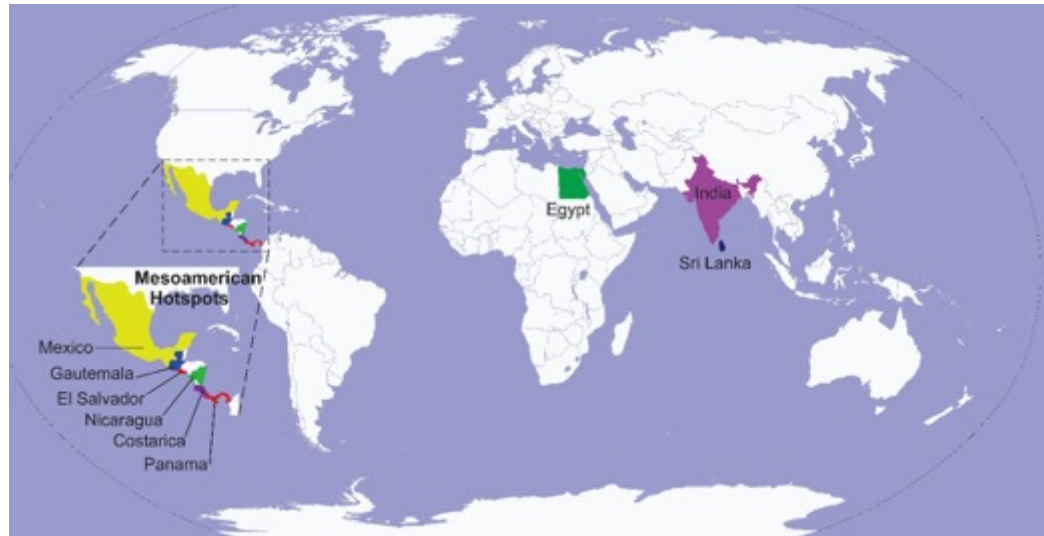


Determining the Role of Environmental Exposures on Pediatric and Adult Kidney Health Outcomes in Tropical Farming Communities

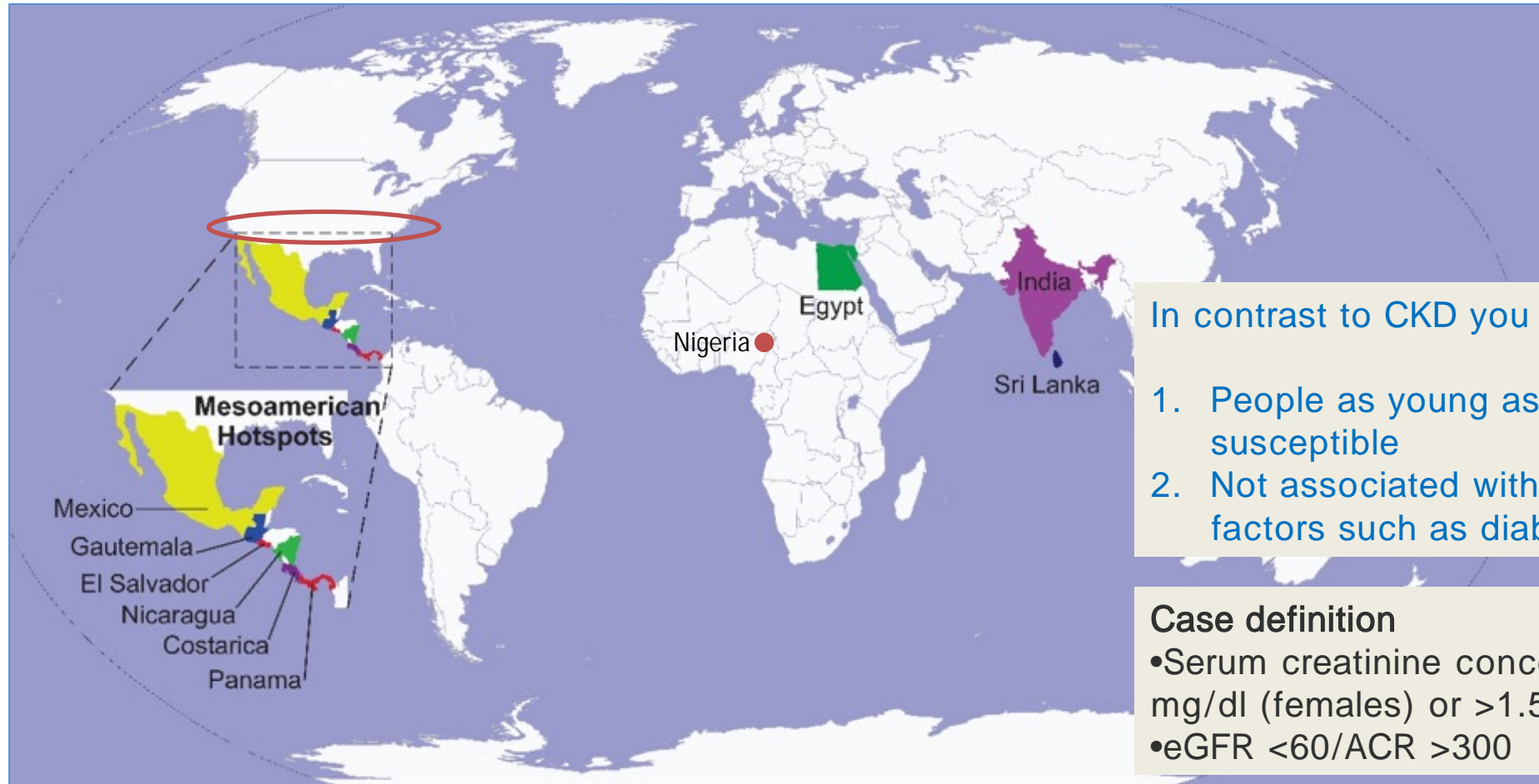


Nishad Jayasundara PhD

Assistant Professor in Environmental Toxicology and Health
The Nicholas School of the Environment & the Duke Global Health Institute
Duke University, Durham, NC.



Disease incidence: CKDu – chronic kidney disease of unknown etiology



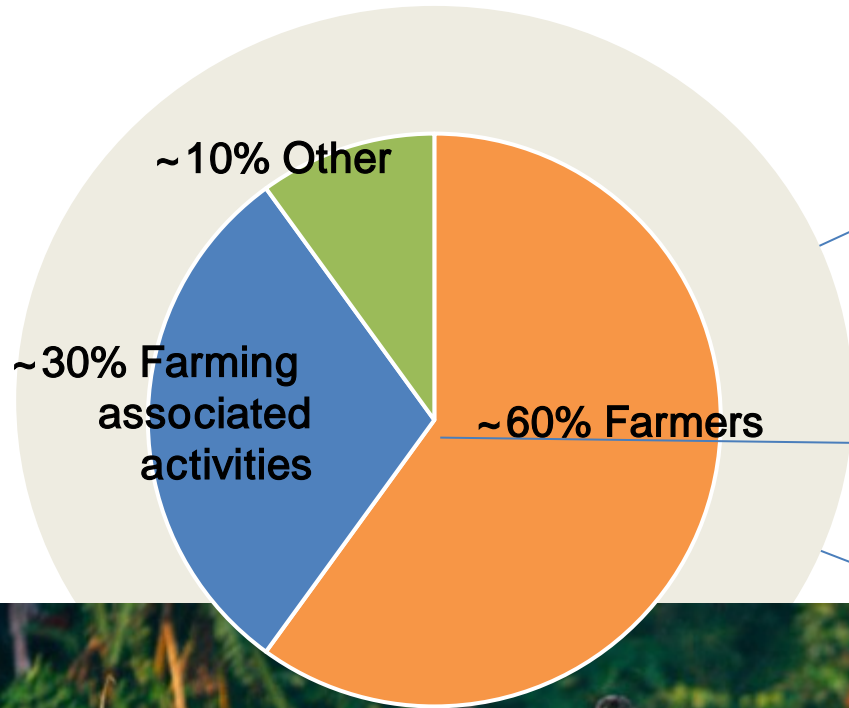
In contrast to CKD you typically see

1. People as young as 35 are susceptible
2. Not associated with any usual risk factors such as diabetes

Case definition

- Serum creatinine concentration >1.2 mg/dl (females) or >1.5 mg/dl (males)
- eGFR <60/ACR >300

CKDu burden around the world



1 - 3 men

are in end-stage renal failure in Chichigalpa in Nicaragua

60%

of the people are impacted in one community (Uddanam) in India

5- fold increase

in number of people dying from CKDu in El Salvador and Nicaragua in 20 years

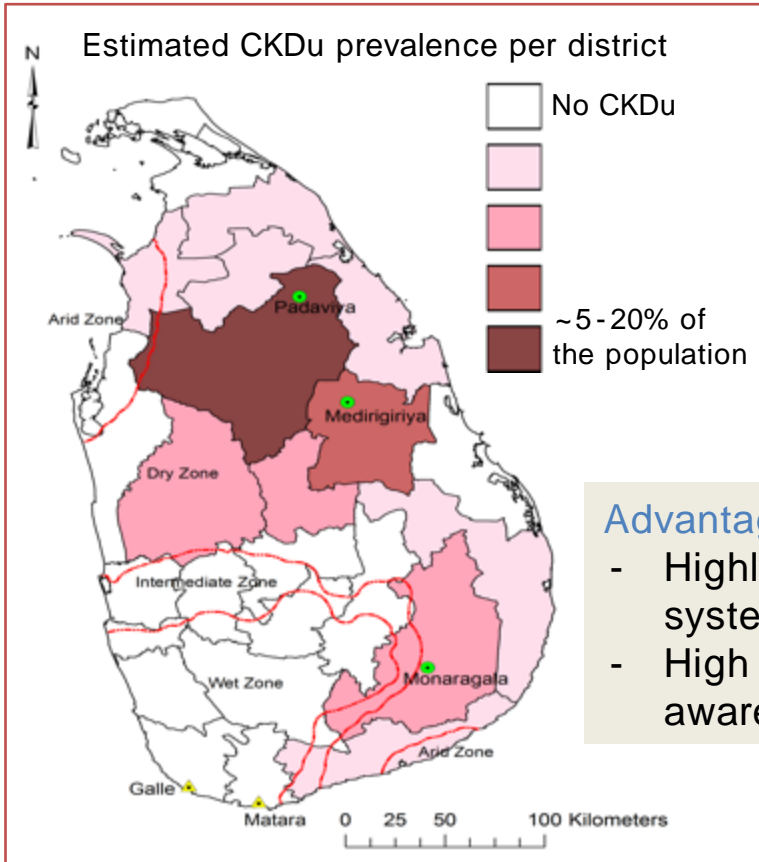
>20,000

are currently diagnosed with end-stage renal failure in Sri Lanka



Sri Lanka –one of the most impacted countries

Prof. Mangala De Silva and the Sri Lankan CKDu team



Advantages of Sri Lanka as a case study

- Highly organized public health system – documentation
- High literacy rates (>95%) – public awareness



A typical CKDu village

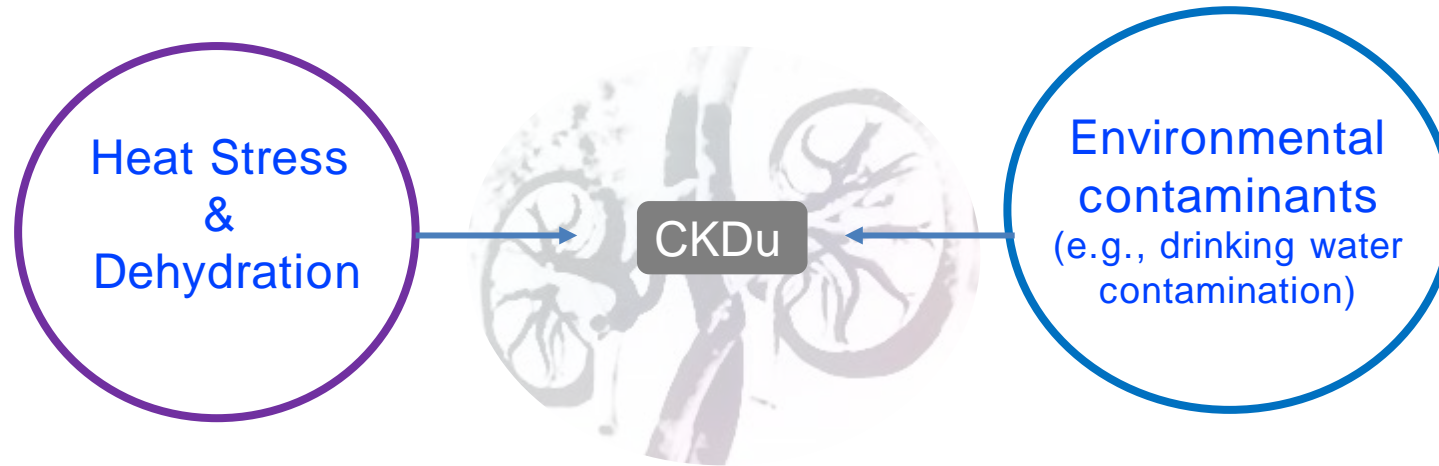


Collaborating partners

- University of Ruhuna, Matara, Sri Lanka
- THEME Institute (Non-profit)



Causes remain unknown, but a role of agrochemicals and heat



Other hypotheses:

- Genetic predisposition
- Infectious agents
- Alcohol consumption
- NSAID consumption
- Snake bites
- Traditional medicine use

What is in the drinking water?

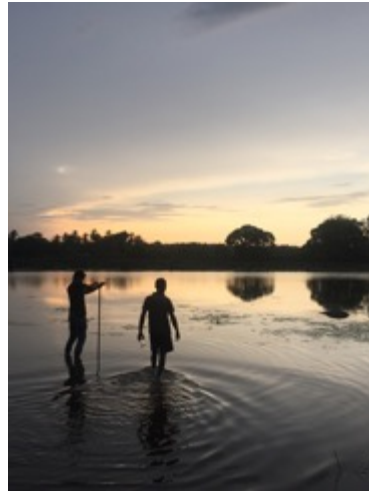
- Collect environmental samples



Drinking water wells from patients and non-patients



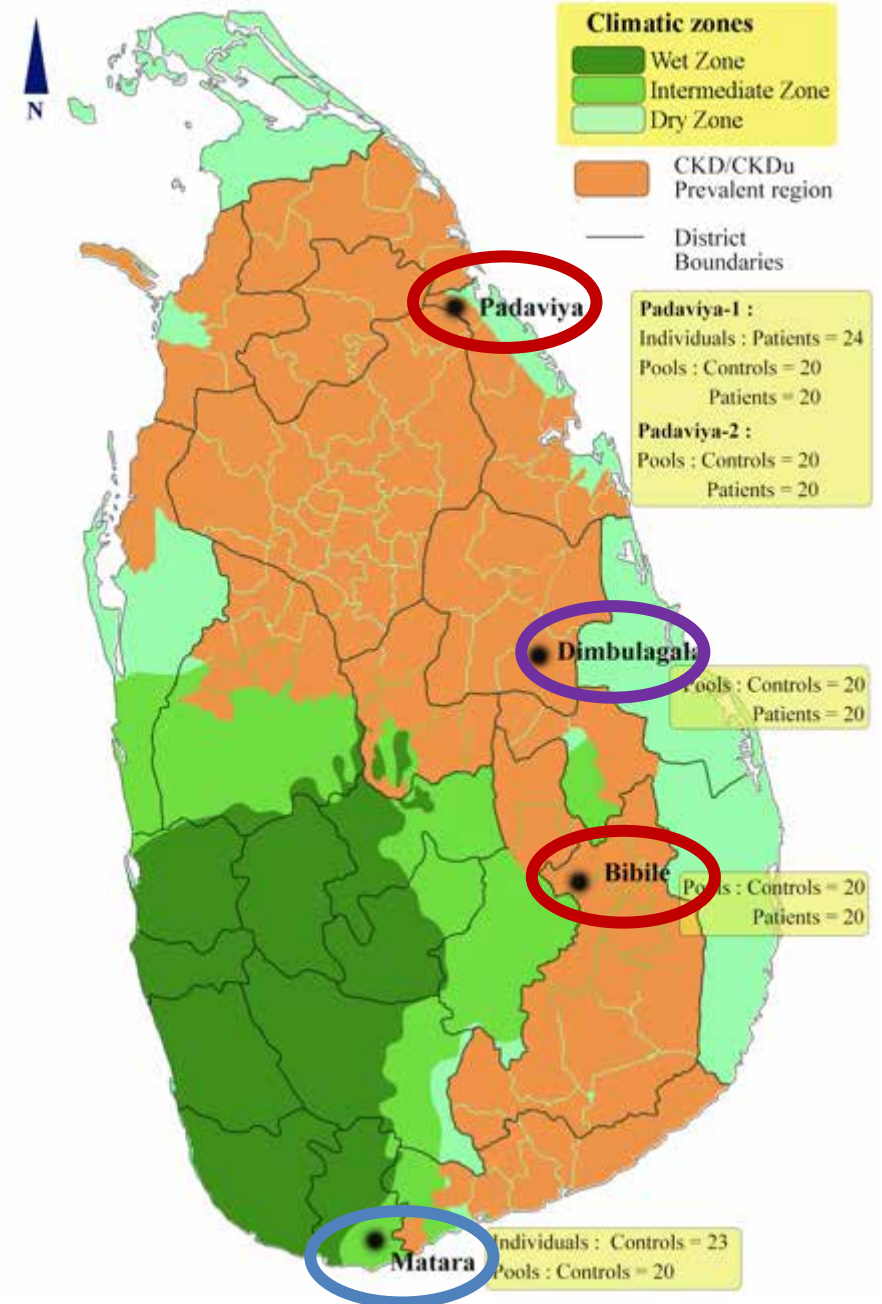
Paddy fields



Reservoirs irrigating paddy fields

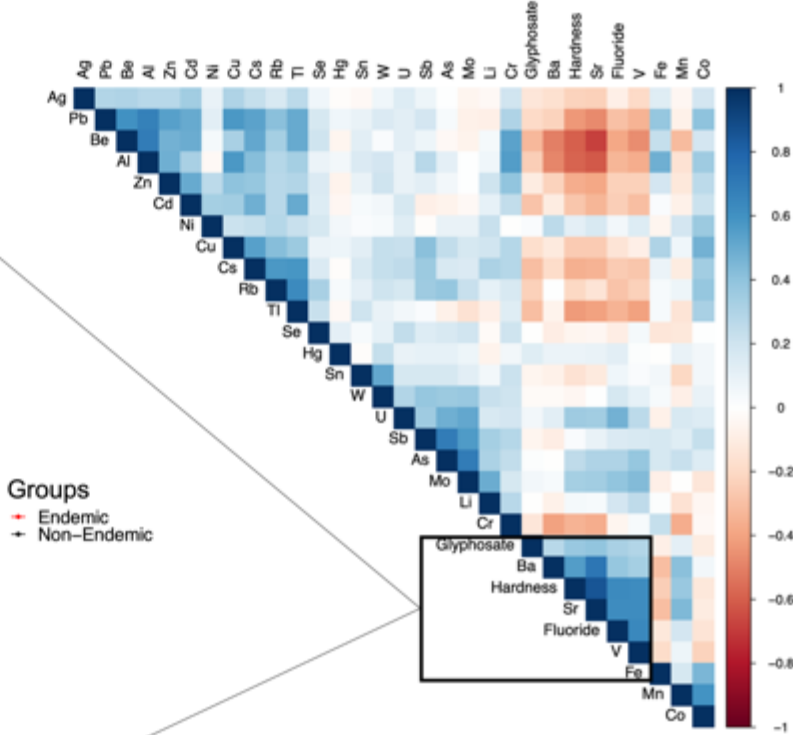
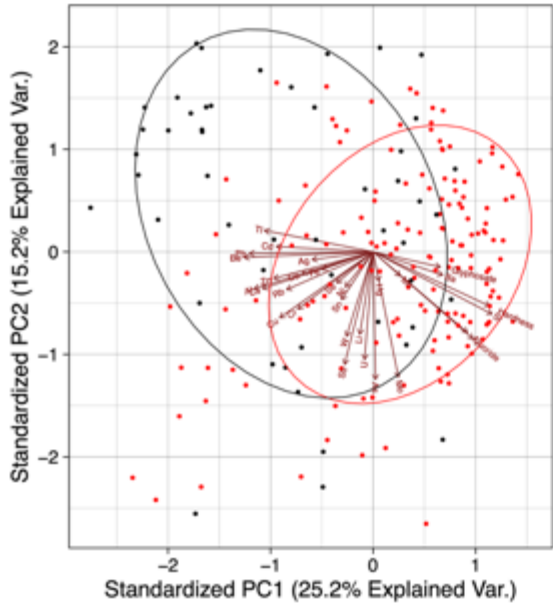
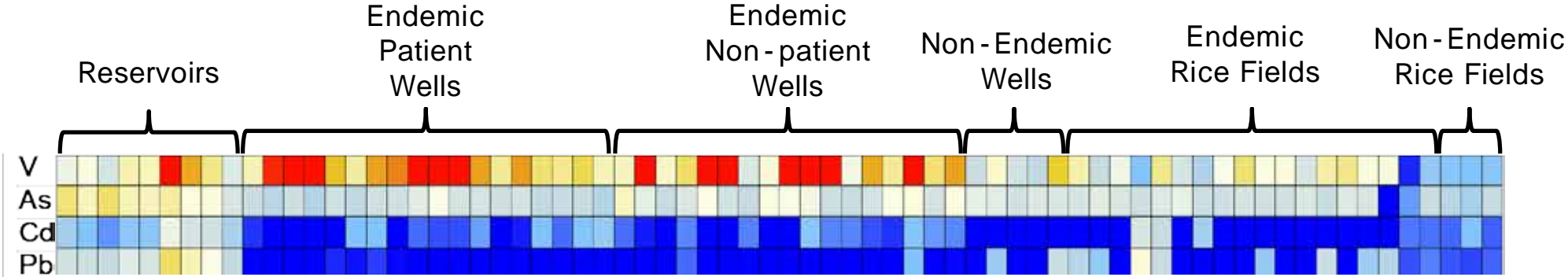


Water purification



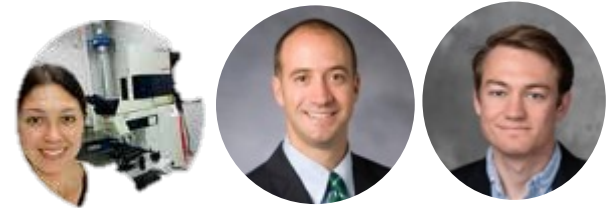
Heavy metals, trace metals, metalloids, fluoride in the drinking water

Level of metals as a % of maximum allowable limits (EPA)



- Vanadium is above regulatory limits (according to CA EPA) in CKDu affected areas
- Principal component analysis separates patient vs non-patient wells

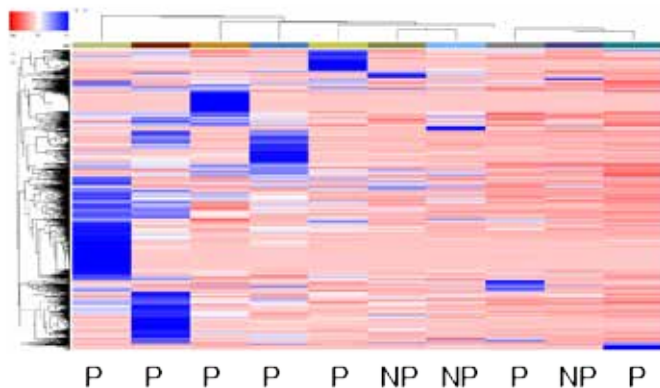
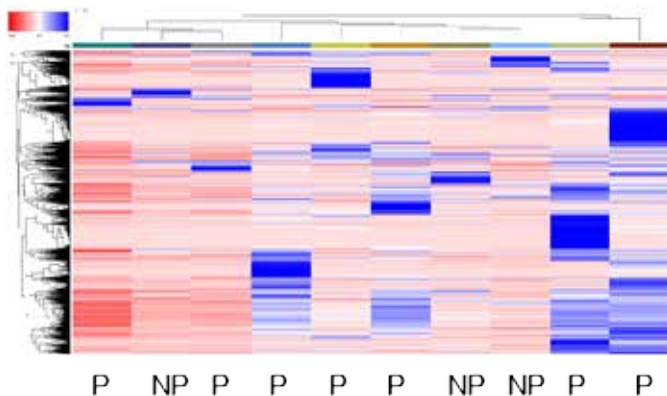
Babich et al. 2021; Ulrich et al. In prep



Dr. Remy Babich, Prof. Lee Ferguson and Dr. Jake Ulrich

Organic contaminants in the drinking water – heavy chemical burden, but heterogeneity

Liquid chromatography high resolution mass - spectrometry



P – Patient NP – Non - Patient

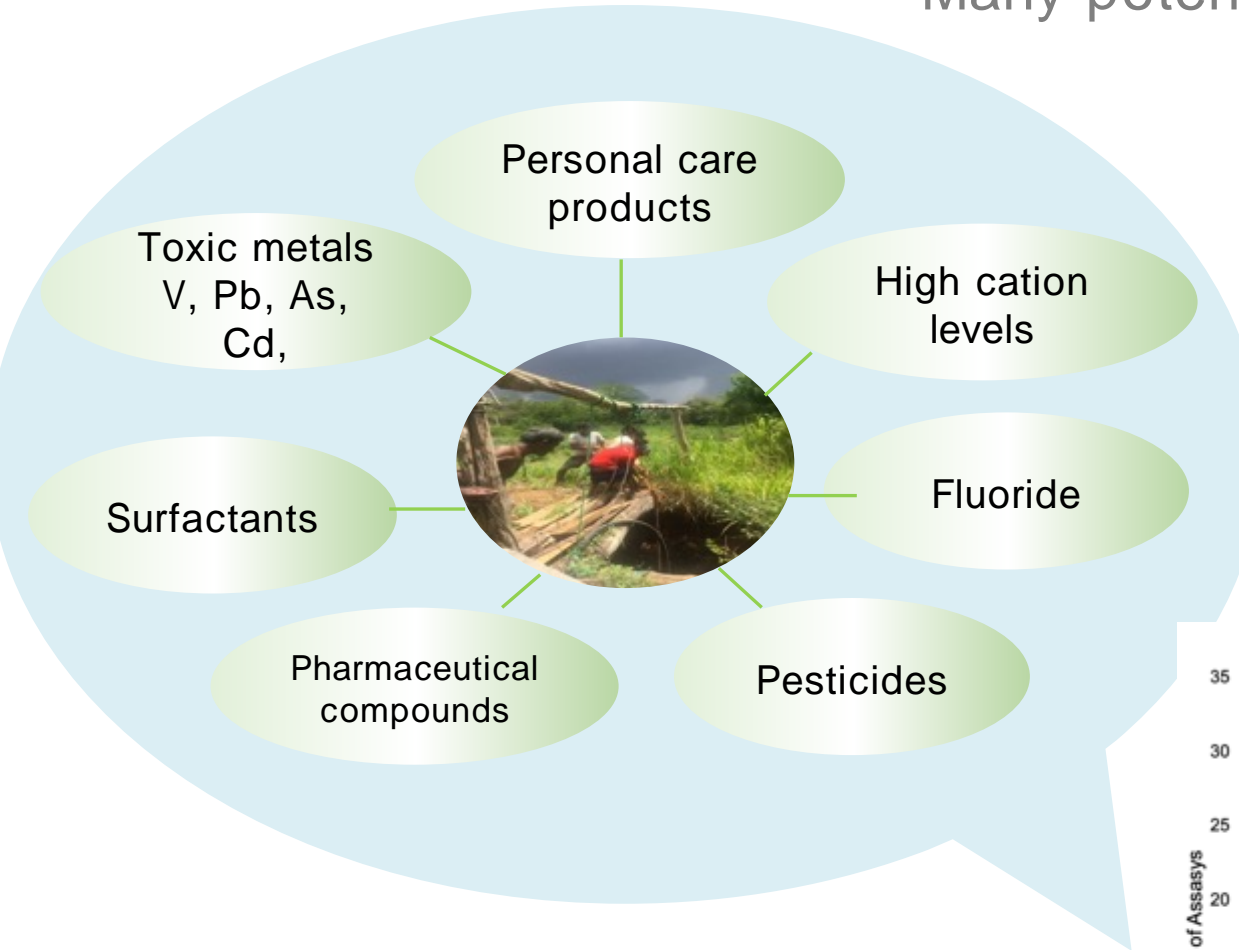


26 / 152 organic compounds have known nephrotoxic effects
(e.g., Carbofuran, Diazinon, Flutriafol)

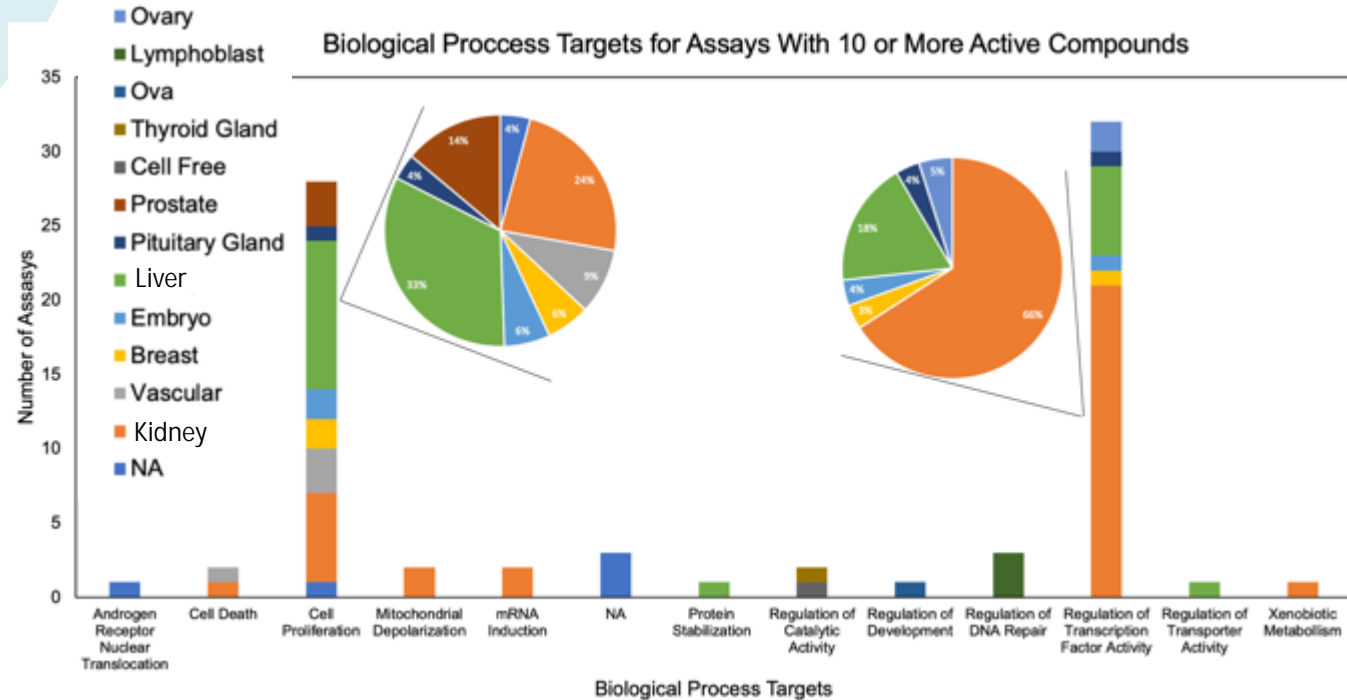


Dr. Remy Babich,
Prof. Lee Ferguson and
Dr. Jake Ulrich
Duke University, NC

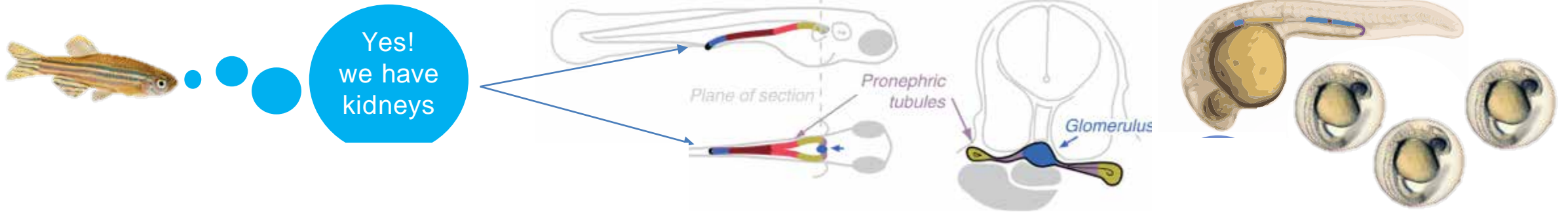
Many potential chemical contributors, but at low levels!



Predicting toxicity:
Toxicity potential of a drinking water sample



Zebrafish to evaluate toxicity of drinking water



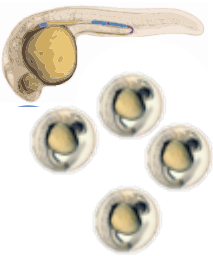
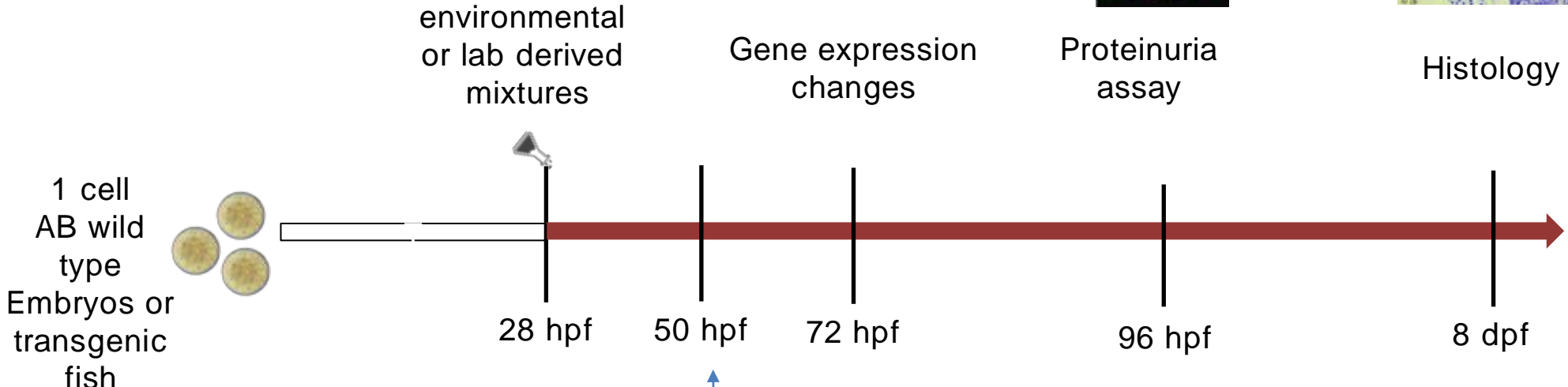
A prominent toxicological and biomedical model for kidney disease and regeneration

- Pronephros share similar cell types with human nephrons
- The glomerular filtration barrier is almost identical ultrastructurally

Zebrafish enable high throughput assessment of multiple chemical and mixtures

- Breed in large numbers (100-300 eggs per batch)
- Easy embryonic exposures and rearing larvae
- Transparent early life stages

Exposure studies with zebrafish



hpf - hours post fertilization

Fully functional pronephric tubule

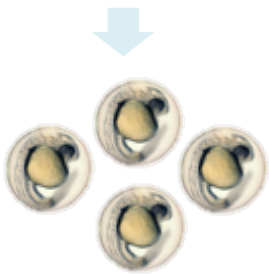


Kidney specific mitochondrial ROS levels are increased with exposure to water samples

Wells



Exposure



Prof. Iain Drummond and Dr. Yuya Sugano

nature REVIEWS NEPHROLOGY

NATURE REVIEWS NEPHROLOGY | REVIEW

Mitochondrial dysfunction in inherited renal disease and acute kidney injury

Samir M. Parikh & Leonardo Salviati

Josephine M. Forbes

PlumX Metrics

DOI: <http://dx.doi.org/10.1016/j.tem.2016.05.002>

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Mitochondrial dysfunction in the pathophysiology of renal diseases

Ruochen Che, Yanggang Yuan, Songming Huang, Aihua Zhang

American Journal of Physiology - Renal Physiology Published 18 February 2014 Vol. 306 no. 4, F367-F378 DOI: 10.1152/ajprenal.00

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Mitochondrial dysfunction and oxidative stress in patients with chronic kidney disease

Jorge L. Gamboa, Frederic T. Billings IV, Matthew T. Bojanowski, Laura A. Gillen, Chang Yu, Babak Roshanravan, L. Jackson Roberts E, Jonathan Himmelfarb, T. Alp Akcay, Nancy J. Brown

Physiological Reports Published 9 May 2016 Vol. 4 no. e12780 DOI: 10.14814/phy2.12780

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Screening for mitochondrial toxicity of drinking water samples

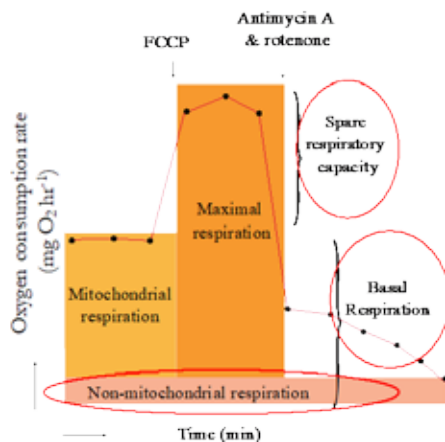
Wells



Exposure

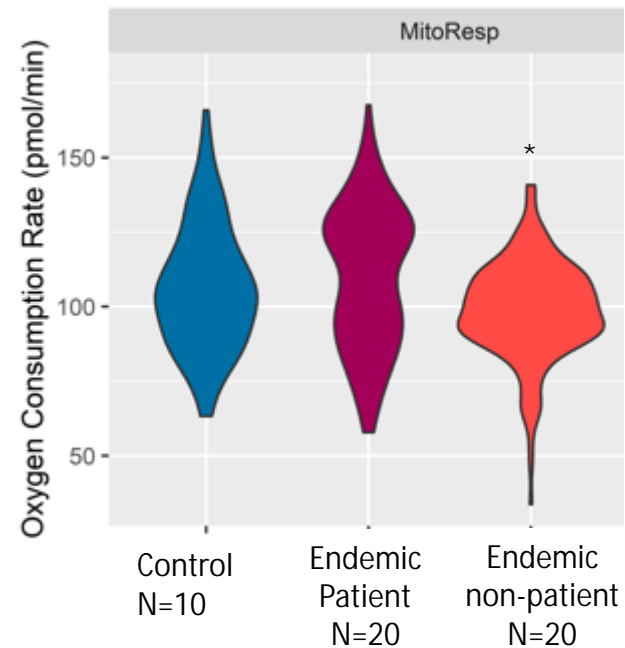


96 - well Extracellular Flux Analyzer

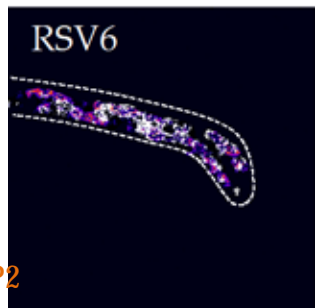
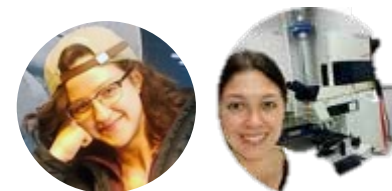


Mitochondrial function profile

Basal mitochondrial oxygen consumption rate

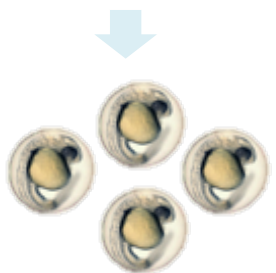


Babich et al. 2020;
Merutka et al. in prep

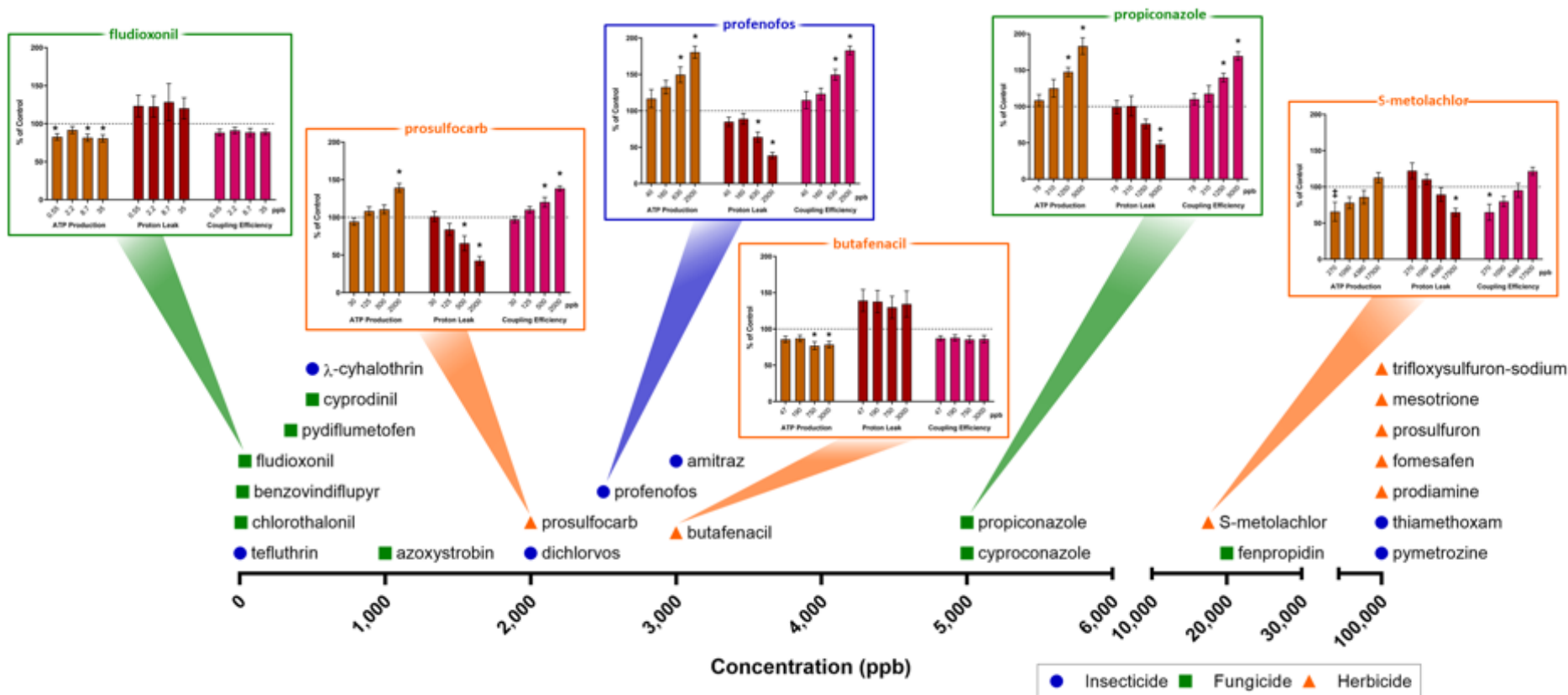


Mitochondrial toxicity of pesticides: Dose-specific toxicity to different mitochondrial parameters, and using machine learning algorithms to predict mixture toxicity

Pesticide
Exposure



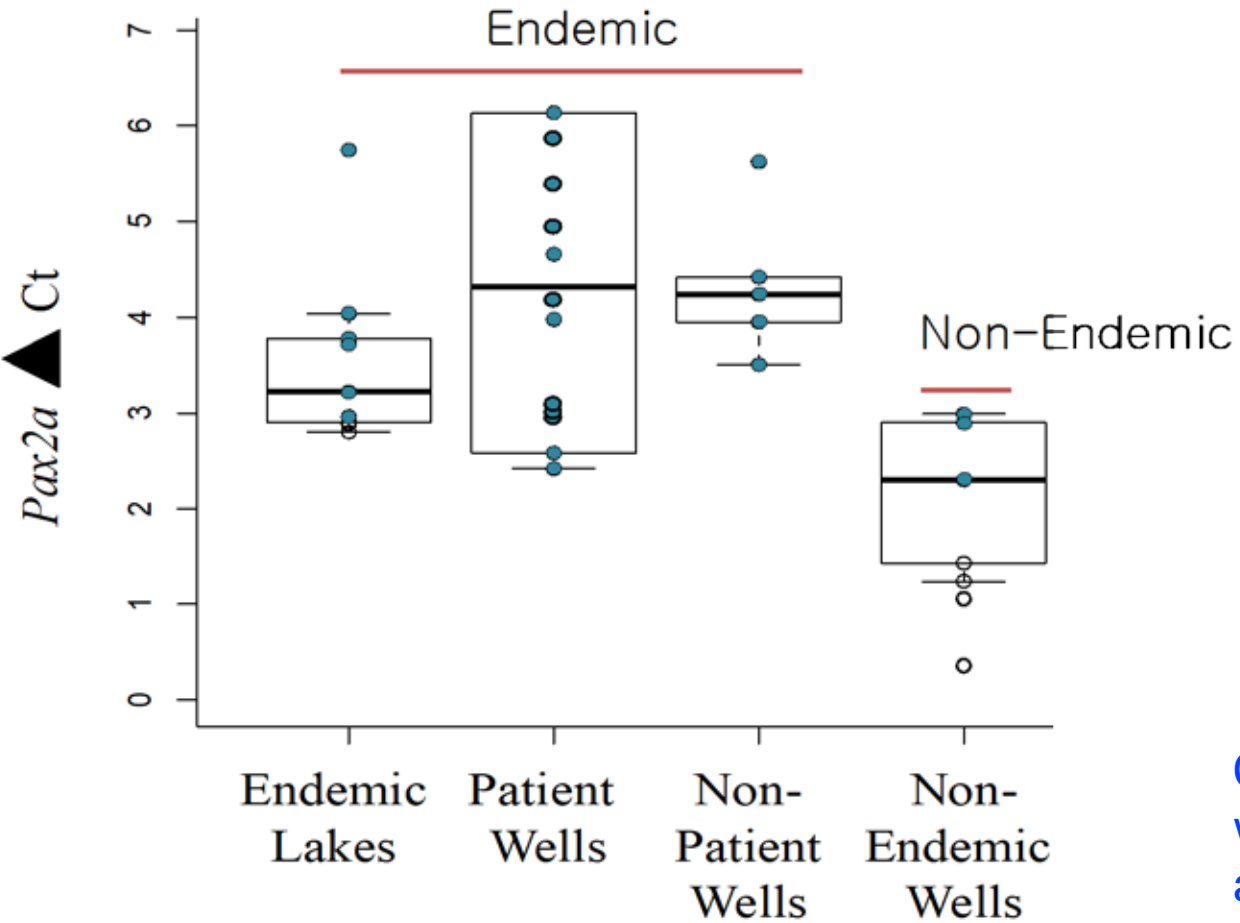
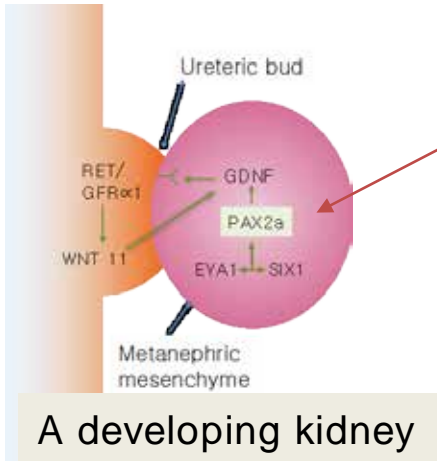
96 - well
Extracellular Flux
Analyzer



Chernick et al. In prep.

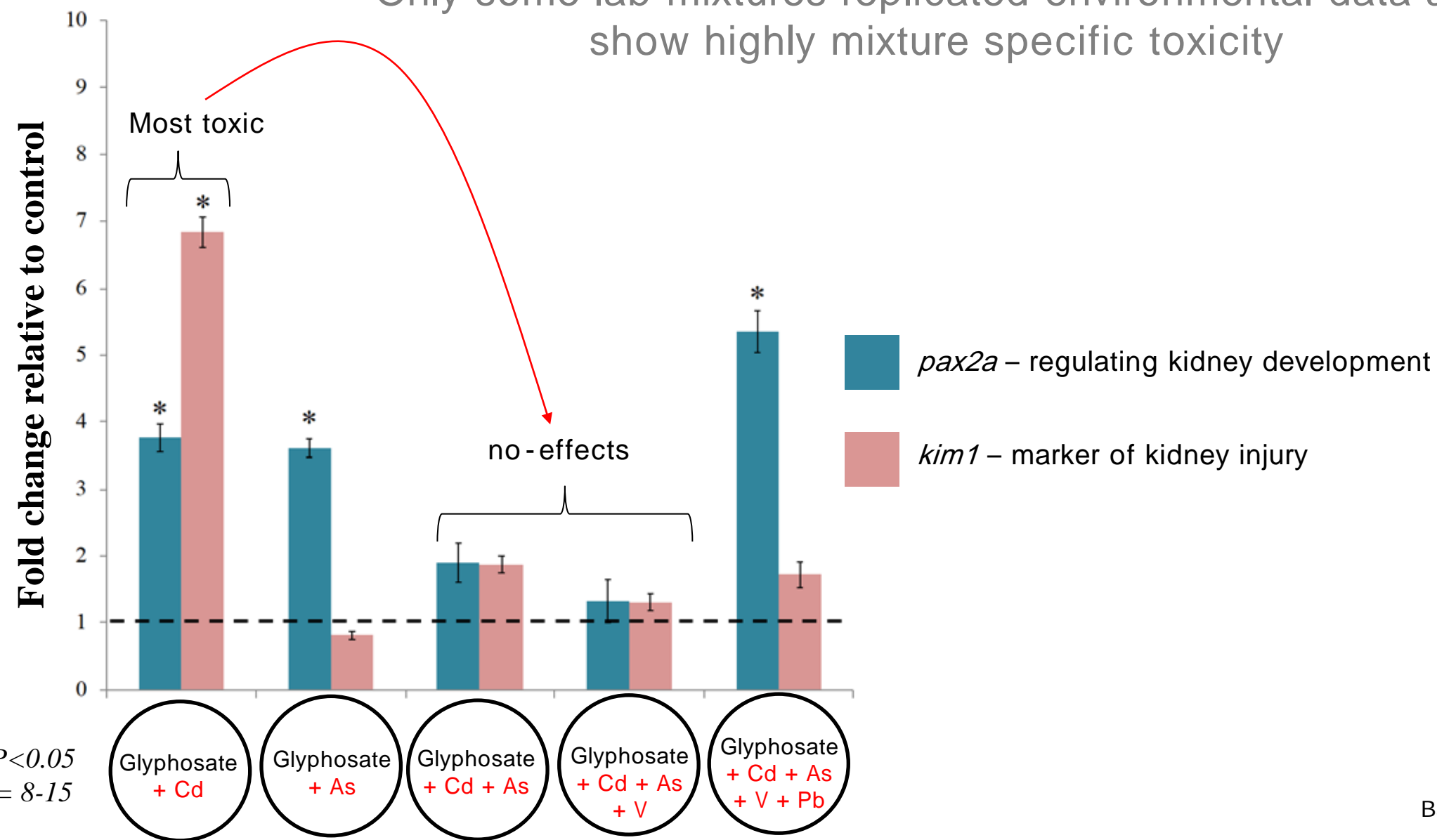
A collaboration with Nicholas Geitner PhD, Syngenta Crop Protection Inc.

Samples from CKDu regions alter a key gene involved in kidney development



Chemical constituents in endemic water samples induce *pax2a*, likely altering kidney development.

Only some lab mixtures replicated environmental data and show highly mixture specific toxicity

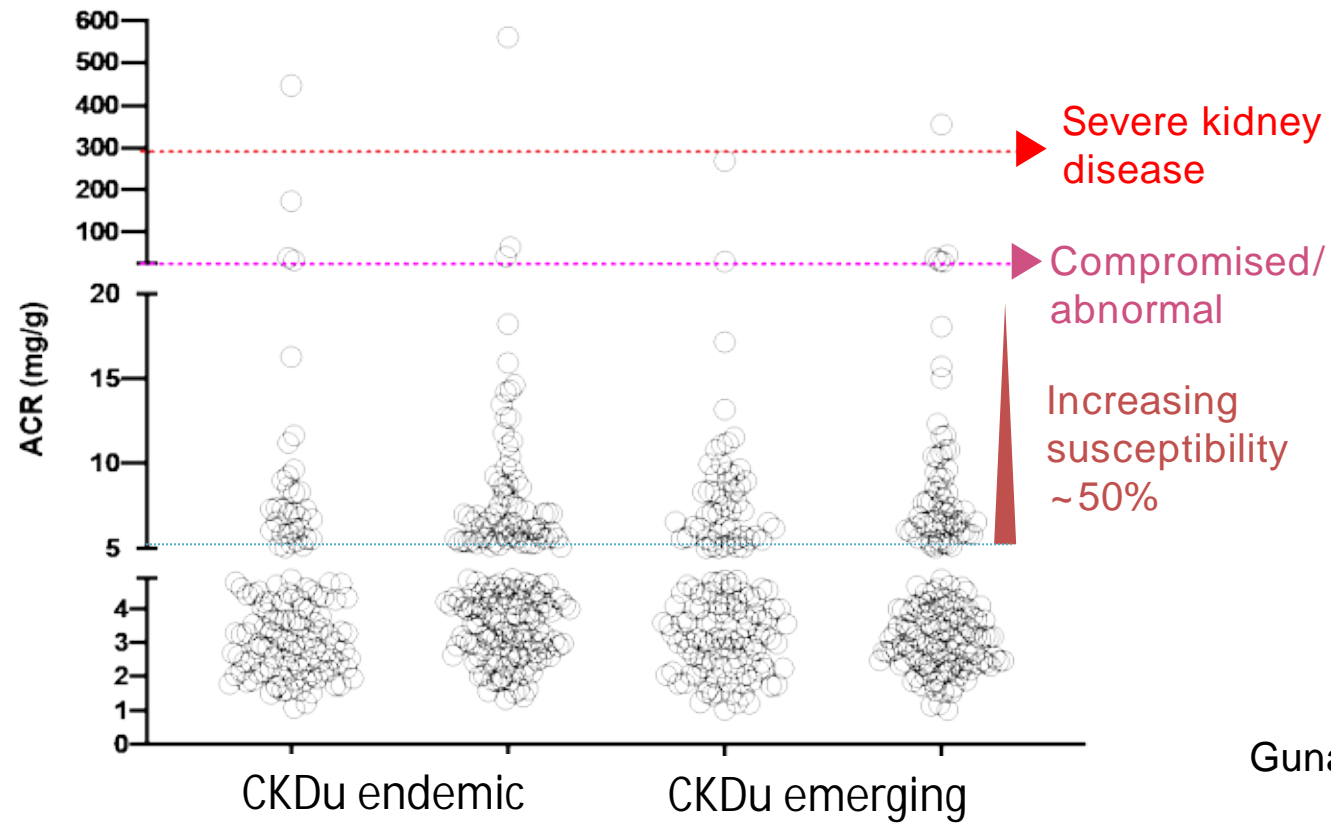


* $P < 0.05$
N = 8-15



Compromised kidney function in ~3% of the children

Microalbumin to creatinine ratio in children 14-17 yrs
(n=674)



Dr. Ramya Kolli and
Dr. Sameera Gunasekera

Gunasekera et al, 2022;

- Follow up with Children Kidney Environmental Exposure Study
(C-KidnEES cohort)

Our paradigm to explore

- 1. Synergistic effects of mixtures
- 2. Kidney as a filter and heavy chemical burden to the kidney
- 3. Developmental/childhood onset
- 4. Interventions through healthy water awareness

Chemical mixtures in the drinking water

Developmental / childhood exposure



Early Life altered kidney structure/ function

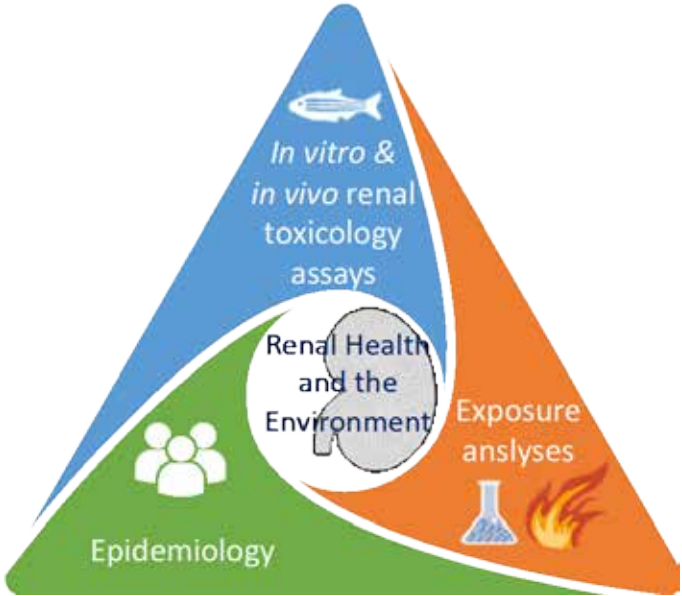


Increased Susceptibility to kidney failure



Lifestyle Associated Risk Factors including heat stress

Chronic Kidney Disease



Health outcomes of environmental exposures are becoming increasingly difficult to predict



- Duration of exposure - time
- Magnitude of exposure - amount
- Gender/race/genetic background
- Age of exposure
- Synergistic effects
- The changing chemosphere due to warming



NAMs could serve as a screening tool at the community level to uncover the complexity not captured through epidemiological studies

Thank you

Lab members (CKDu team past and present)

Ramya Kolli PhD
Remy Babich PhD
Akila Harishchandra (PhD candidate)
Ilaria Merutka (PhD student)
Kelsie Dougherty DVM
Ramya Kolli PhD
Kasun Gunawardena (Undergraduate Student)
Melissa Chernick MS

Collaborators at Duke
Richard Di Giulio PhD
Andrey Massarsky PhD
Lee Ferguson PhD
Jake Ulrich
Truls Ostbye MD

Harvard University/
Mount Desert Island Biological Laboratory
Iain Drummond PhD
Yuya Sugano PhD
Hermann Holler PhD
Jane Disney PhD
Anna Farrell
Dartmouth University
Brian Jackson

Collaborators in Sri Lanka
Mangala De Silva PhD
Kamani Wanigasuriya MD
Pathmalal Manage PhD
Sameera Gunasekera PhD



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Duke University Startup Funds



National Science Foundation
(One Health and the Environment: Convergence of Social and Biological Sciences NRT program grant DGE - 1922560)



THEME Institute, Sri Lanka.



Community
engagement



Capacity
building

While we figure out CKDu

Citizen Science
approaches for monthly
well-water monitoring and
building RO facilities



Establishment of Water filter unit

Ambagaswewa Maha Vidyalaya

Medirigiriya, Sri Lanka



Contaminated drinking water consumption is one of the major drives of chronic kidney disease of unknown etiology (CKDu) in Sri Lanka. Many areas impacted by CKDu have received water purification units and have had a positive impact on the well-being of the community. However, schools are often not included in these water filter unit projects and there are some rural schools with no safe water to drink. This project was aimed to provide clean drinking water to rural school children in CKDu endemic areas in Sri Lanka. We hope this project is one of many focusing establishing water filter units in schools.

Sponsored by
North Carolina Sri Lankan
Community

Coordinated by:
THEME Institute, Sri Lanka