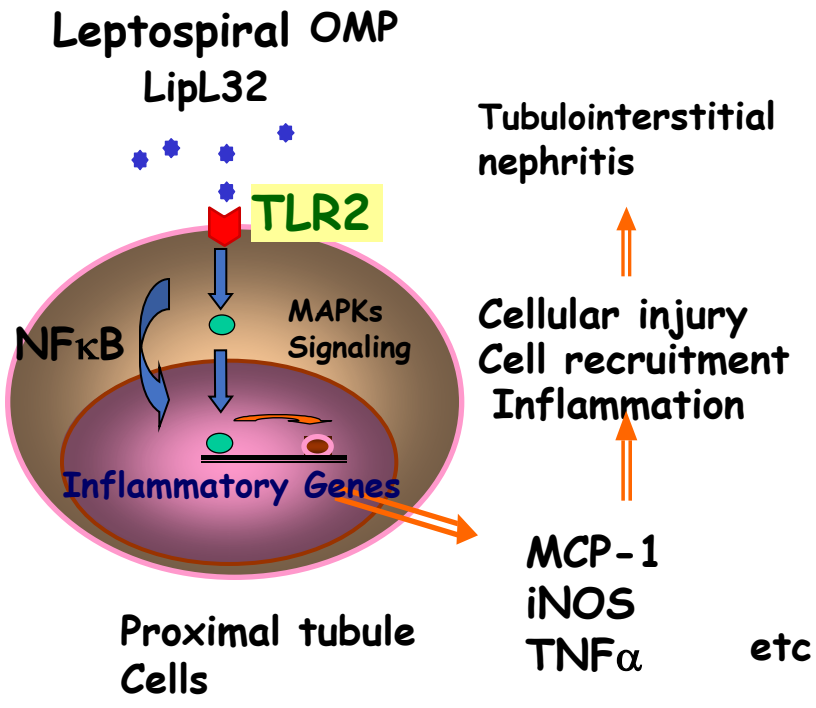






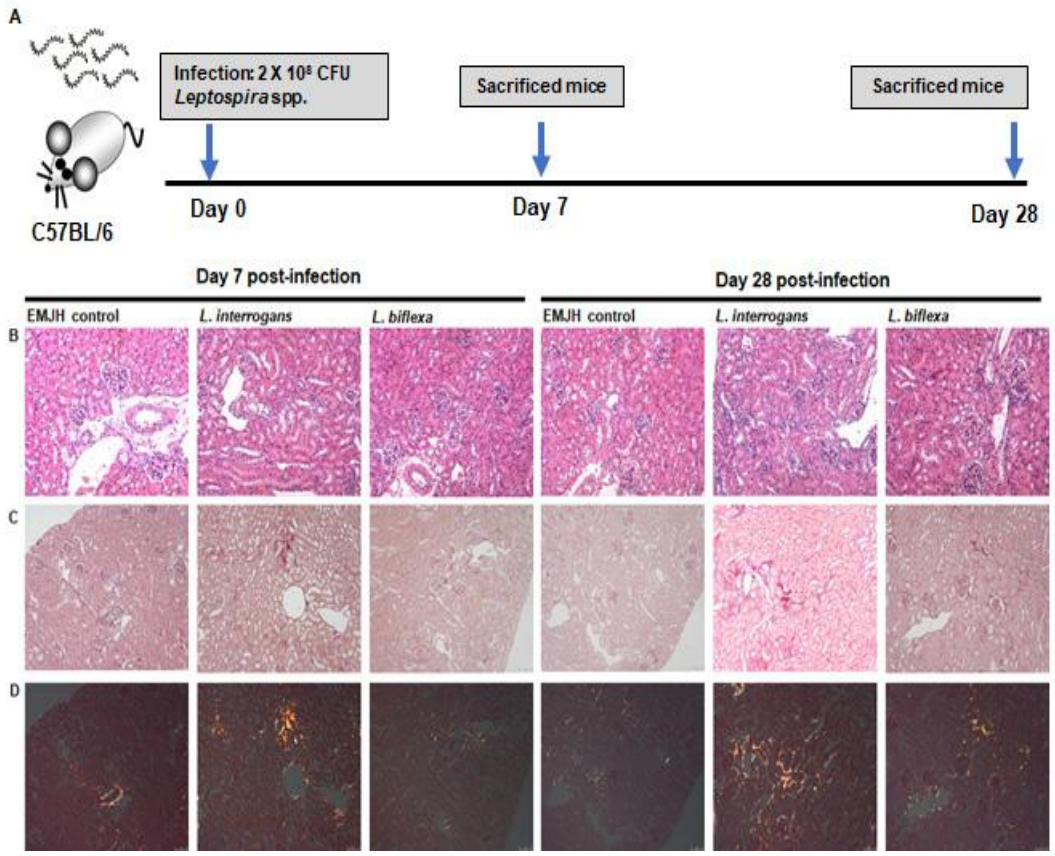
鉤端螺旋體病



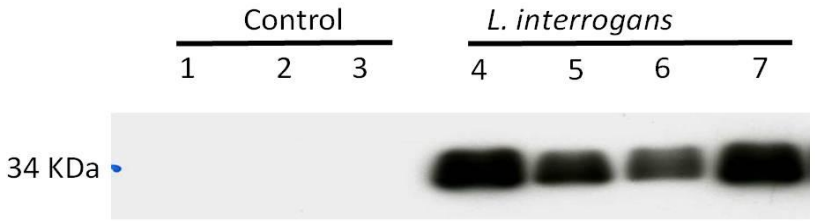


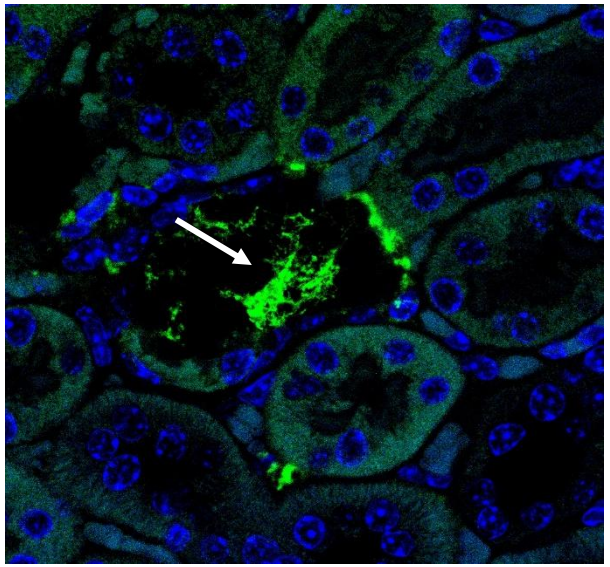
Yang CW, *Am.J.Kidney Dis.* 30:840-845, 1997.
Lin CL, *Nephrol. Dial. Transplant* 14:193-195, 1999
Yang CW *J.Am.Soc.Nephrol, 11:1017-1026, 2000*
Yang CW, *Nephrol Dial Transpl, 2001*
Yang CW, *J.Am.Soc.Nephrol*, 13:2037-2045, 2002
Wu MS,*Nephrol Dial Transplant*. 19(10):2472-9. 2004

Chronic Leptospirosis Mouse Model

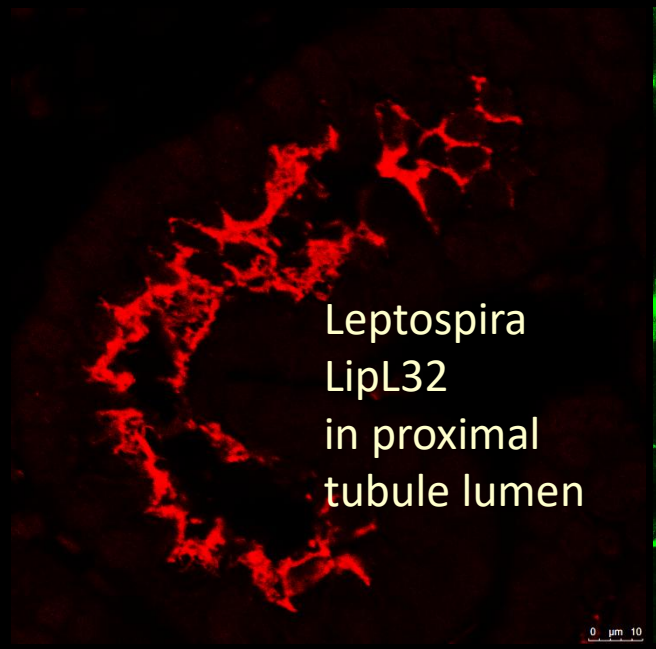


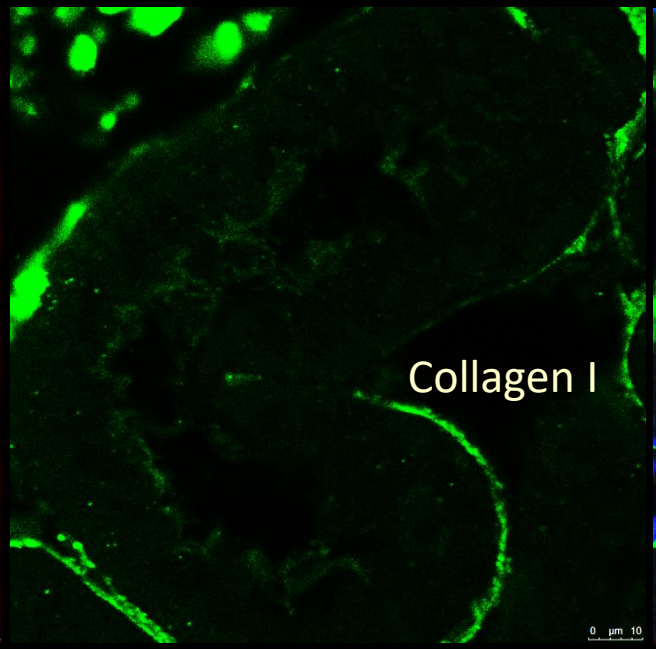
L. interrogans shed in urine of chronically infected mouse at day 28 post-infection

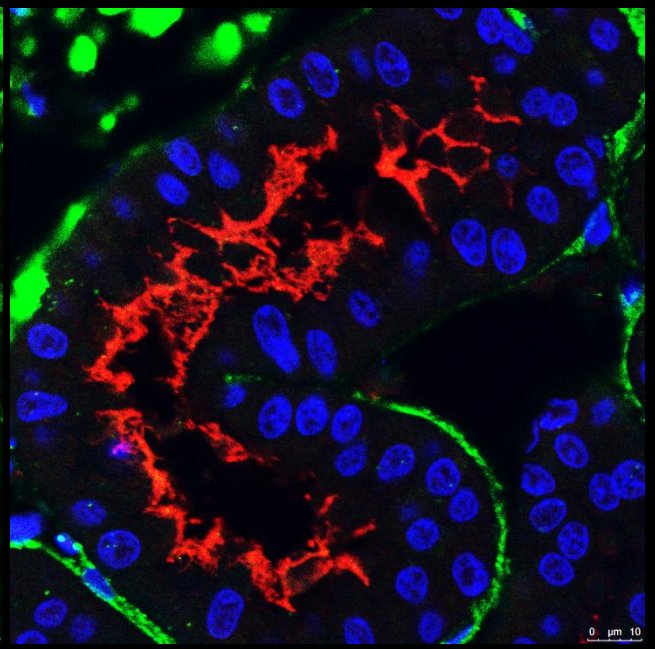




Anti-leptospiral LipL32 (green; white arrow)



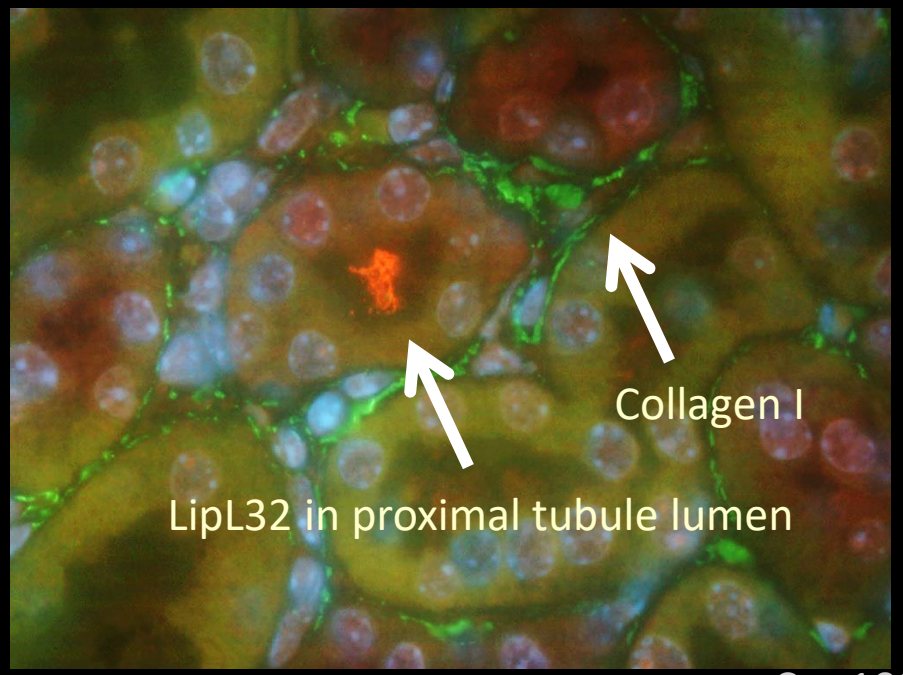




Chronic Kidney Disease Model

(Tubulo-interstitial Nephritis)

C57BL/6J mice
83 days post
leptospiral infection



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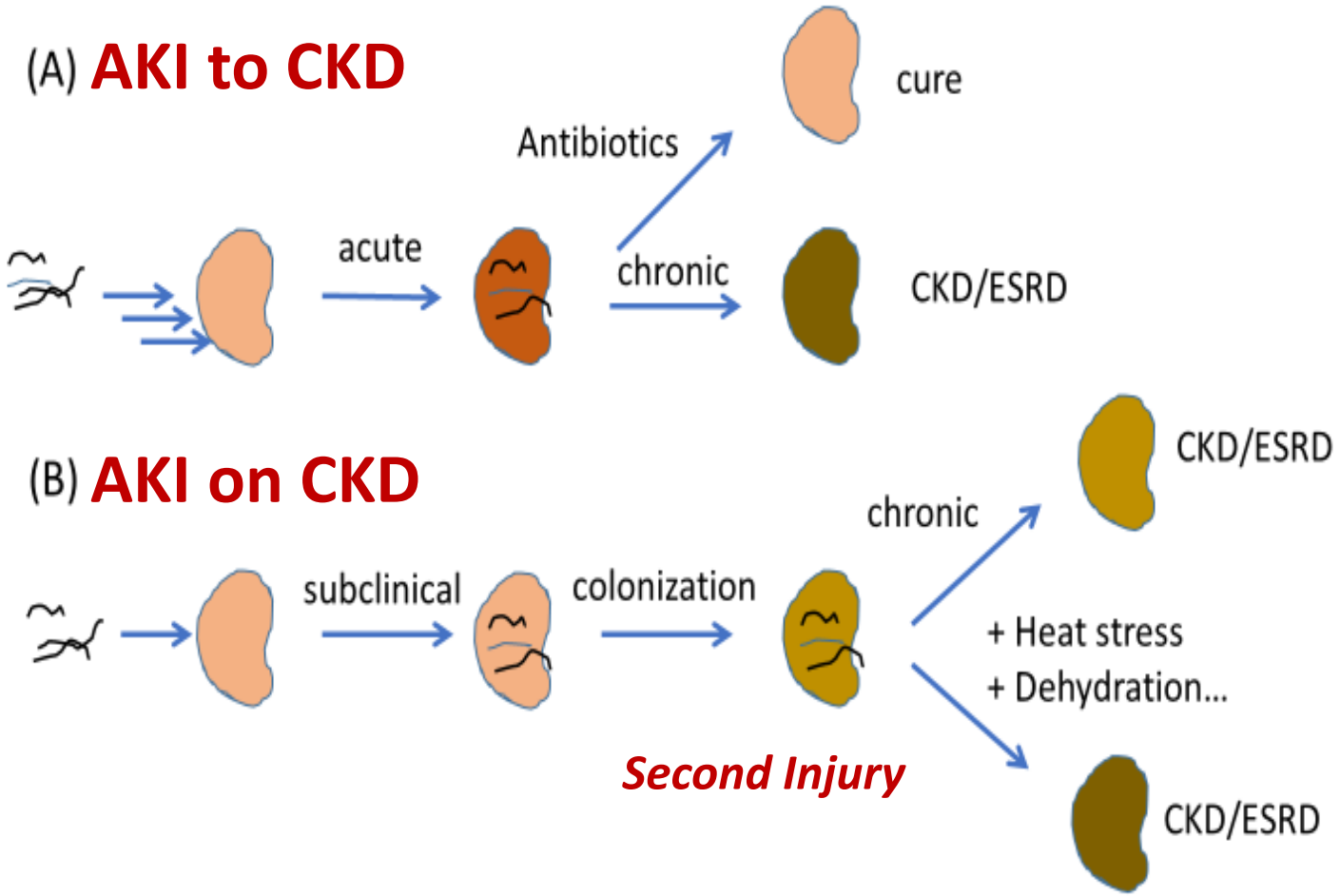
Leptospirosis Kidney Disease

Leptospirosis is a potential contributing factor as a cause for CKD

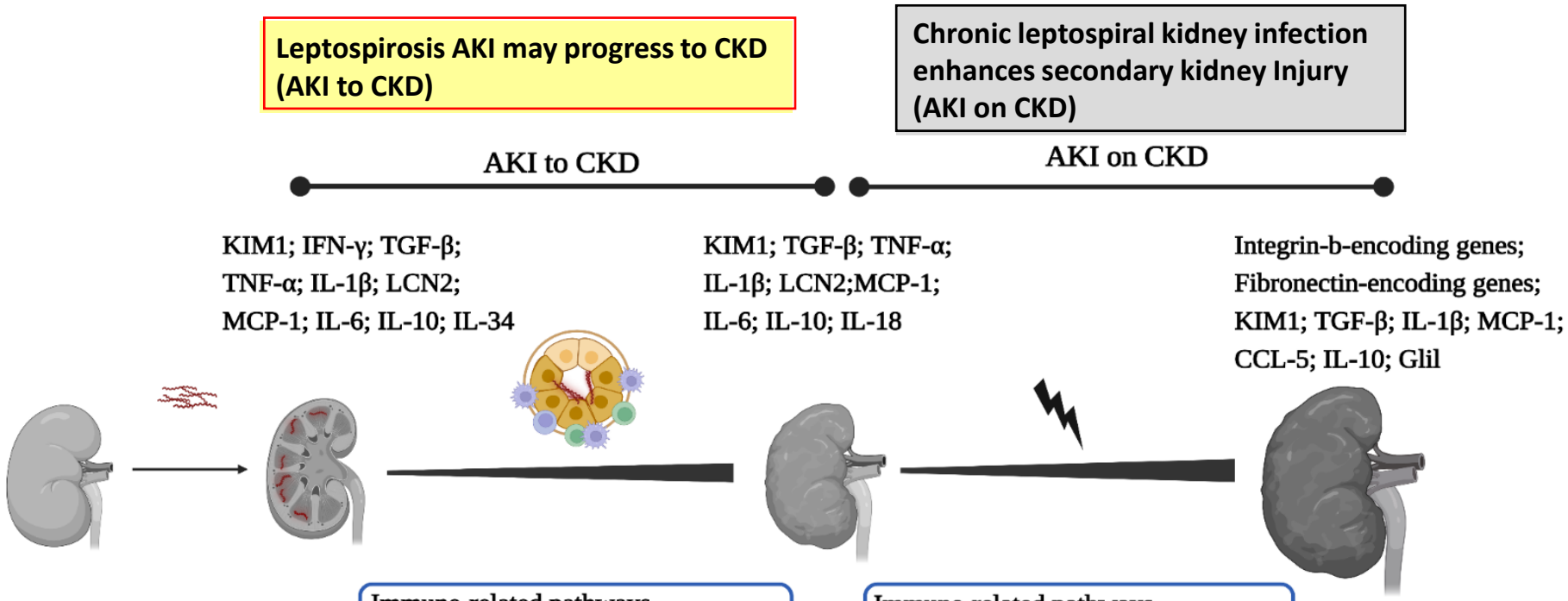


Yang CW, Nephron 2018

Leptospirosis Kidney Disease: Evolution from Acute to Chronic Kidney Disease

Leptospirosis AKI may progress to CKD (AKI to CKD)

Chronic leptospiral kidney infection enhances secondary kidney Injury (AKI on CKD)



Immune-related pathways
- Toll-like receptor signaling
- Complements activation
- T-helper 1 type immune response
- T cell-mediated responses

Fibrosis-related pathways
- TGF-β1/SMAD

Maladaptive repair processes (??)

Immune-related pathways
- Toll-like receptor signaling
- Complements activation
- T-helper 1 type immune response
- T cell-mediated responses

Fibrosis-related pathways
- TGF-β1/SMAD

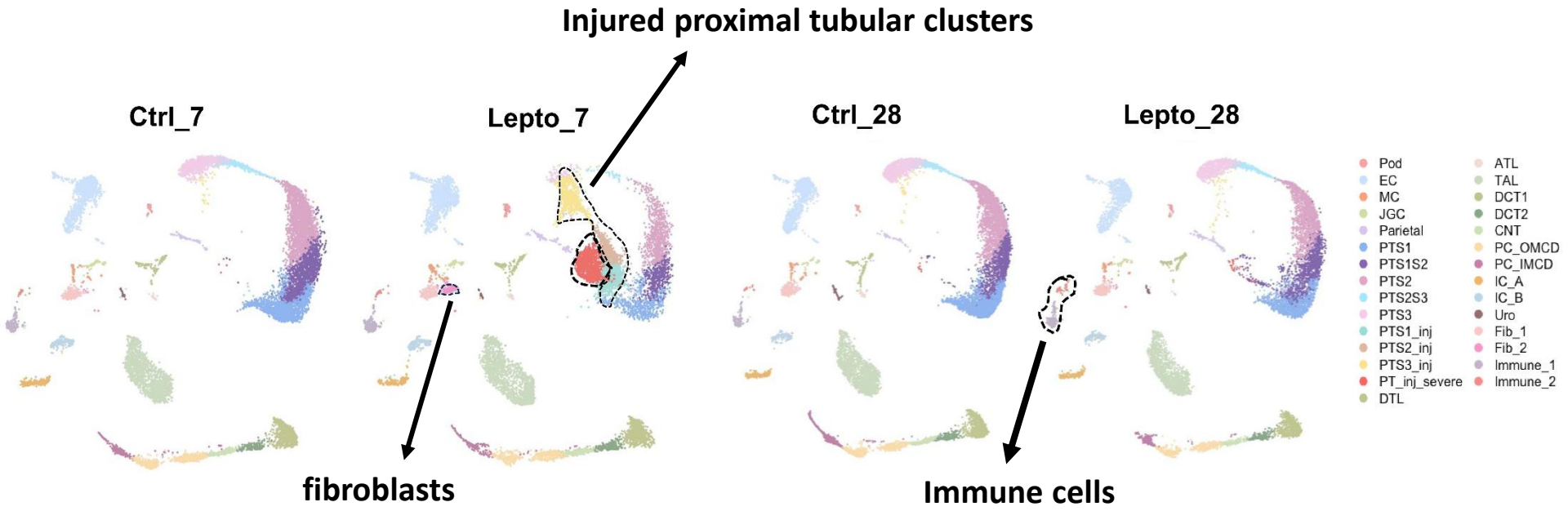
Maladaptive repair processes (??)

Biomed J. 2023;46(4):100595.

The proximal tubule is the main site of *Leptospira*-induced injury

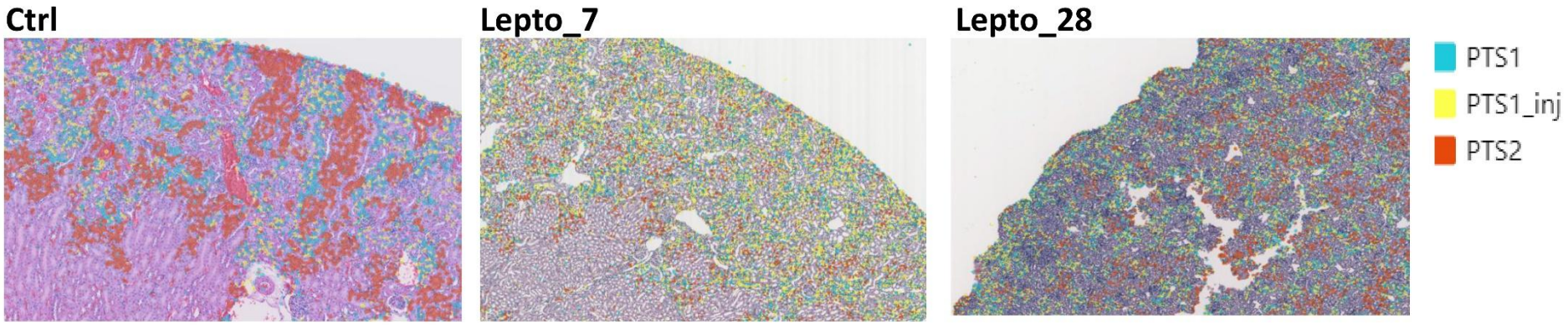
Dr. Yueh-An Lu

Single-Nucleus RNA sequencing



1) Injured proximal tubular clusters and increased fibroblasts were prominent after infection at day 7.
2) After infection at day 28, proximal tubules partially recovered, while immune cells increased

Spatial mapping of proximal tubular injury during *Leptospira* infection

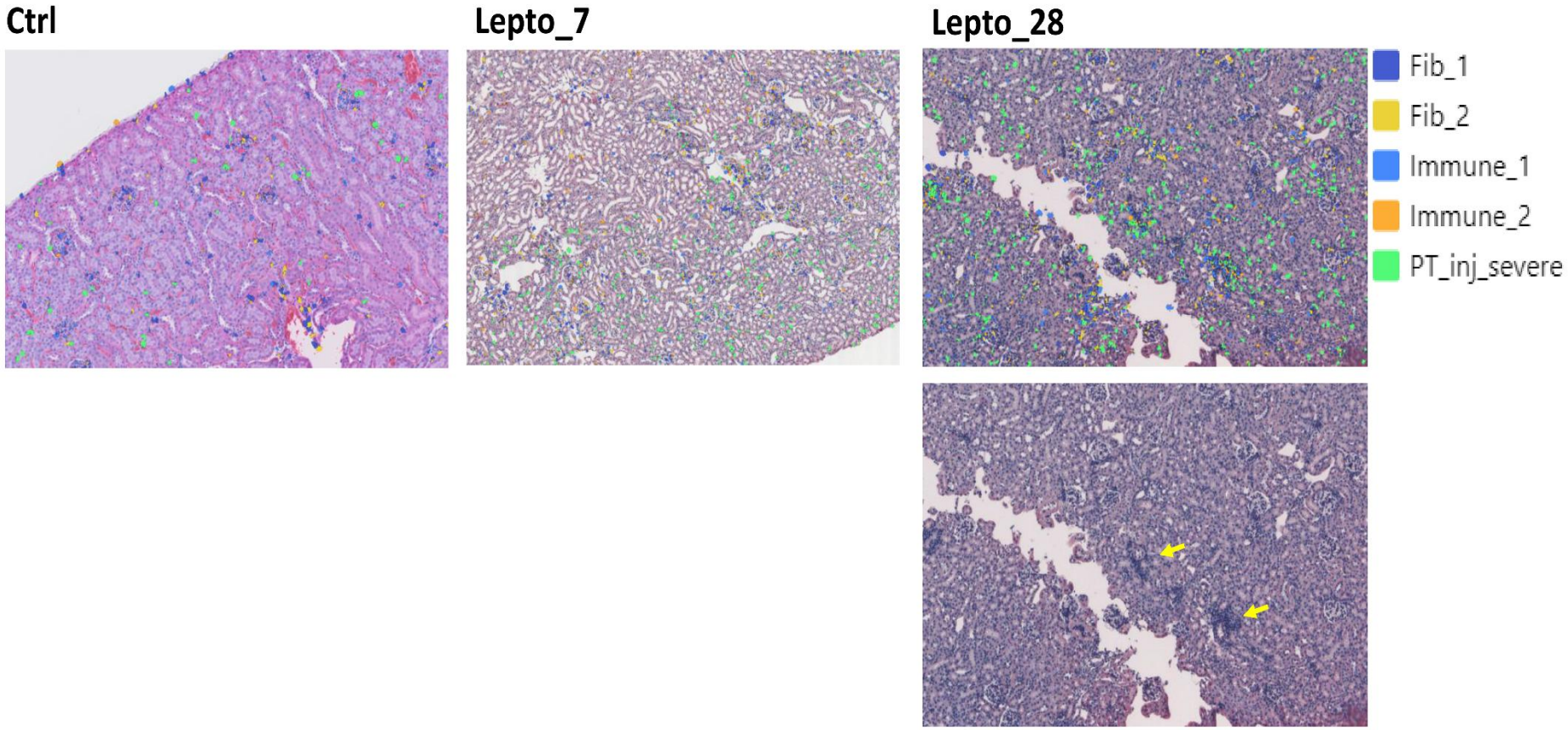


PTS2 ↓ ; PTS1_inj ↑

***Leptospira* infection at day 7, spatial transcriptome maps reveal pronounced proximal tubular injury**

Chou LF 2025

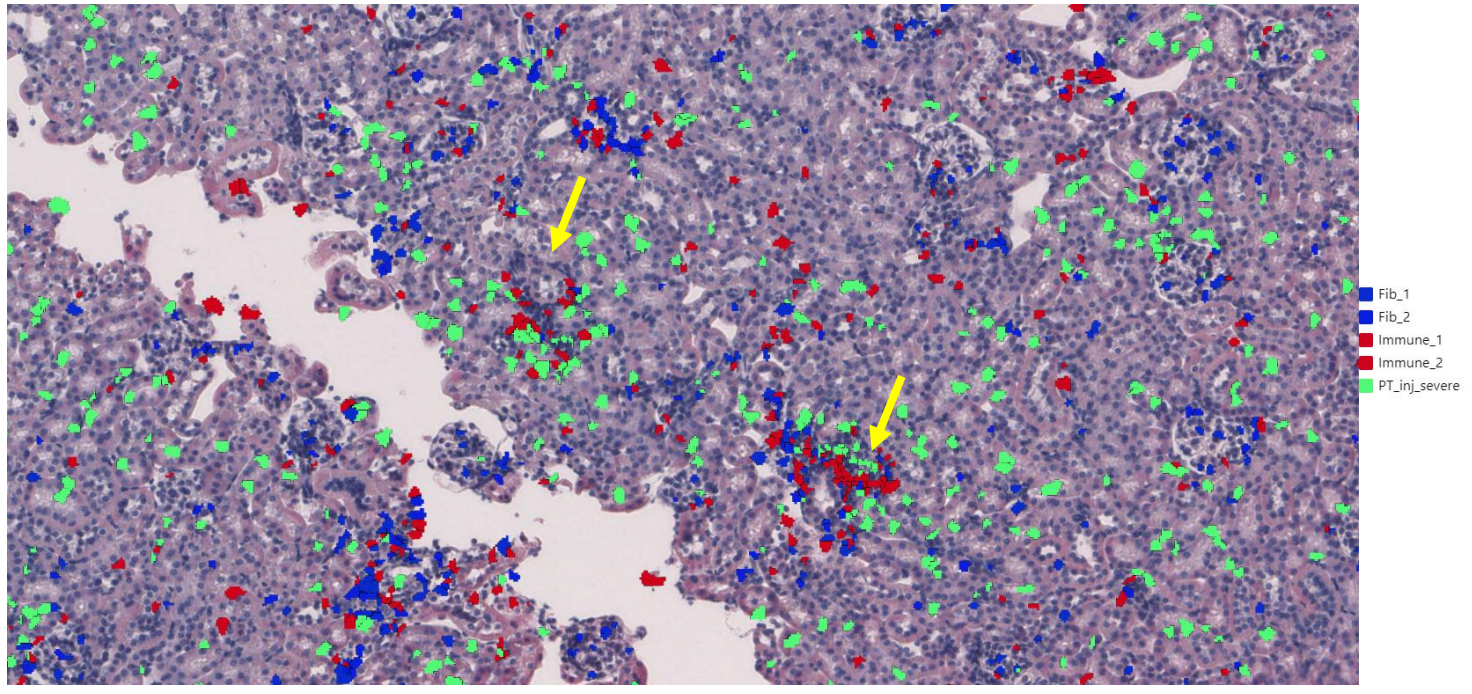
Spatial mapping of fibroblast-immune cells-tubular interactions during *Leptospira* infection

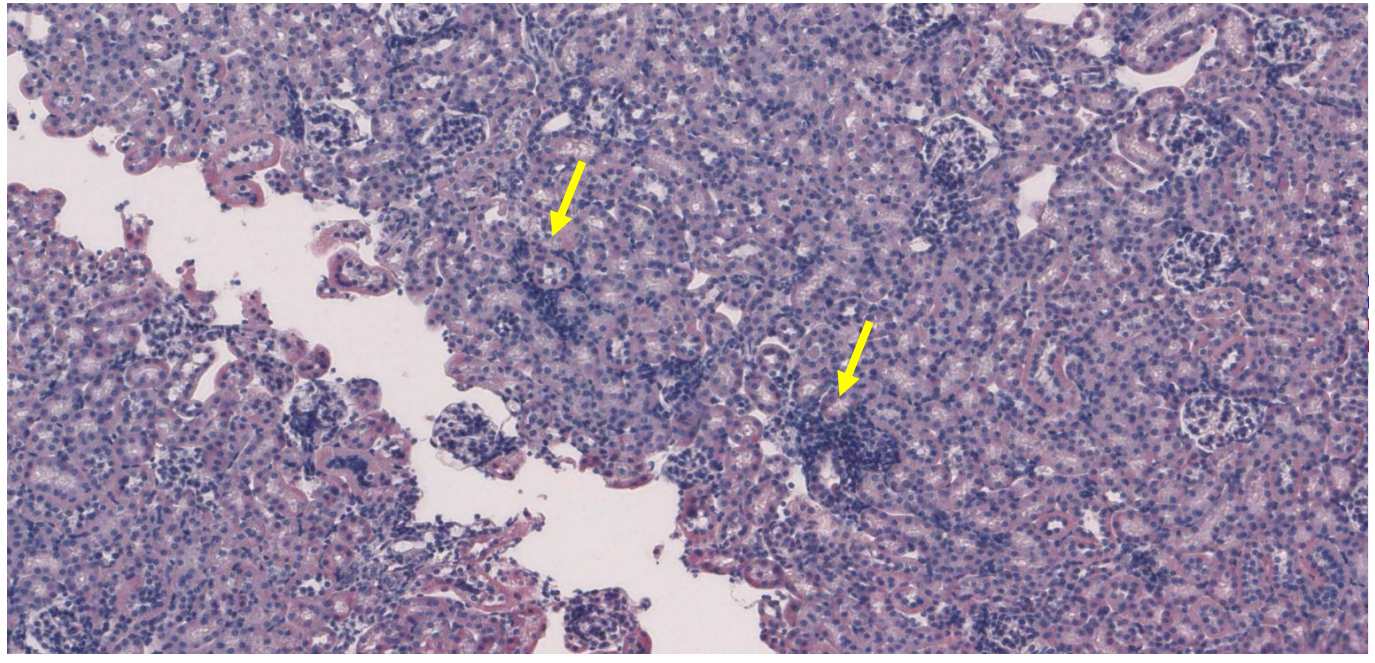


***Leptospira* infection at day 28, fibroblasts and immune cells surround injured proximal tubules, indicating enhanced cell-cell interaction**

Chou LF 2025

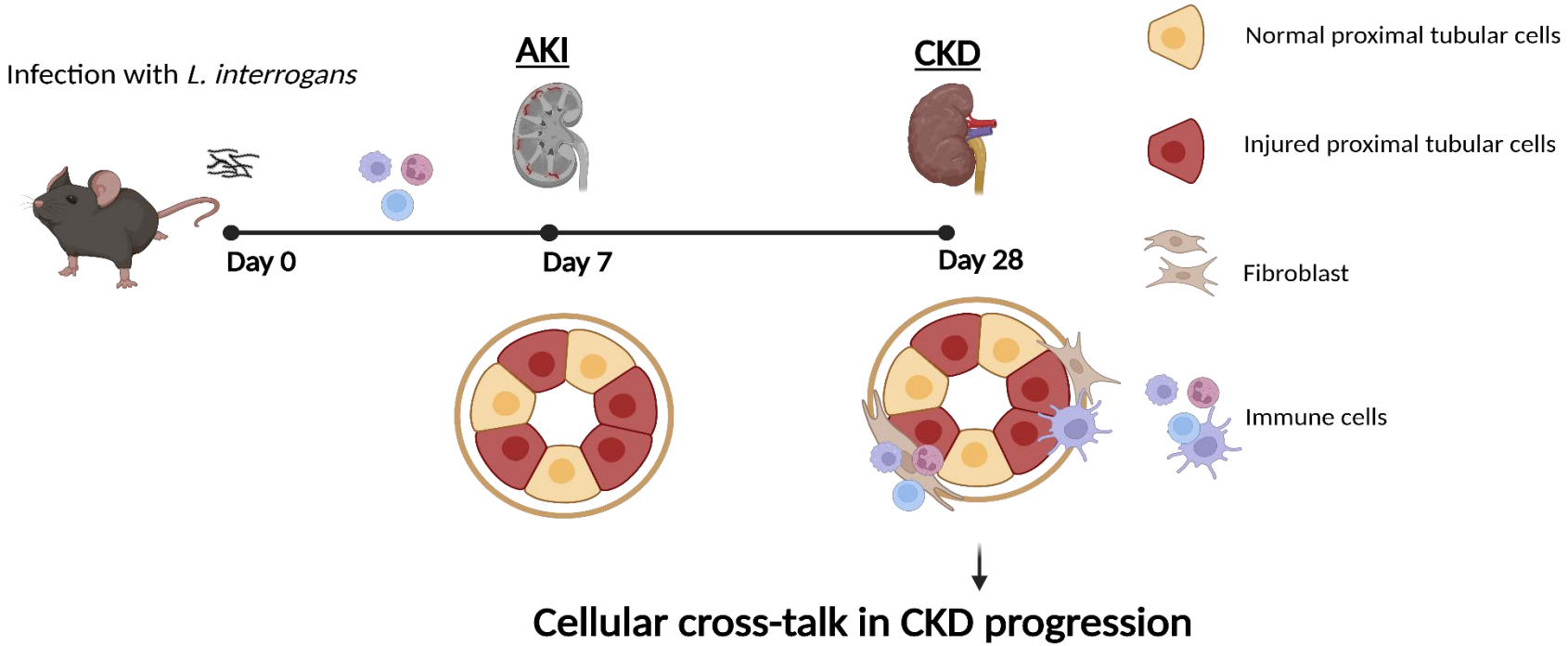
Leptospira infection at day 28





Chou LF 2025

Leptospirosis Kidney Disease
From AKI to CKD



Leptospira infection disrupts renal proximal tubules cells, leading to fibroblast activation and immune cell infiltration with enhanced cell-cell interactions among these population that may contribute to the progression of CKD.

Chou LF 2025

Cellular Senescence Links Severe Leptospira Infection To Chronic Kidney Disease Progression

Aim:

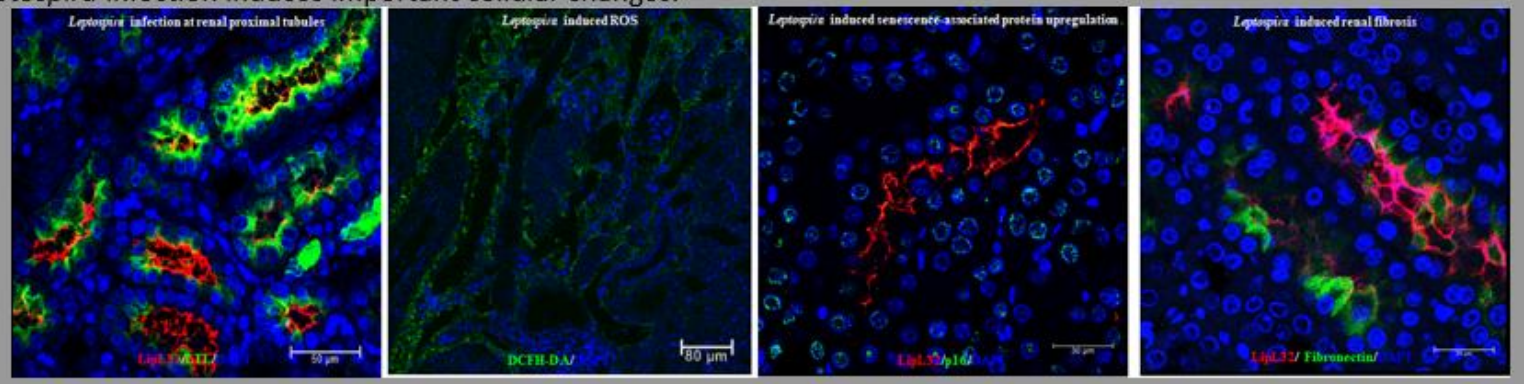
The aim of this study is to investigate the potential pathogenic mechanisms underlying the progression from acute kidney injury (AKI) to chronic kidney disease (CKD) following *Leptospira* infection, with a focus on the role of cellular senescence in this process.

Methods

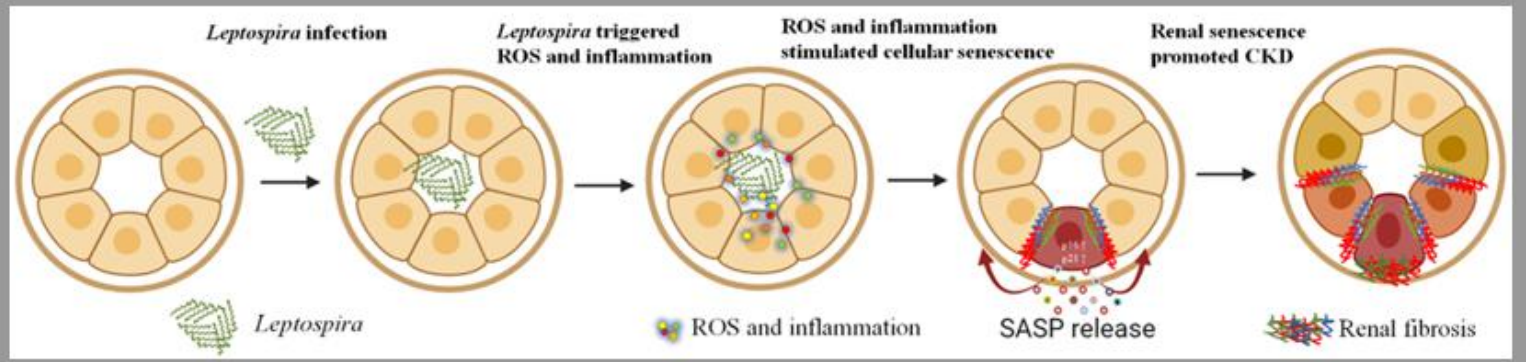
1. **Establishment of the severe Leptospira-infected hamster model to obtain the kidney tissues and blood from hamster.**
2. **Through tissue staining techniques to examine kidney damage caused by *Leptospira* infection and analyzed renal function markers to assess the impact on kidney injury score.**
3. **The quantitative analysis of genes expression related to inflammation, aging, and ROS using Q-PCR.**
4. **Using confocal microscopy-based imaging analysis to investigate the effects of *Leptospira* infection, focusing on inflammation, ROS production, cellular senescence, and renal fibrosis.**

Results

Leptospira infection induces important cellular changes.



Proposed model of the *Leptospira* infection triggered renal senescence that bridging AKI to CKD.



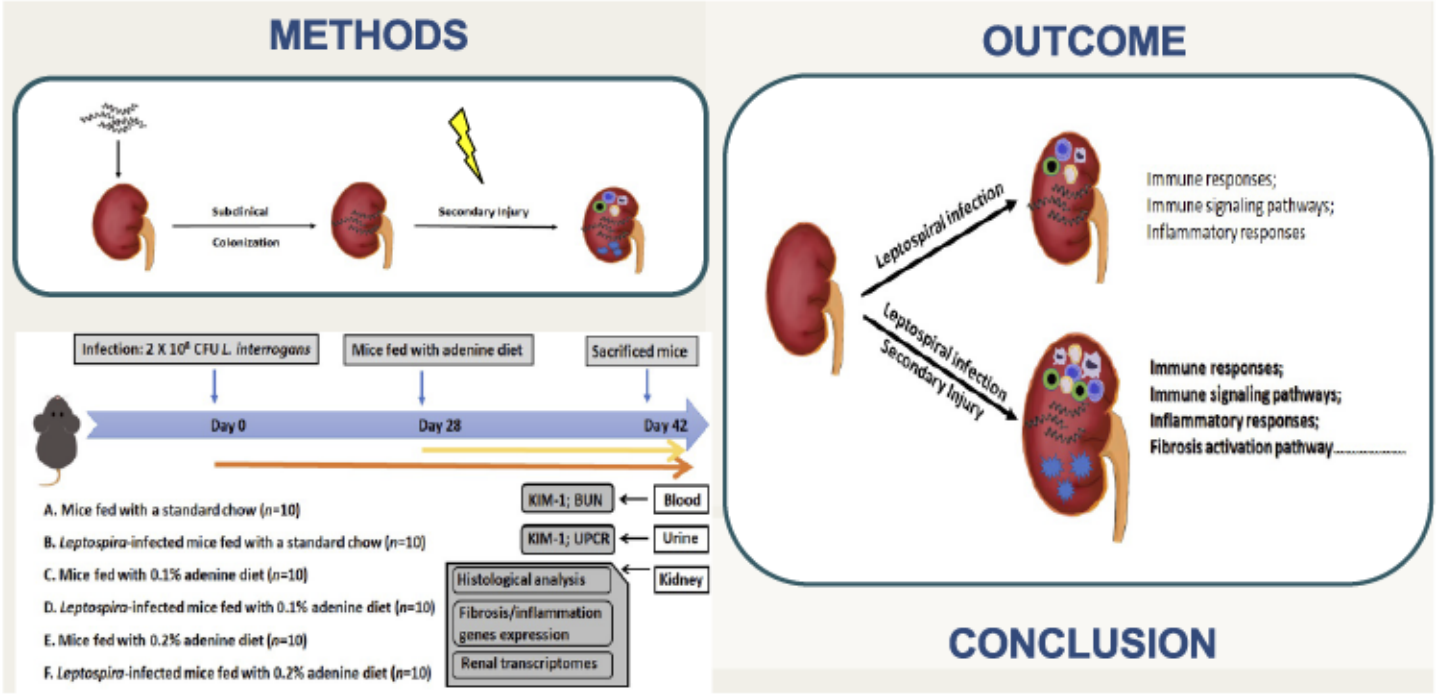
CONCLUSION Severe leptospirosis triggers ROS, cytokines, and chemokines, driving renal cell senescence, SASP secretion, and fibrosis, contributing to CKD progression.

Hsu, 2024

Hsu SH & Yang CW, Life Sciences 383 (2025) 124057

AKI on CKD

Transcriptomic Signatures of Exacerbated Progression in Leptospirosis Subclinical Chronic Kidney Disease with Secondary Nephrotoxic Injury



Chronic *leptospira* kidney infection superimposes with secondary kidney injury may aggravate kidney inflammation, damage and fibrosis dependent on the degrees of secondary injury

AMERICAN JOURNAL OF PHYSIOLOGY
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american physiological society

Chou LF 2021

1. Leptospirosis AKI may progress to CKD (AKI to CKD)

2. Chronic leptospiral kidney infection enhances secondary kidney Injury (AKI on CKD)

CKD of Unknown Etiology (CKDu)

Mesoamerican Nephropathy in Central America

Affecting primarily in men workers in the sugarcane fields

"The Island of Widows"
Chichigalpa, Nicaragua


LENS | Making Pictures, Finding Solutions in Nicaragua

that negativity."

Family and friends grieved at the burial of a 36-year-old man who died of chronic kidney disease of unknown origin, after working in the sugar cane fields for 12 years. Ed Kashi/VII Photo

Causality candidates for MeN

Infectious Diseases (Leptospires, Hantavirus, Malaria)

Extreme labor and Heat Stroke

Dehydration

Repeated Kidney Injury

Heavy Metals and Agrochemicals

Interstitial Fibrosis
Tubular Atrophy
Glomerular Sclerosis

CKD → ESRD

Leptospirosis Renal Disease: Emerging Culprit of Chronic Kidney Disease Unknown Etiology
(Yang CW; 2018; Nephron. 2018;138(2):129-136, IF: 3.457)

Similarities
Leptospirosis Kidney Disease and CKDu

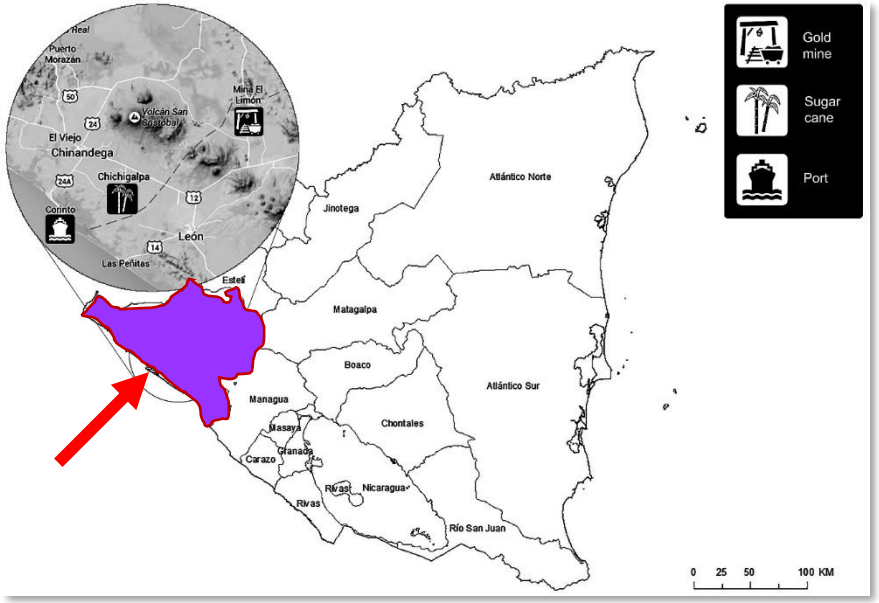
	Leptospirosis renal disease	CKDu
Risk factors	Hot climate, flooding	Hot climate
Field worker	Paddy, sugarcane	Paddy, sugarcane
Animal contact	+	?
Gender preference	Middle age male	Middle age male
Tubulointerstitial nephritis	+	+
Interstitial fibrosis	+	+
Nonproteinuria	+	+
Proximal tubule dysfunction	+	+
Hypokalemia	+	+

Yang CW, Nephron 2018, IF:3.457

CKDu and Leptospirosis
Overlapping Epidemiology

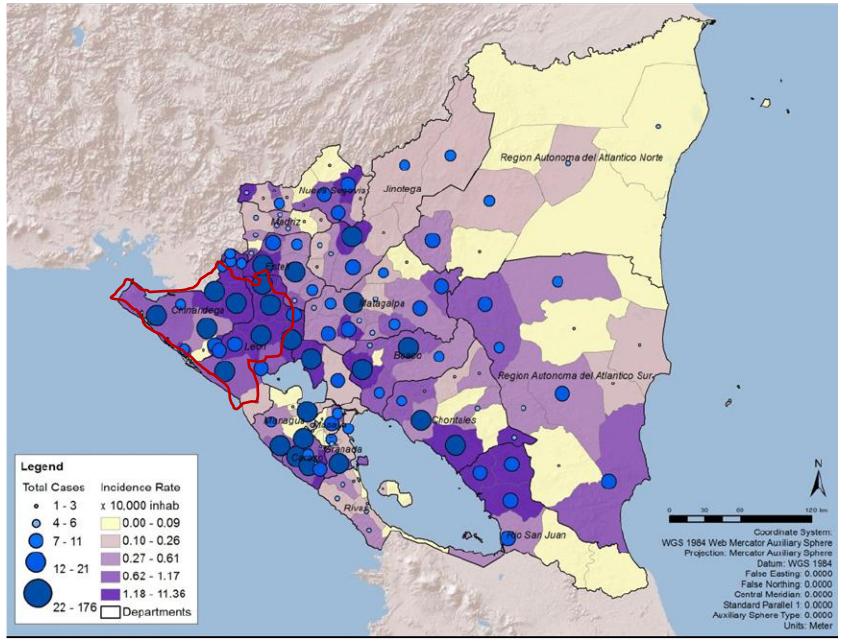
Chinandega, Leon

CKD Hotspot



Alejandro Riefkohl, *International Journal of Occupational and Environmental Health* 2016.

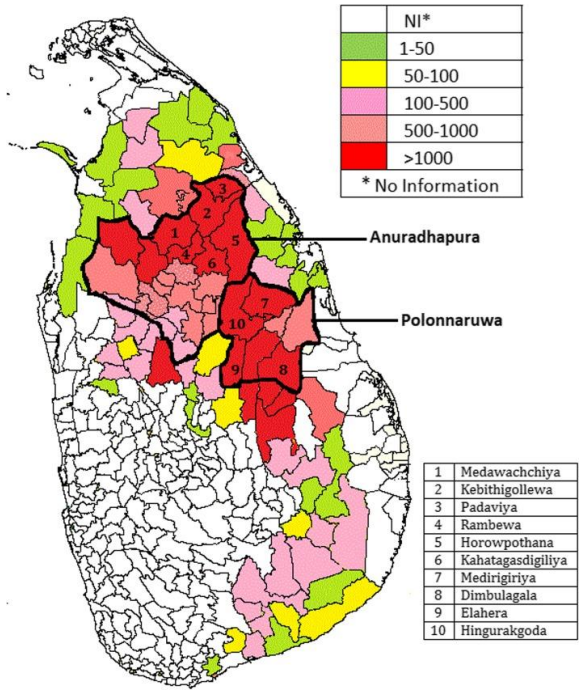
Cumulated Incidence of **Leptospirosis**
Leon, Chinandega in Nicaragua, 2004-2010



Maria Cristina Schneider,
Int. J. Environ. Res. Public Health 2012, *9*, 3883-3910

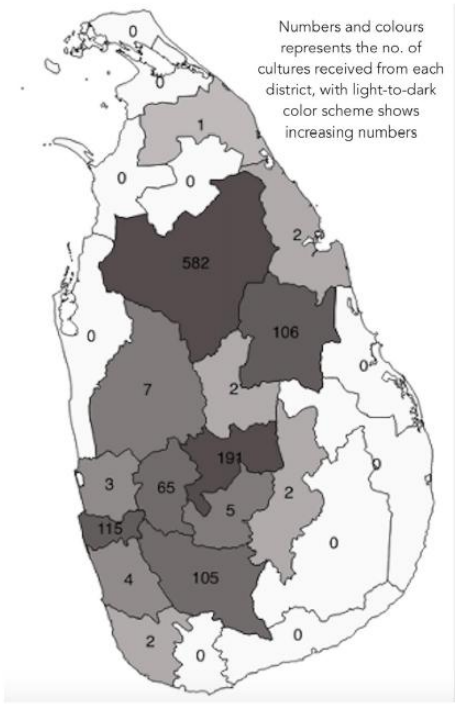
Nicaragua

CKDu in Sri Lanka



Ranasinghe et al. BMC Nephrology (2019) 20:338

Leptospirosis in Sri Lanka

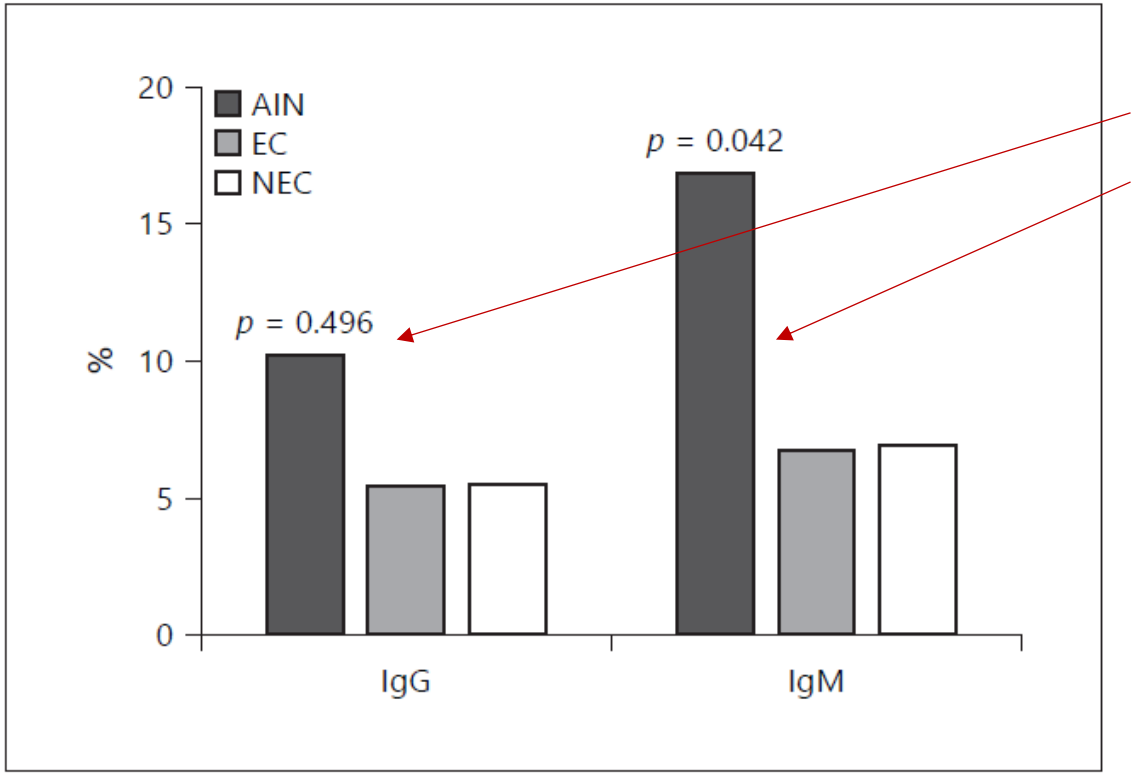


Dinesha Jayasundara, PLoS Negl Trop Dis 2021 Mar 18;15(3):e0009272.

Sri Lanka

Leptospirosis:

A Potential Culprit for Chronic Kidney Disease of Uncertain Etiology



Higher rate of anti-leptospira IgM and IgG antibodies in AIN group

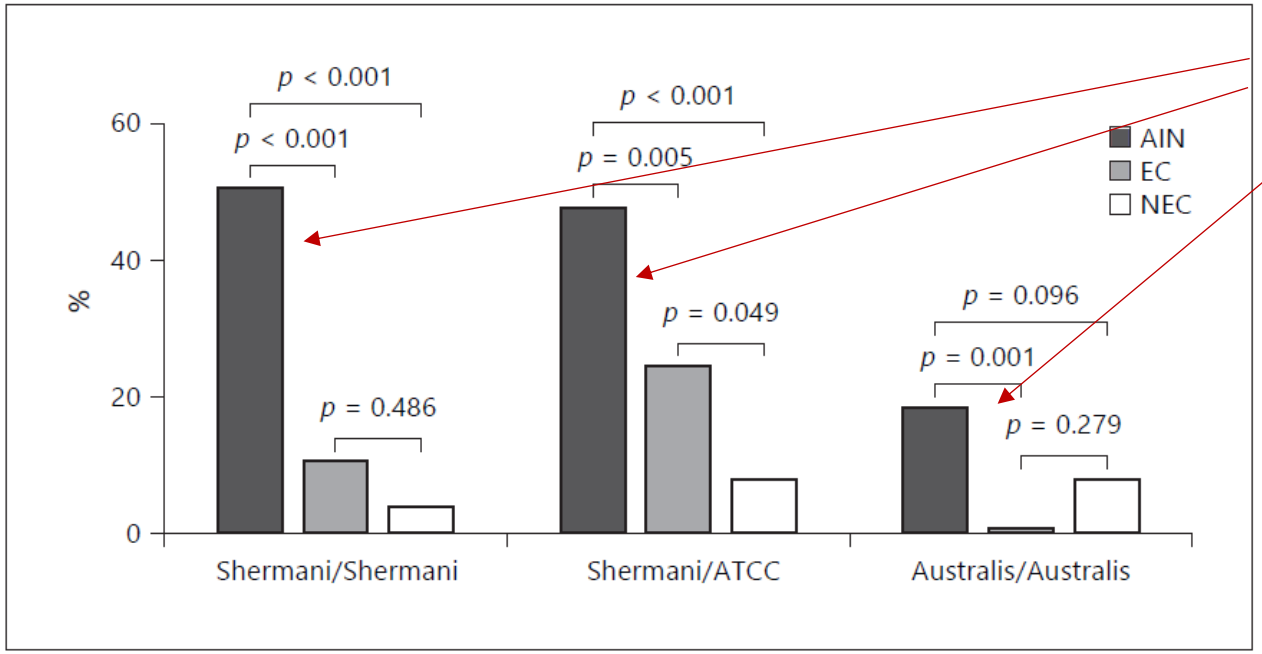
AINu: acute interstitial nephritis without known reason N=59
ECs: endemic controls N=72
NECs: non-endemic controls N=71

Seroprevalence of three groups against IgG and IgM in rapid test

Premarathne SS, Yang CW.
Nanayakkara N
Nephron, 2023

Leptospirosis:

A Potential Culprit for Chronic Kidney Disease of Uncertain Etiology



Higher rate of anti-leptospira antibodies (MAT) in AIN group

AINu: acute interstitial nephritis without known reason N=59
ECs: endemic controls N=72
NECs: non-endemic controls N=71

MAT positive rate for predominantly affecting serovars

Premarathne SS, Yang CW. Nanayakkara N
Nephron, 2023

Nephron

World Kidney Health: Research Article

Nephron
DOI: 10.1159/000528703

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Leptospirosis: A Potential Culprit for Chronic Kidney Disease of Uncertain Etiology

Shakila Sudarshani Premarathne[a, b] Chandika Gamage[b] Rohana Chandrajith[c] Neelakanthi Vajira Ratnatunge[d] Sulochana Wijetunge[d] Abdul Wazil[e] Li-Fang Chou[f] Yi-Ching Ko[f] Chiung-Tseng Huang[f] Huang-Yu Yang[f, g, h] Amanda Fonseka[b] Thamalu Sonnadara[a] Dulanjali Herath[a] Pasan Hewavitharane[a] Chih-Wei Yang[f, g, h] Nishantha Nanayakkara[e]

[a]Centre for Research, National Hospital, Kandy, Sri Lanka; [b]Department of Microbiology, Faculty of Medicine, University of Peradeniya, Kandy, Sri Lanka; [c]Depatment of Geology, Faculty of Science, University of Peradeniya, Kandy, Sri Lanka; [d]Department of Pathology, Faculty of Medicine, University of Peradeniya, Kandy, Sri Lanka; [e]Nephrology and Kidney Transplant Unit, National Hospital, Kandy, Sri Lanka; [f]Kidney Research Center, Chang Gung Memorial Hospital, Linkou, Taiwan; [g]Department of Nephrology, Chang Gung Memorial Hospital, Linkou, Taiwan; [h]College of Medicine, Chang Gung University, Taoyuan, Taiwan

Advancing CKD Care and Combating Infectious Diseases

Early Identification of Leptospirosis and Timely Treatment

Zero Death: Rapid IgM Test Rescues Acute Leptospirosis Patients

2000-2023

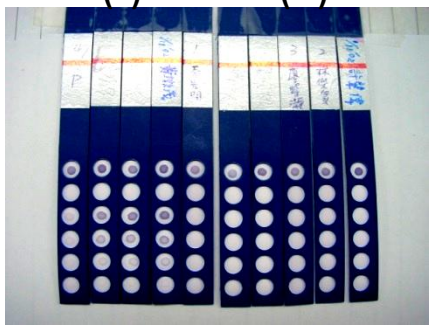
Confirmed

N=70/1281 (5.5%)

Zero Death

Dipstick (Panbio)

(-) (+)

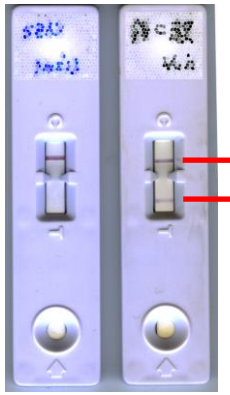


30 min

Lateral-Flow (Biomerieux)

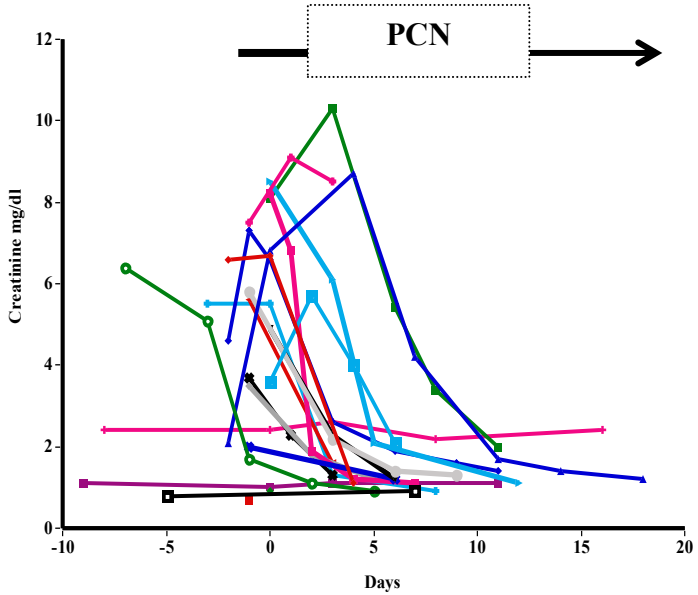
10 min

Lateral-Flow (Life Assay Diagnostics)

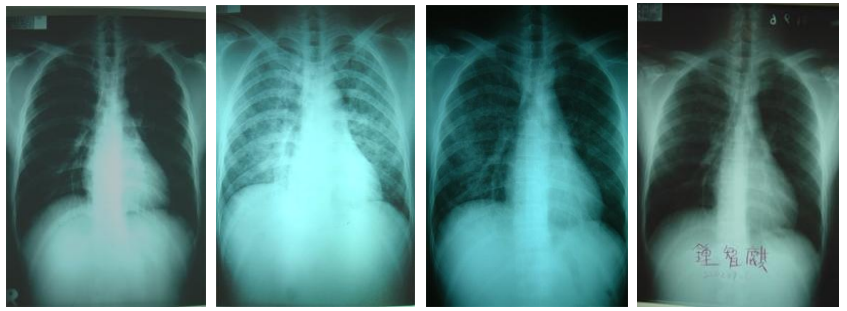


10 min

Rapid Improvement of AKI after appropriate Antibiotics Penicillin

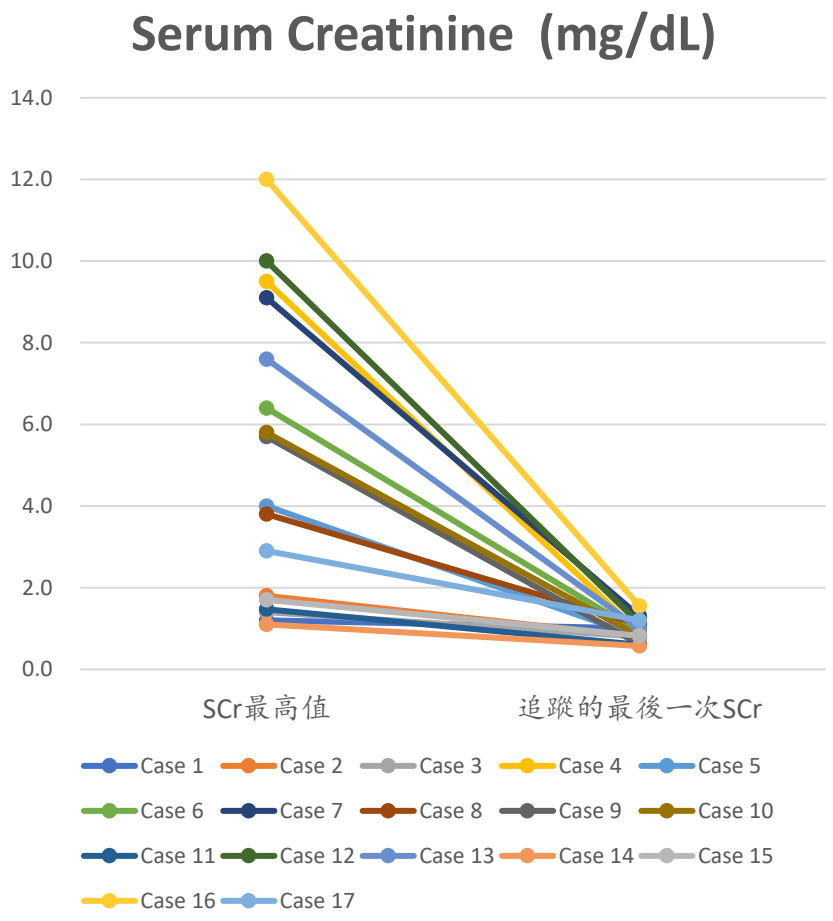


Effect of Penicillin

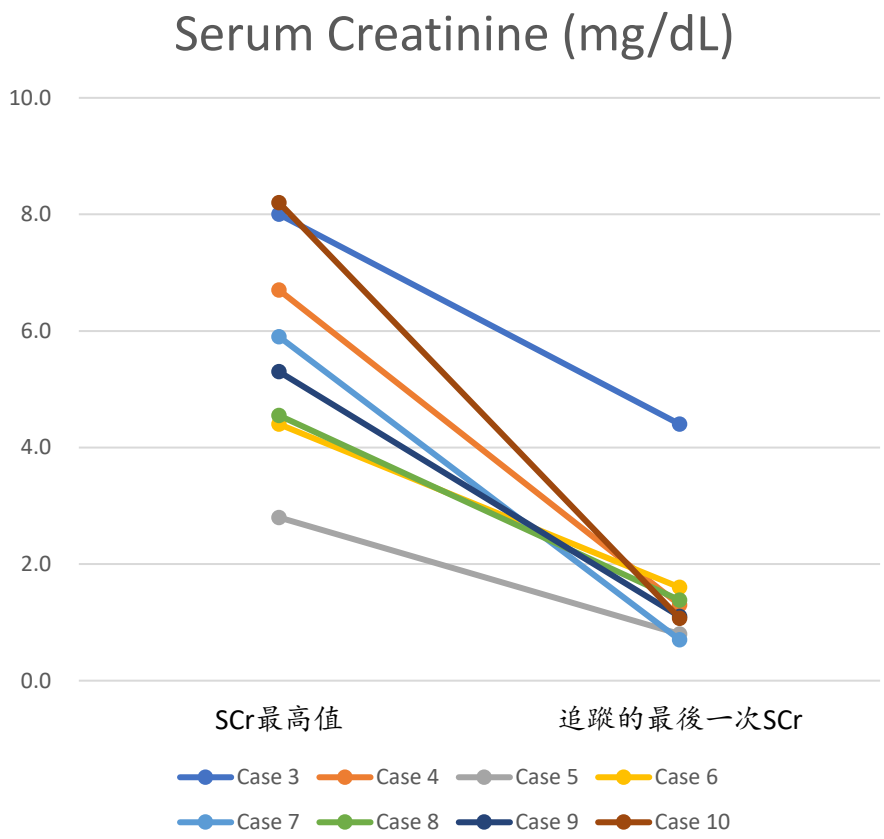


2002-9-1 2002-9-2 2002-9-3 2002-9-6

Effective Treatment of Leptospirosis
Ceftriaxone vs Penicillin



Ceftriaxone



Penicillin

劉怡君

Unmet Clinical Need for Rapid DX

Microscopic Agglutination Test – serologic test

耗時繁瑣 - Time Consuming

Rapid IgM assay (Lateral Flow, ELISA)–

篩檢非確診- screening not confirmation

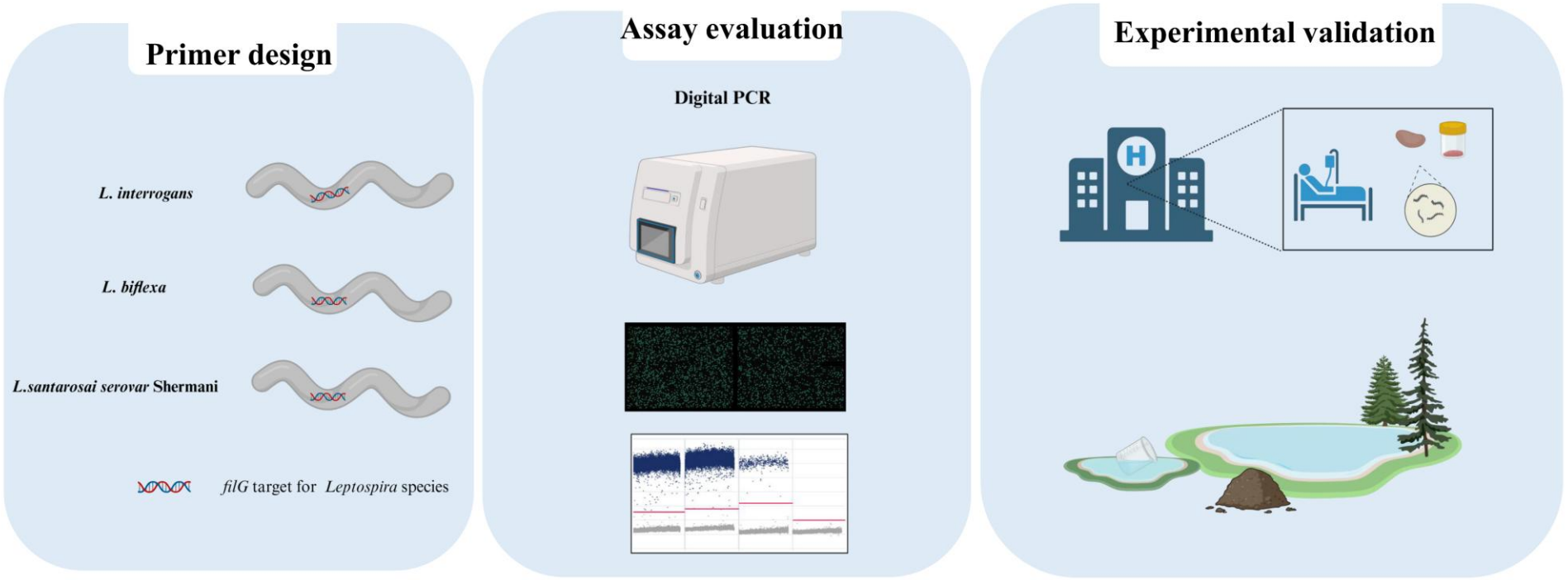
Leptospiral culture –

成功率不高 - Low success rate

PCR – for leptospira DNA

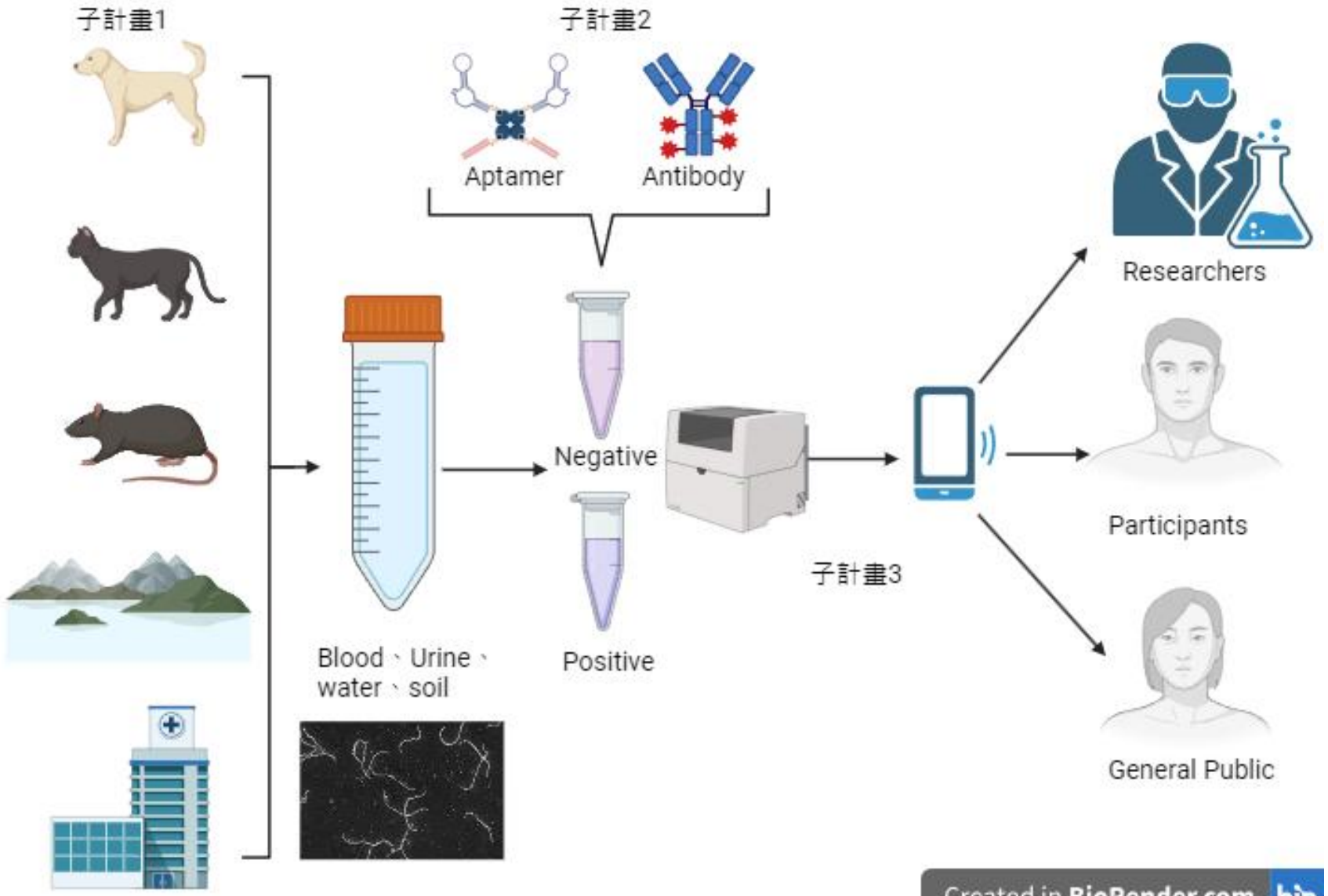
敏感度待加強 – Sensitivity needs improvement

Digital PCR-based detection strategy for *Leptospira* spp.: From experimental infection models to clinical and environment validation



1. Digital PCR with a novel *fliG*-targeting assay for differential detection with improved sensitivity X10 times
2. Improved diagnosis in chronic infection for animal leptospirosis

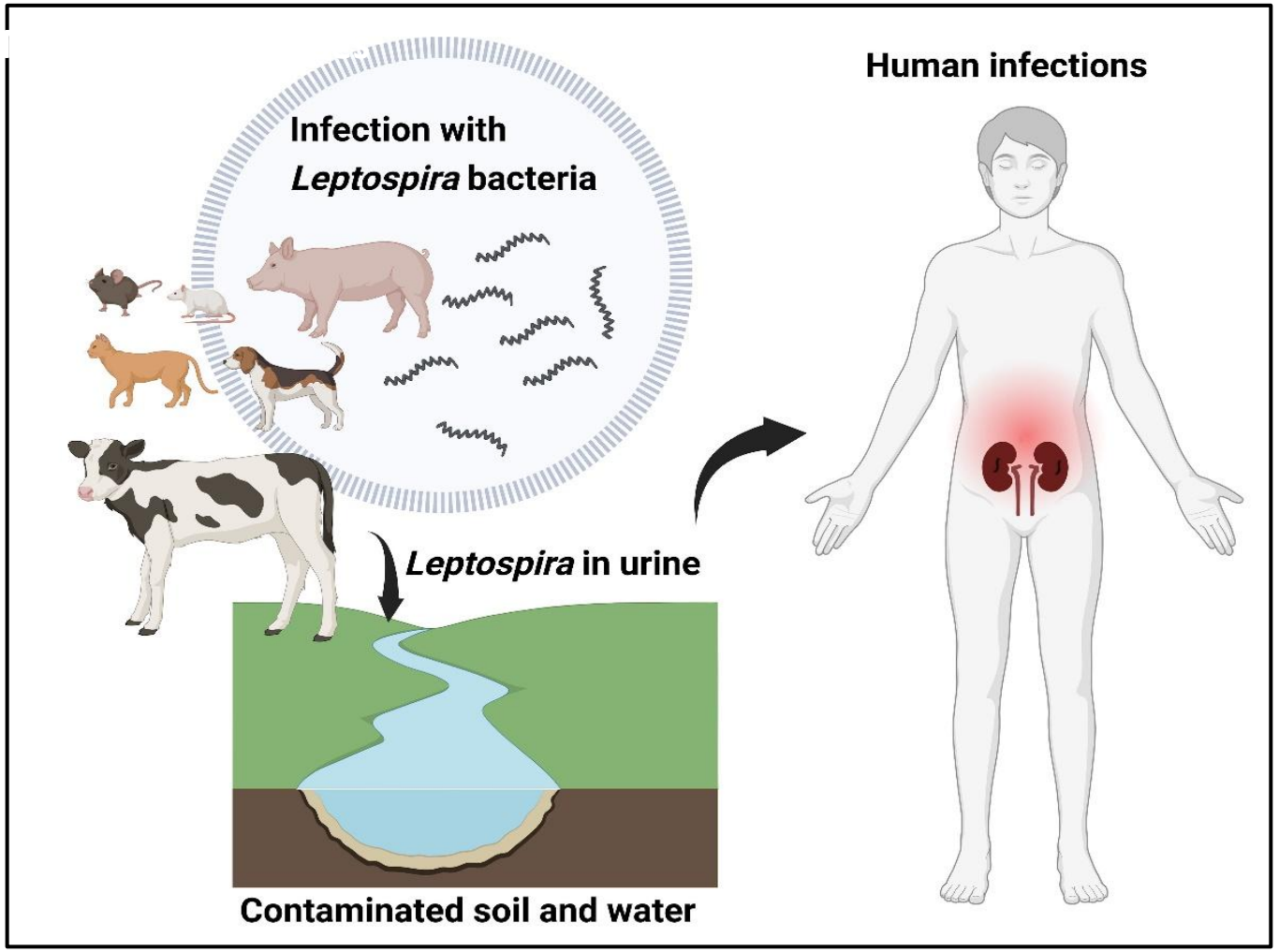
Development of a multi-platform detection system for leptospirosis and its clinical application



Leptospirosis : Emerging Infectious Disease

One Health Approach

Human-Animal-Environmental health



(Yang CW Semin Nephrol. 2023 Sep;43(5):151472)

Early Identification of Leptospirosis and Timely Treatment May Rescue Kidney Function From AKI to/on CKD

長庚醫療財團法人
Chang Gung Medical Foundation

Summary

- Leptospirosis is a neglected infection requiring alertness with improved sensitive tests to rescue patients.
- AKI to CKD: Leptospirosis AKI may lead to fibrosis and CKD.
- AKI on CKD: Chronic leptospira kidney infection superimposes with secondary injury aggravate kidney inflammation, damage and fibrosis.
- CKDu hot-spot areas where leptospirosis, as an endemic subclinical infection, could be a cause and aggravating etiology of CKDu.
- Early screening and antibiotic treatment may reduce the risk to CKD/ESKD.
- One Health approach to reduce leptospirosis burden.

Thank You