



Life Make Rock: 4 Billion Years of Biomineralization

Bruce W. Fouke

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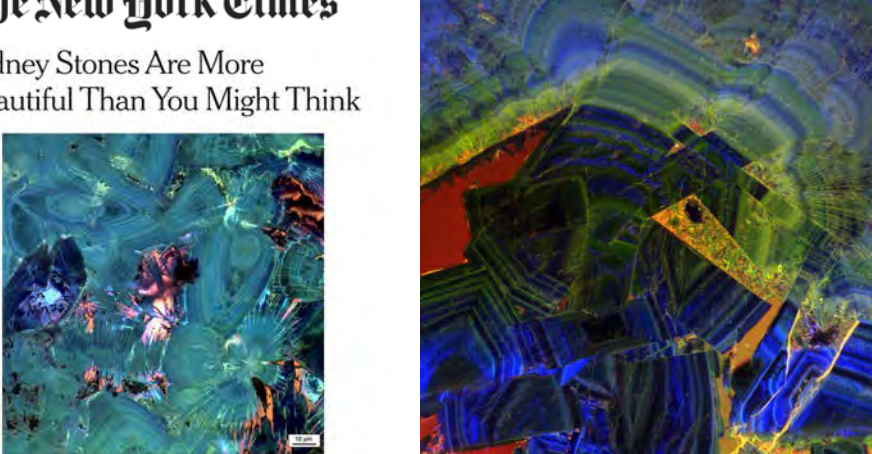
SCIENTIFIC REPORTS
Article | Open Access | Published: 13 September 2018

Geobiology reveals how human kidney stones dissolve *in vivo*

The New York Times
Kidney Stones Are More Beautiful Than You Might Think

nature REVIEWS COMMENT

GeoBioMed sheds new light on human kidney stone crystallization and dissolution



Incorporate Newly Developed Omics Technologies
<https://biotech.illinois.edu/>



Incorporate Newly Developed Microscopy Technologies



IGB Core Facilities, University of Illinois Urbana-Champaign <https://www.igb.illinois.edu/corefacilities>



Sivaguru et al. (2019) *Nature Reviews Urology*



Convergence
Facilitating Transdisciplinary Integration of
Life Sciences, Physical Sciences,
Engineering, and Beyond
NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

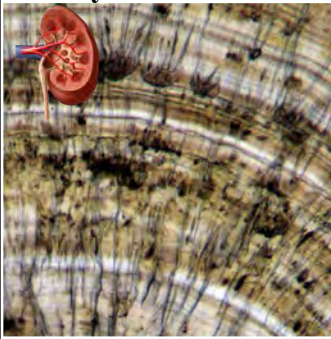

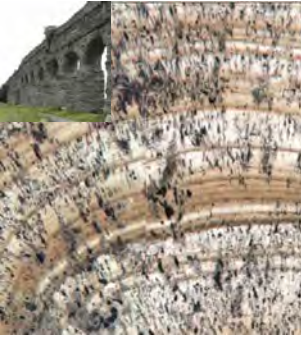
Sivaguru et al. (in preparation)

Mayo-Illinois Alliance
Mayo O'Brien Foundation
Rare Kidney Stone Consortium

**Mayandi Sivaguru, Jessica J. Saw, John Lieske, Michael Romero,
Amy Krambeck, Nicholas Chia, Glenn Fried, Yiran Dong,
Annette Merkel, James Bruce, Derek Wildman, and Bruce Fouke**


Mayo Clinic School of Medicine, Mayo Clinic
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Department of Geology, University of Illinois at Urbana-Champaign
Department of Microbiology, University of Illinois at Urbana-Champaign

 **1672 Law of Superposition
Biomineralization
Fossil Microbial Biofilms** 

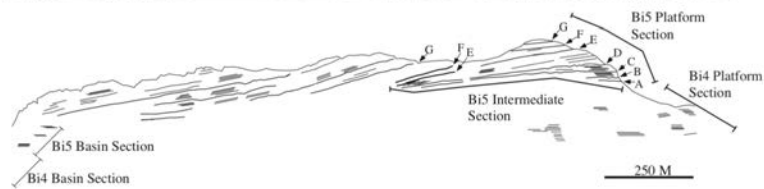
Kidney Stones  **Cave Speleothems**  **Roman Aqueduct Travertine** 

Integrated Field and Laboratory Controlled Experimentation

Research conducted with permission under Yellowstone US National Park Service Permit YELL-2019-SC-E3060  Conducted under Australian Great Barrier Reef Marine Park Authority Permit G15/37167.1

Sedimentology, Stratigraphy, Geochemistry, Diagenesis



Fouke et al. (2005) *Sedimentary Geology*

GeoBioMed

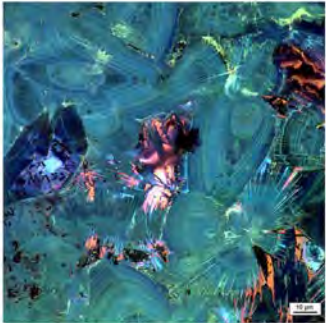
1. Ongoing integration of newly developed technologies:
Super Resolution Auto-Fluorescence (SRAF) microscopy, suite of Microscopy-to-Omics, Microfluidics, and many others
2. Ongoing integration of geoscience concepts and approaches:
Powers of 10, Paragenetic Sequence, Growth Rates, Dissolution Rates, Timing, Magnitude, Layer Frequency
3. GeoBioMed = Feedback between Geobiology and Medicine
4. Kidney stone research is now advancing geoscience research, just as geoscience research is propelling kidney stone research

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Geobiology reveals how human kidney stones dissolve in vivo
<https://www.nature.com/articles/s41598-018-31890-9>

The New York Times

TRILOBITES
 Kidney Stones Are More Beautiful Than You Might Think



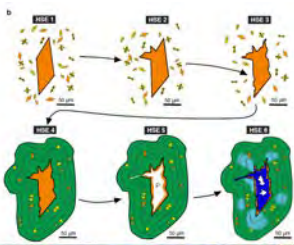
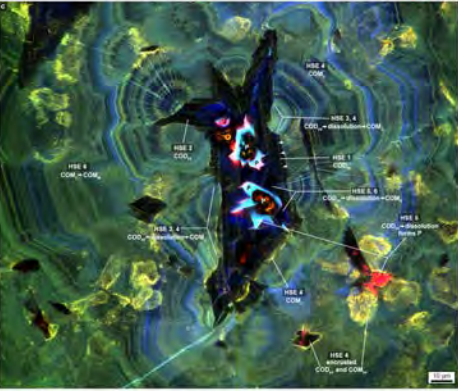
An extreme close-up of a very thin slice of a human kidney stone reveals the intricate patterns of its mineral layers.

Mayandi Sivaguru, Jessica Saw from Bruce Finke Lab, Carl R. Wicker
 Institute for Genomic Biology, U. of I.

Paragenetic Sequence reveals how >80% of CaOx crystalline stone volume dissolves in vivo

Historical Sequence of Events (HSE)

- HSE 1** Fine biogenic calcian oxalate dihydrate (CO₂) and monohydrate (COM₁) crystals grow in the calyx and pelvis.
- HSE 2** CO₂ continues to form crystal aggregates and hollows.
- HSE 3** Outer surfaces of CO₂ crystals dissolve.
- HSE 4** COM continues (COM₂) grows on CO₂, replacing areas COM₁ and CO₂ left in and are excluded by COM₂.
- HSE 5** CO₂, COM₁, and COM₂ dissolve during passage in the form of subacute crystal clasts and regular void spaces.
- HSE 6** COM replacement (COM₃) forms in pore spaces and as remnant COM (COM₄).

Life Makes Layered Rock

Kidney Stones

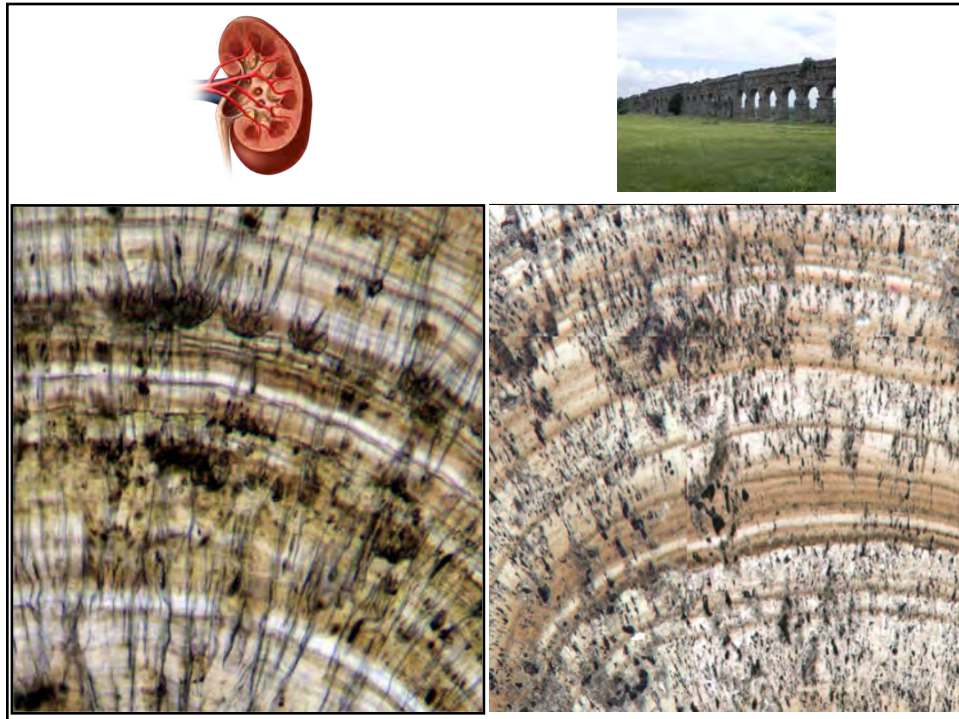


Cave Speleothems



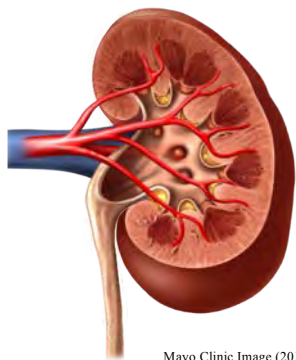
**Roman Aqueducts
Travertine**





Kidney Stones

- afflict >10% of global human population
- associated with other significant health problems
- ~70% are primarily composed of calcium oxalate
- limited available treatment options (therefore *StoneLab*)

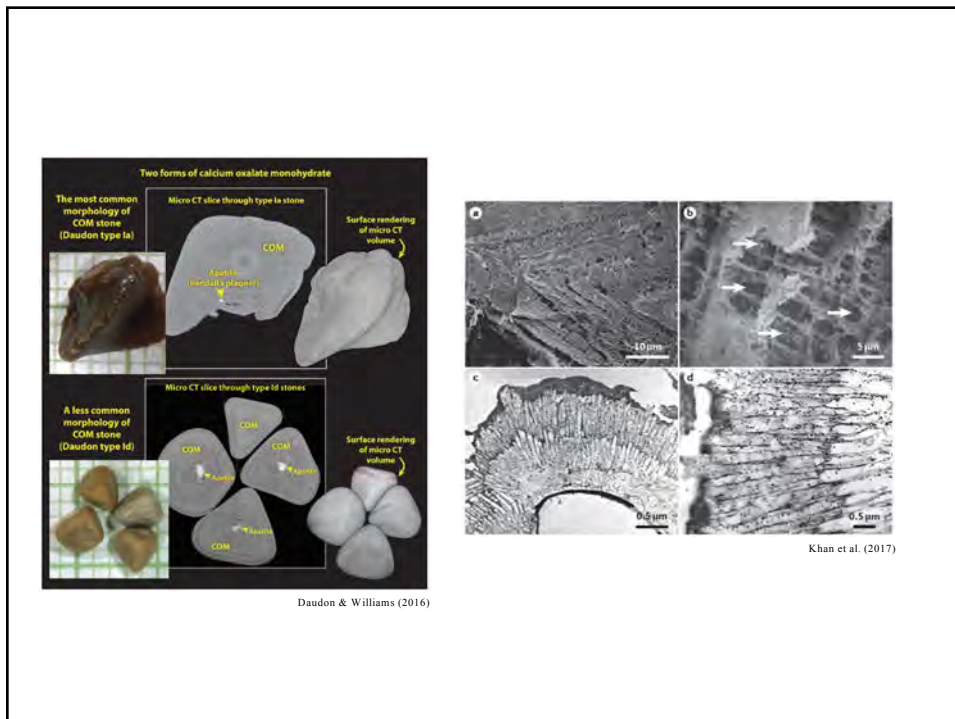
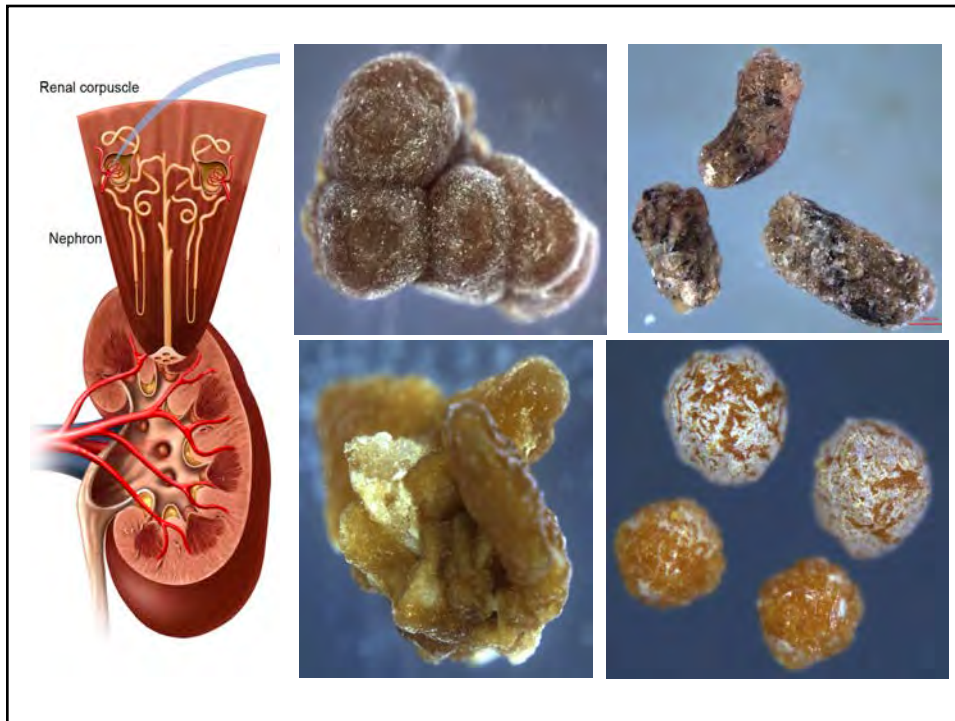


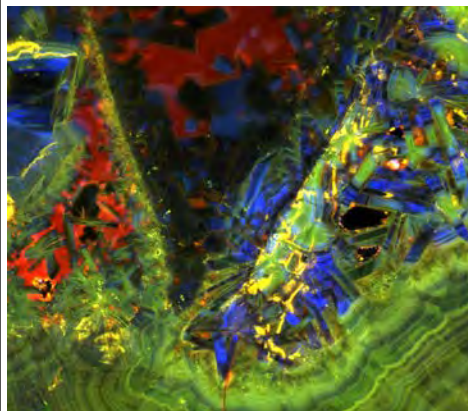
Mayo Clinic Image (2016)



Cook Medical (2016)

<https://www.cookmedical.com/urology/world-kidney-day-a-global-look-at-a-growing-concern/>

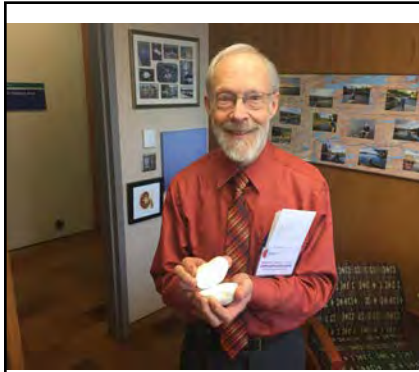
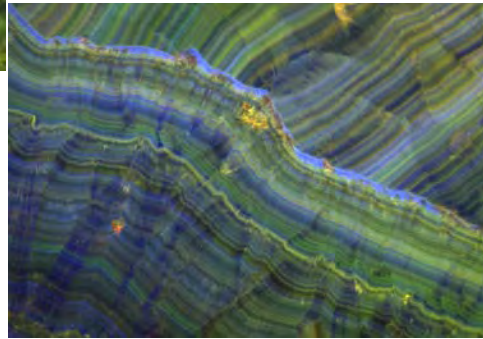




>70% of human kidney stones are composed of the following minerals:

AP = Apatite $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$
 CaOx = Calcium Oxalate CaC_2O_4
 COD = CaOx Dihydrate ($\bullet 2\text{H}_2\text{O}$)
 COM = CaOx Monohydrate ($\bullet \text{H}_2\text{O}$)

Funding to Date:
 Mayo Clinic – Illinois Alliance;
 NIH Mayo Clinic O'Brien Urology Research
 Center; NASA Astrobiology Institute



nature
REVIEWS

COMMENT

GeoBioMed sheds new light on human kidney stone crystallization and dissolution

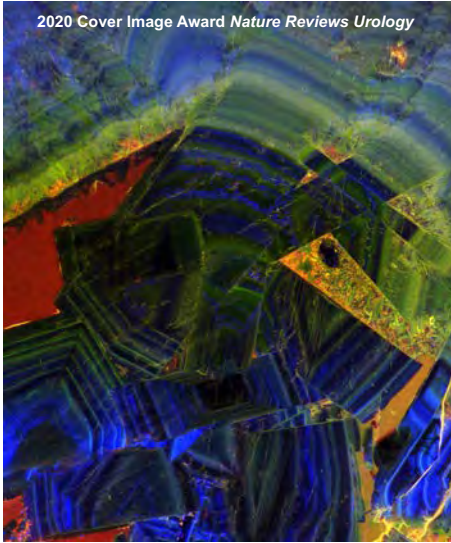
Sivaguru et al. (2020)
Nature Reviews Urology Comment

GeoBioMed - synthesis that identifies unexpected therapeutic targets for prevention and treatment:

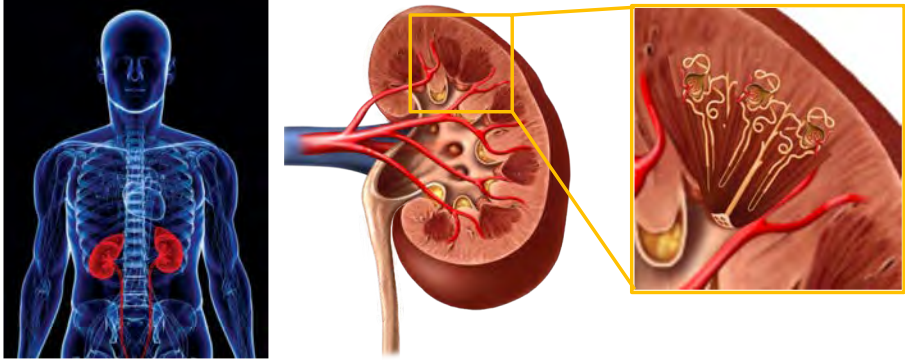
- 1) Prevent COD and COM crystallization
- 2) Promote and maintain COD growth
- 3) Continue COD surface dissolution
- 4) Fully dissolve COD prior to COM
- 5) **Strategically induce COD growth**
- 6) Enhance later-stage events
- 7) Disrupt crystal and urine biochemistry
- 8) Control organic matter and crystal layers

Sivaguru et al. (2020) *Scientific Reports*

2020 Cover Image Award *Nature Reviews Urology*

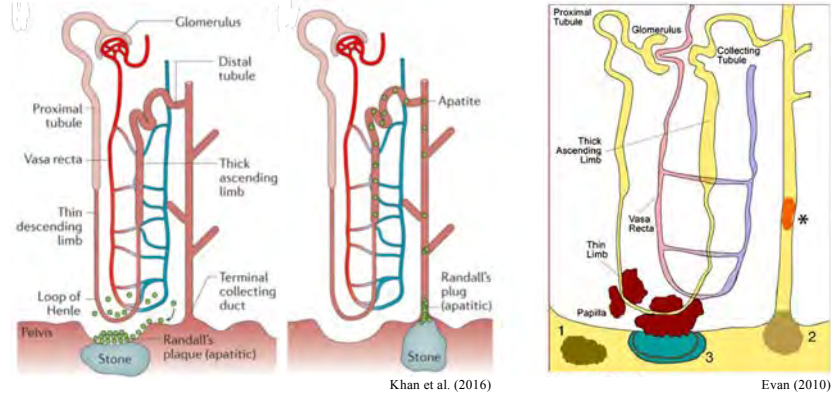


Spatial and Temporal 3D Contextualization of Kidney Stone Formation Through Time

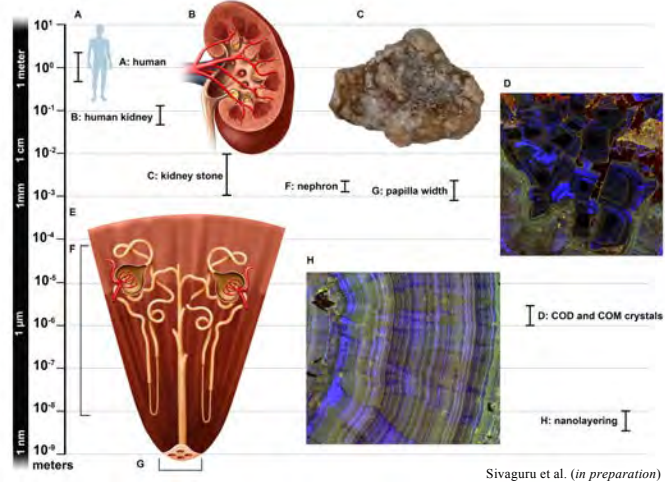


Mayo Clinic (2016)

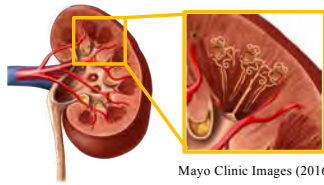
Spatial and Temporal 3D Contextualization of Kidney Stone Formation Through Time



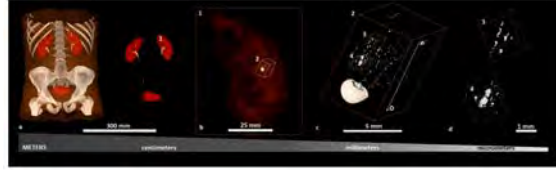
Powers of 10 – Spatial Dimensions and 3D Structure



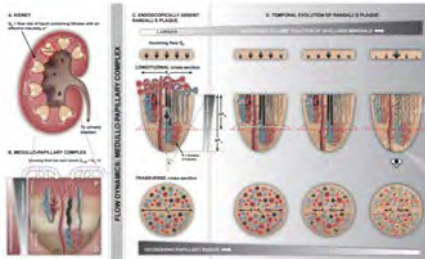
Spatial and Temporal Contextualization of Kidney Stone Formation



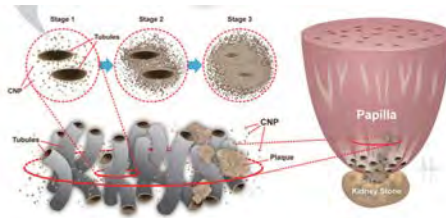
Mayo Clinic Images (2016)



Ho et al. (2019)

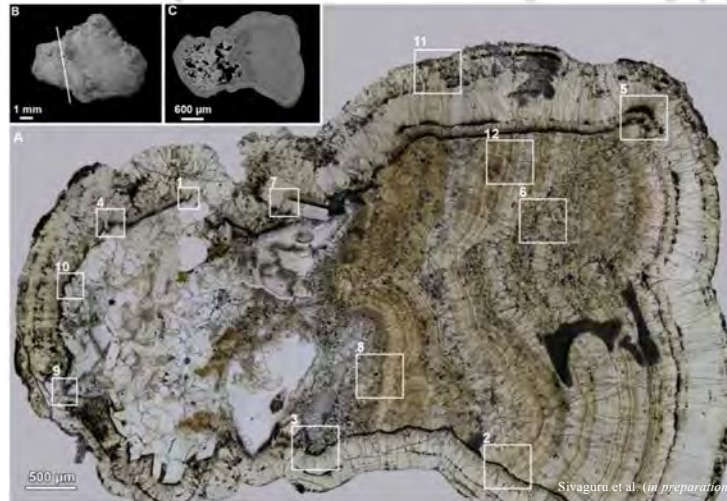


Ho et al. (2019)

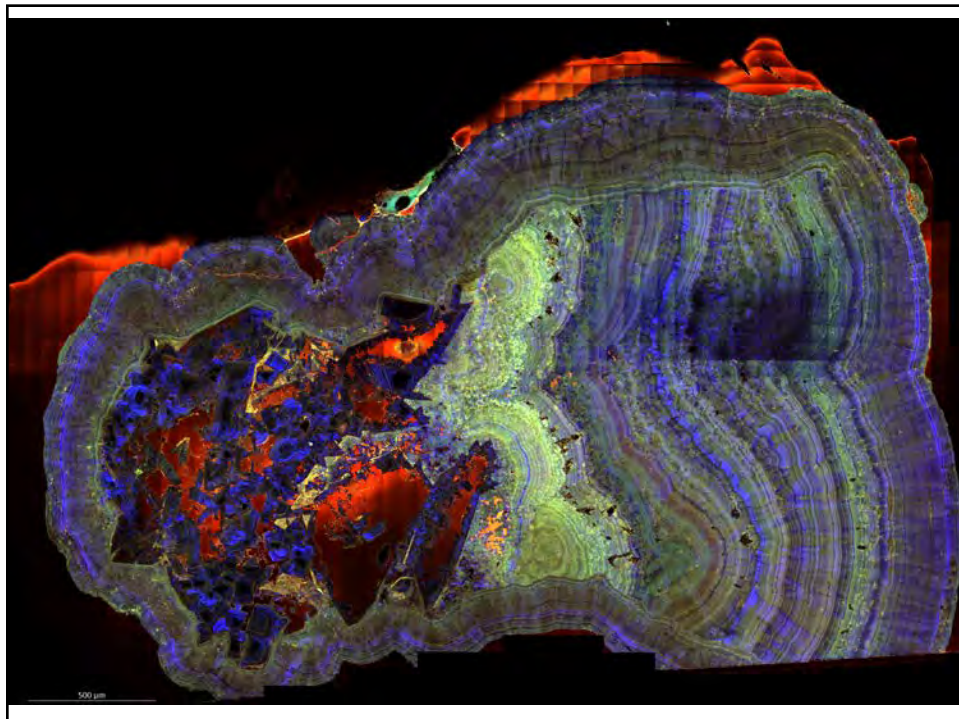
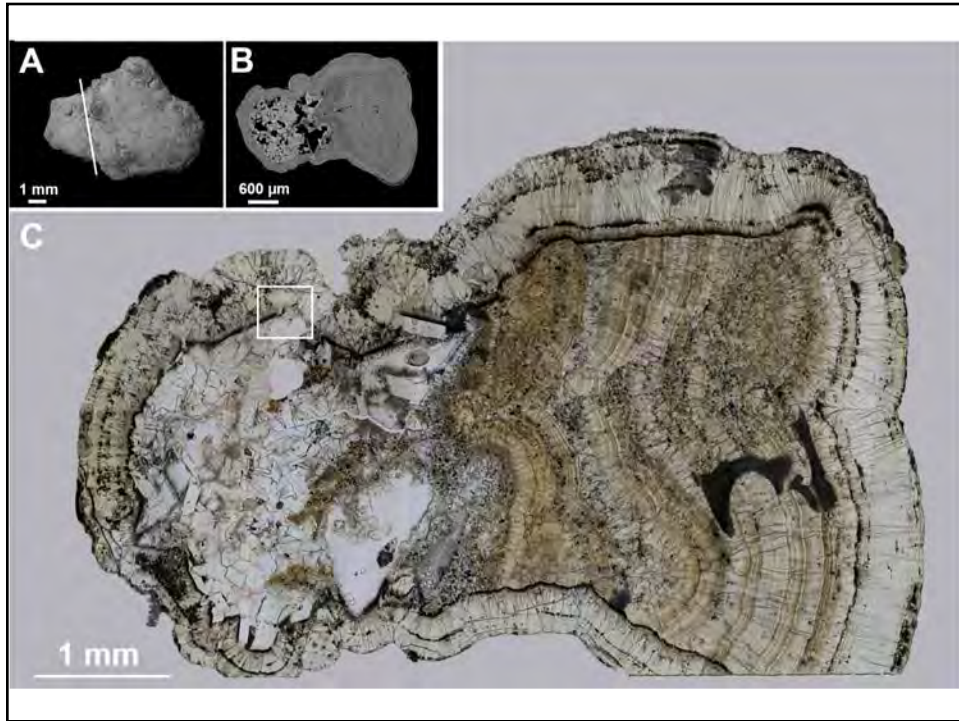


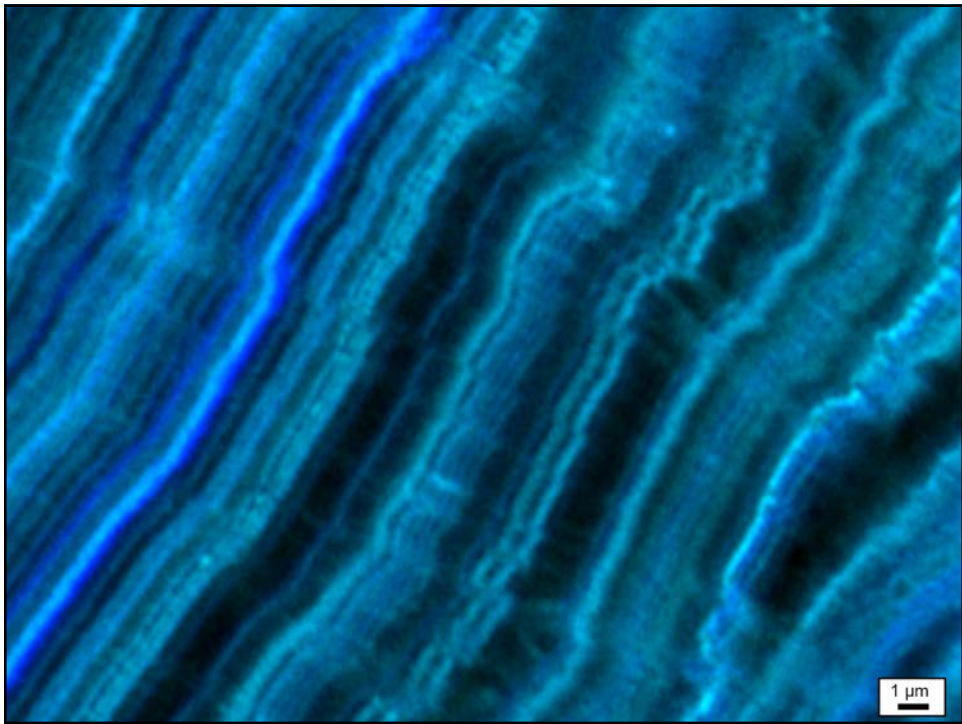
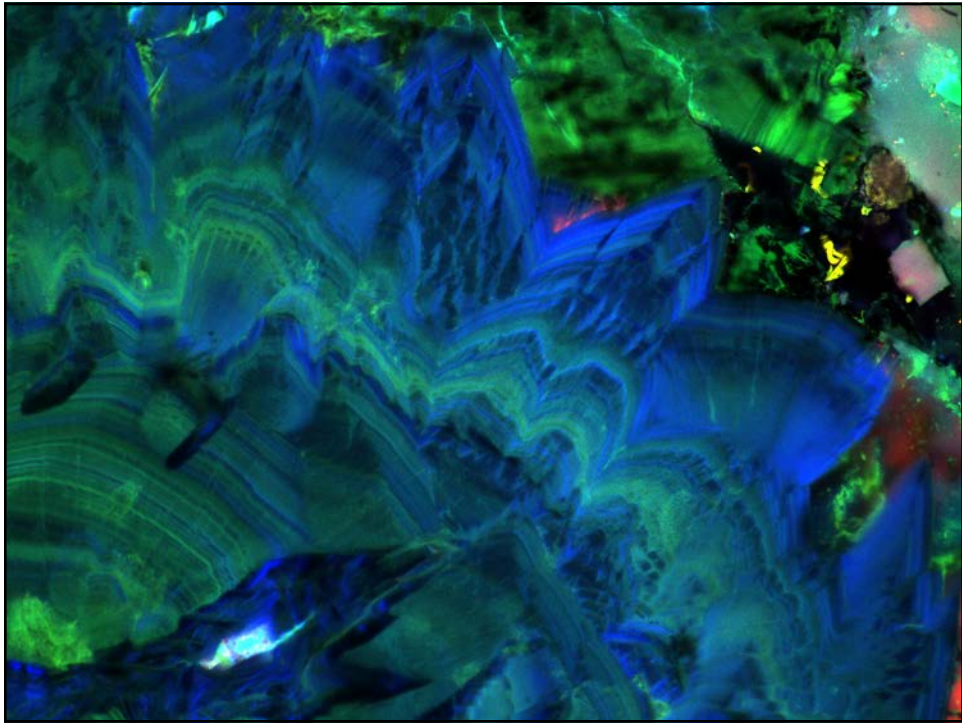
Scherer et al. (2018)

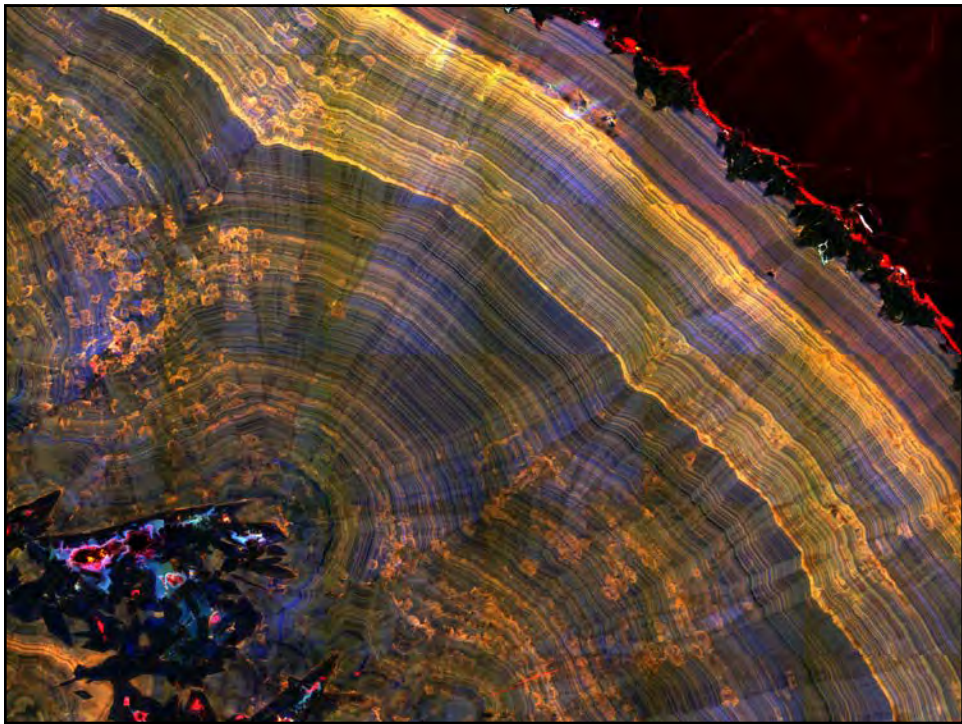
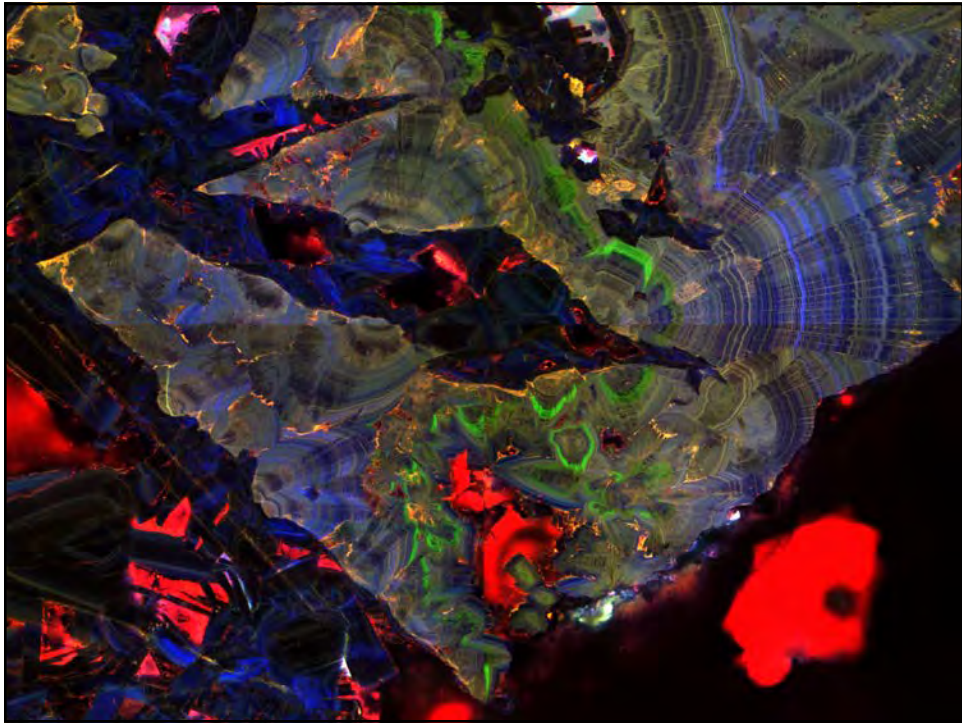
Randall's Plaque MicroCT and Transmitted Brightfield Petrography

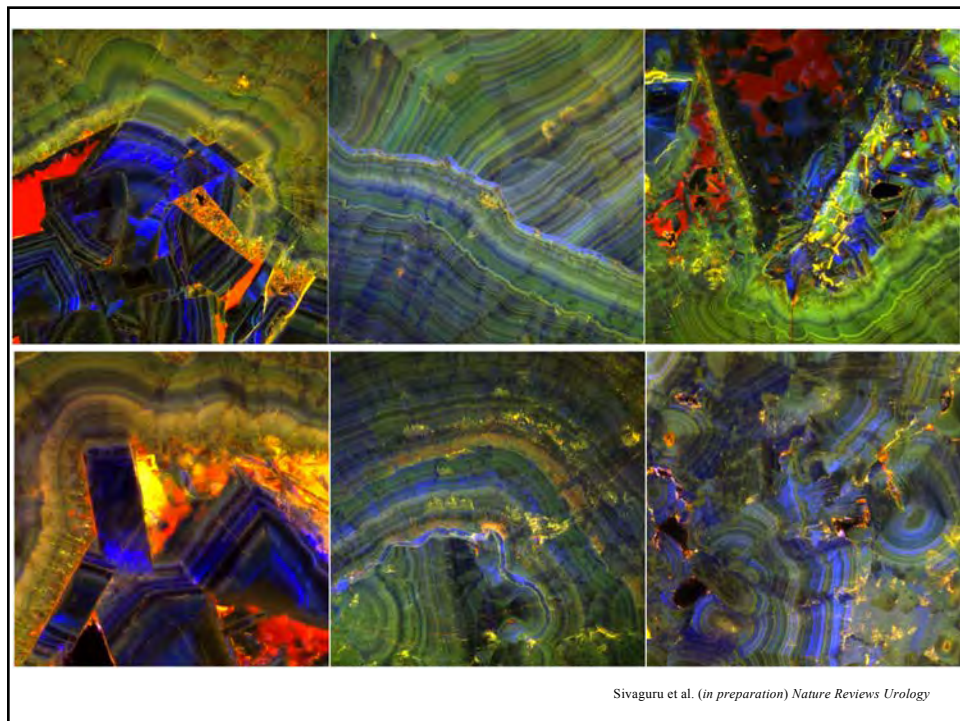
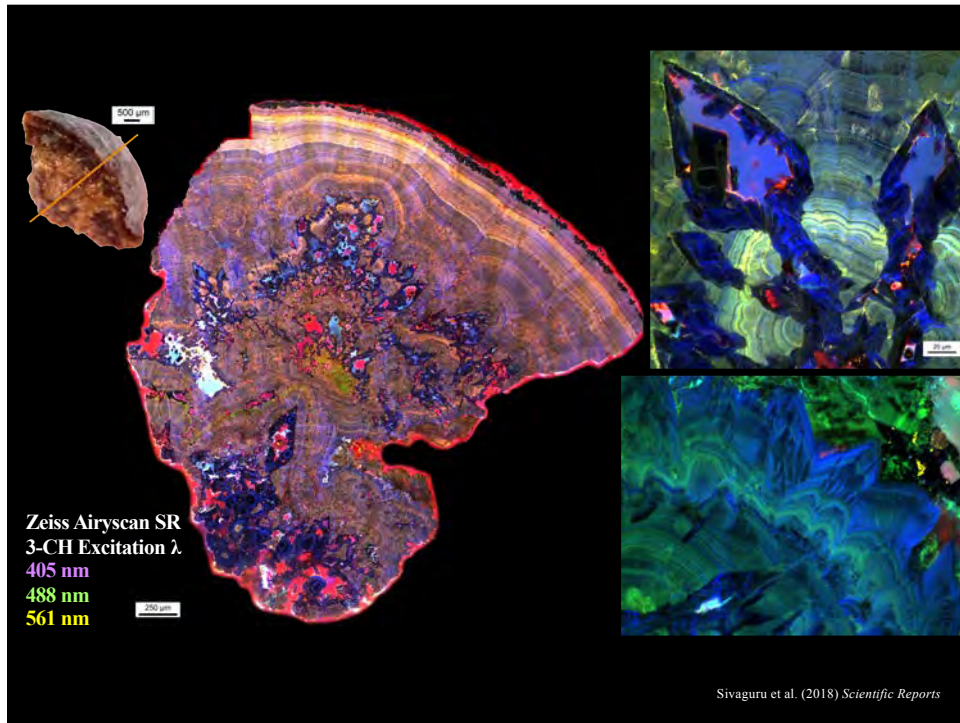


Sivaguru et al. (in preparation)









New Insights on *In Vivo* Kidney Stone Dissolution by Integrating SRAF Microscopy and Geoscience Approaches

New: Analysis of ultrahigh-resolution SRAF imaging crystal nanolayer stratigraphy with geoscience approaches allows a detailed *paragenetic history* reconstruction of multiple repeated cycles of crystallization, dissolution and recrystallization

Previous: SRAF microscopy and geoscience approaches were not applied and as a result a detailed paragenetic sequence could not be reconstructed

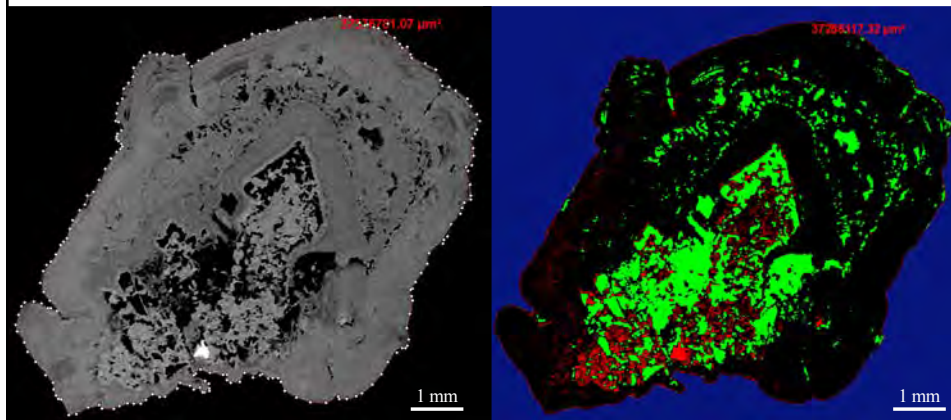
New: Multiple repeated cycles of crystallization, dissolution and recrystallization occur throughout the paragenetic history of kidney stone formation

Previous: Dissolution clearly observed and documented, but the time frame of repeated cycles of crystallization, dissolution and recrystallization not known

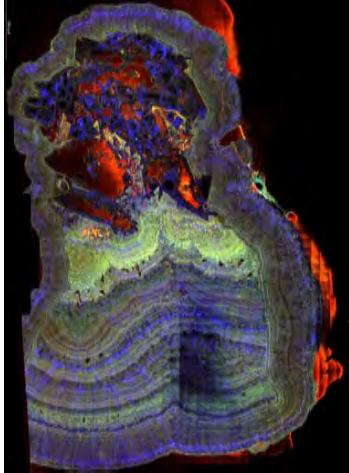
New: 60-80% of all 50 CaOx stones analyzed to date have dissolved and recrystallized

Previous: Dissolution % not estimated - previous non-SRAF imaging suggested low %

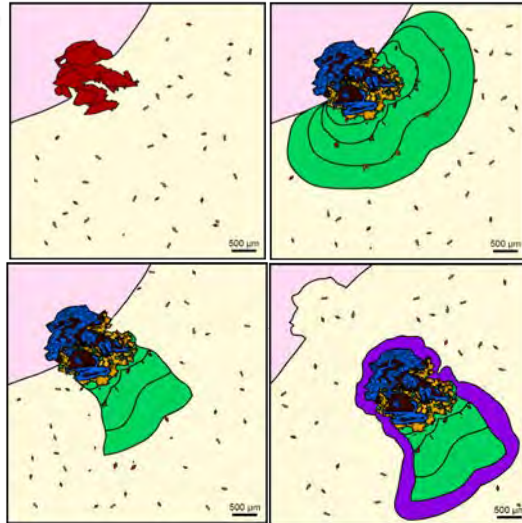
60-80% of Kidney Stone Volume Dissolves *In Vivo* during Multiple Repeated Events of the Paragenetic Sequence



Randall's Plaque Paragenetic Sequence



Sivaguru et al. (in preparation)



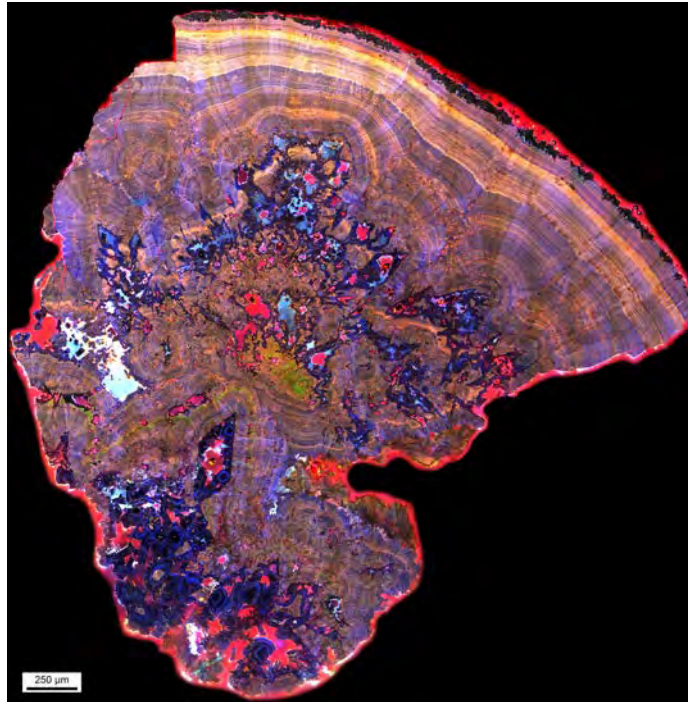
A New Perspective

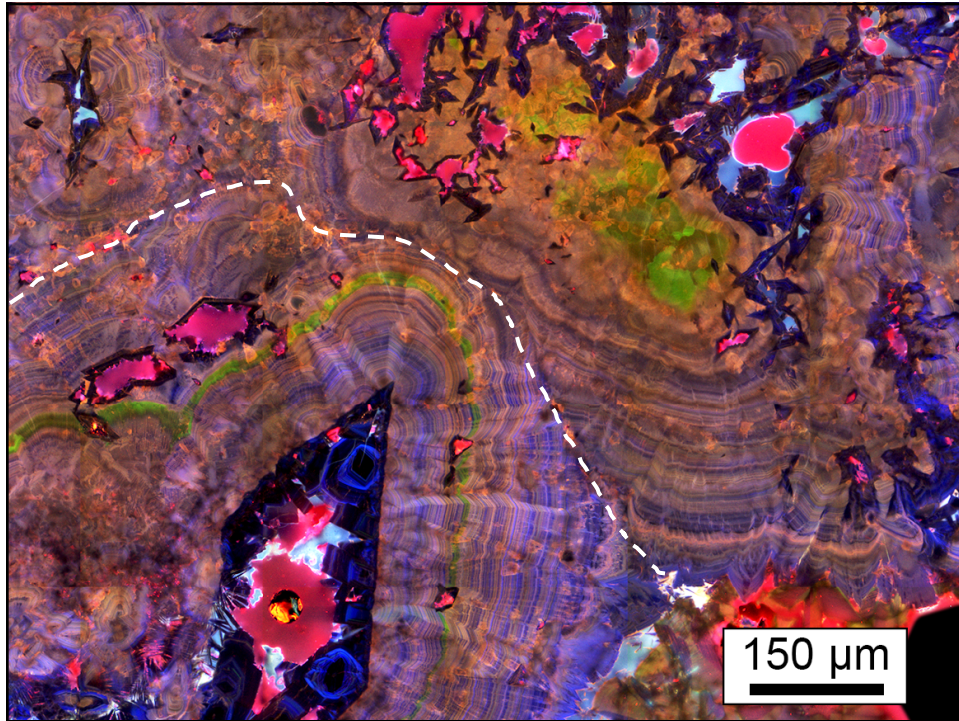
Kidney Stones are dynamic bioreactors that provide an ultrahigh-frequency minute-by-minute record of renal function and health.

Kidney Stones are composed of intricate crystalline architectures (crystal size, shape, layering, chemistry) that entomb host human and microbiome organic matter (cell debris, biomolecules) during multiple repeated cycles (*paragenetic sequence*) of crystal growth, dissolution and recrystallization that identify unexpected therapeutic targets.

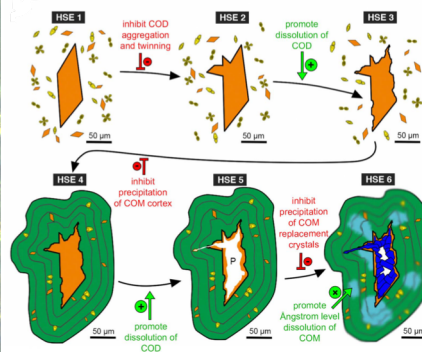
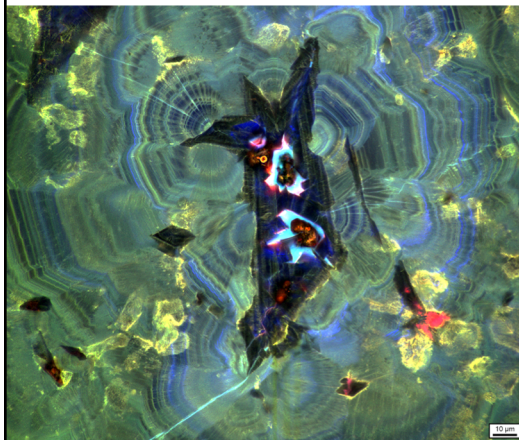
Collection of Samples And Study Flow

- 51-year-old female with bilateral kidney stones
- Stone on right side was removed via percutaneous nephrolithotomy (PCNL) under sterile operating procedures
- Metagenomic sequencing and superresolution microscopy completed on 30 micron-thick doubly polished thin sections



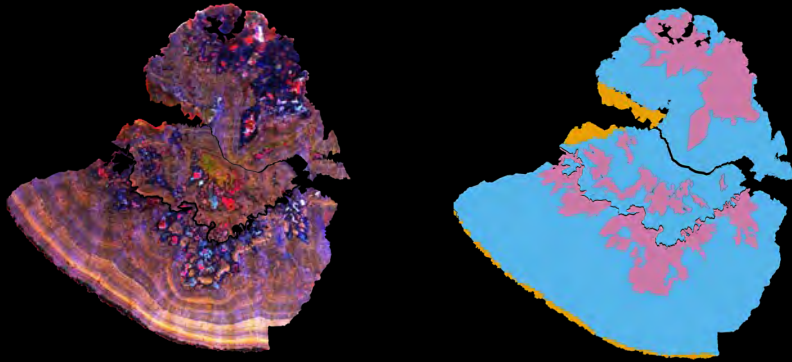


Paragenetic Sequence – a spatial and temporal framework of multiple repeated events of crystal growth, layering geometry and dissolution

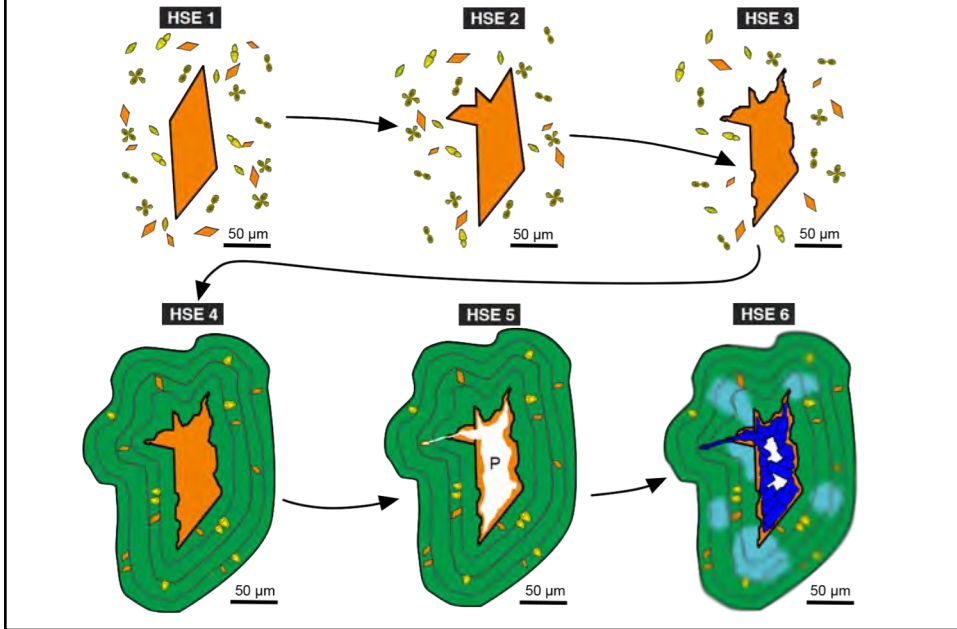


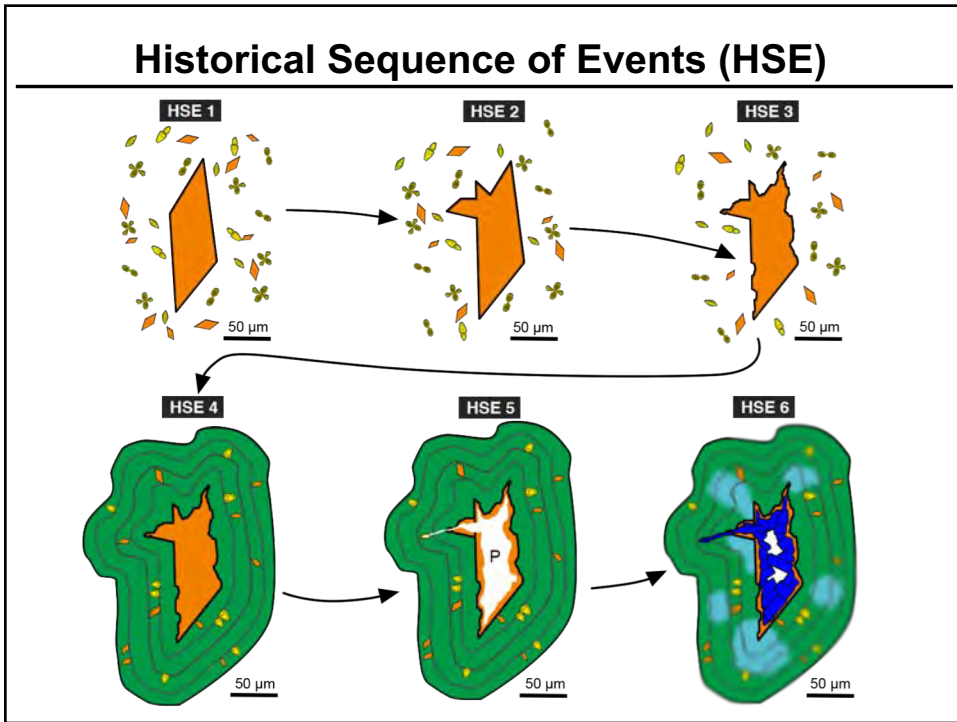
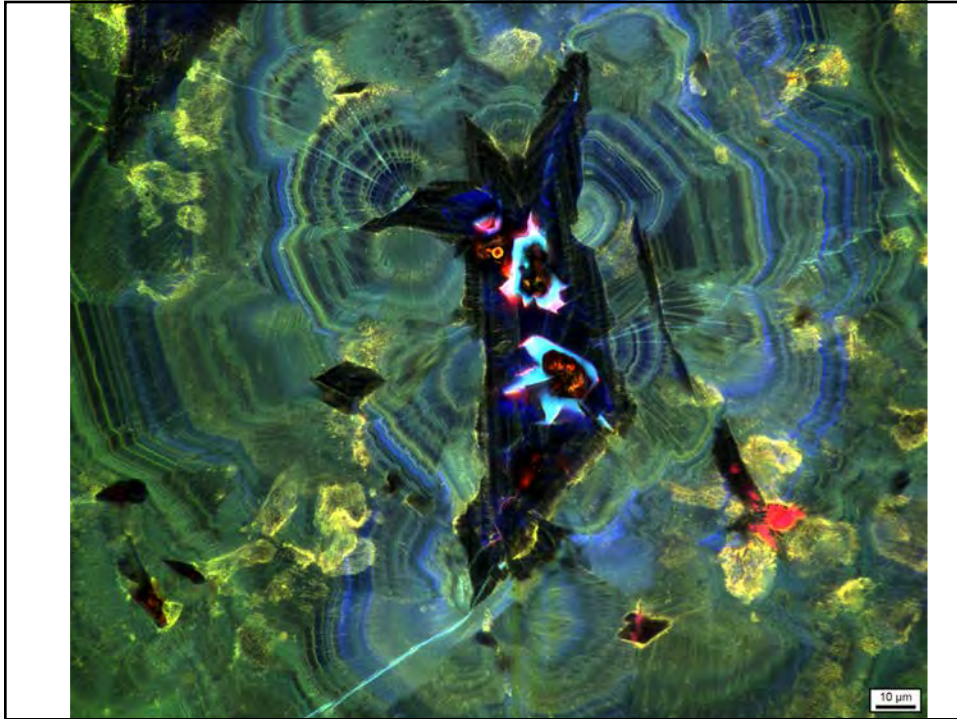
Sivaguru et al. (2018) *Scientific Reports*

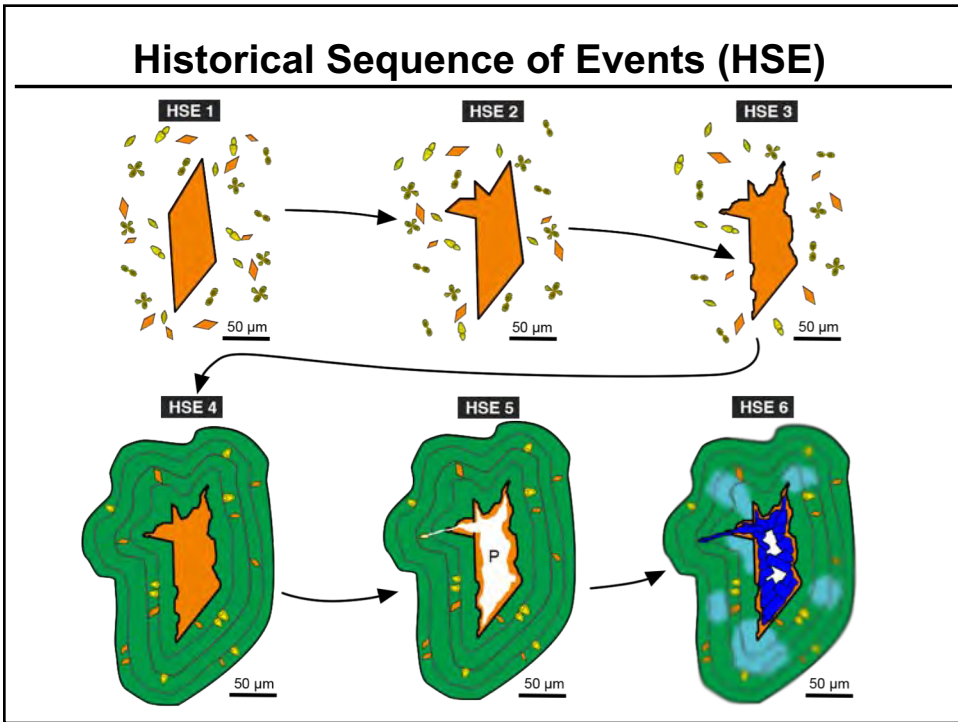
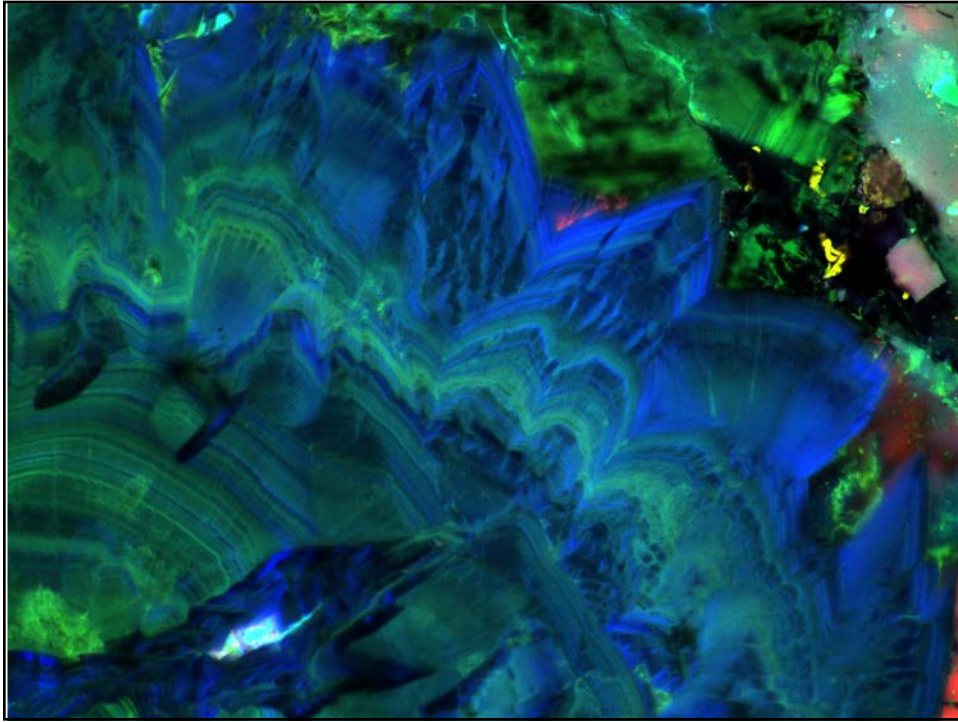
3 stones are aggregated into 1 stone complex

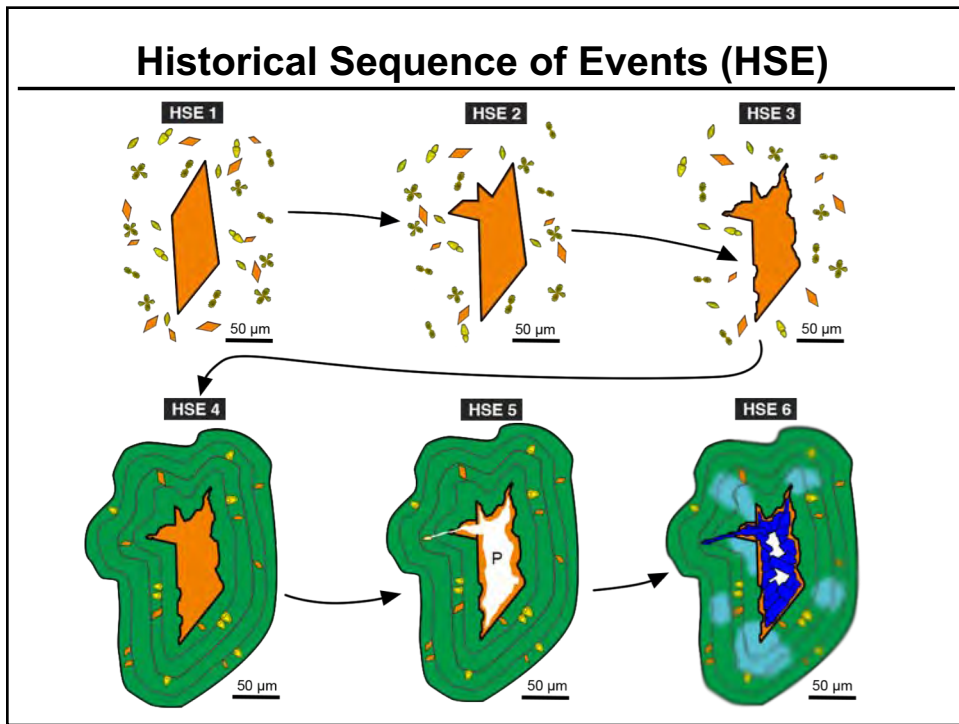
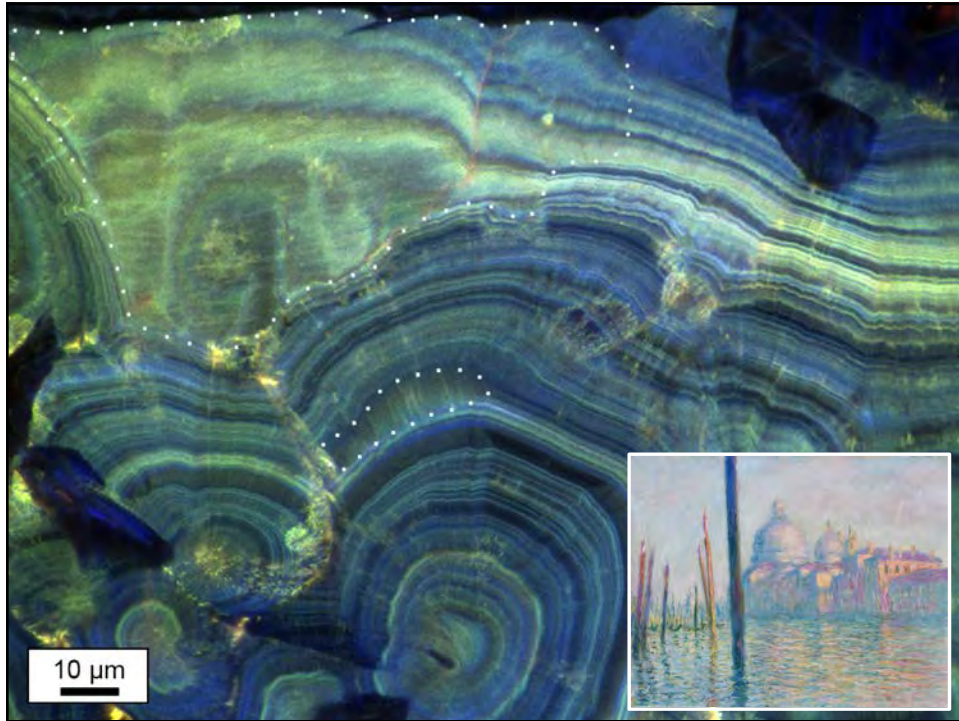


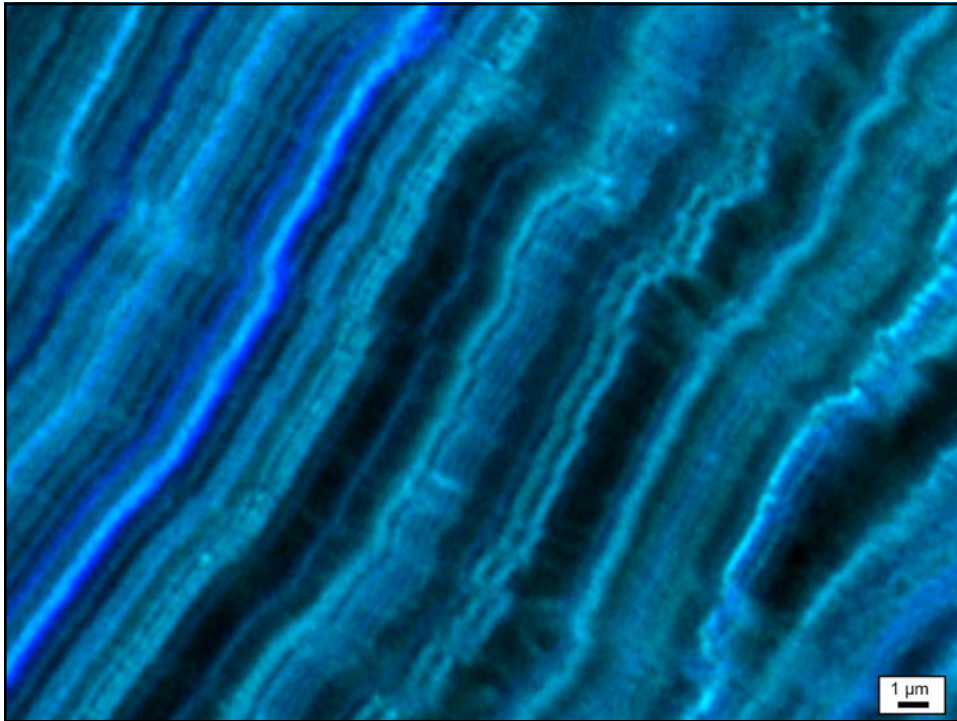
Historical Sequence of Events (HSE)



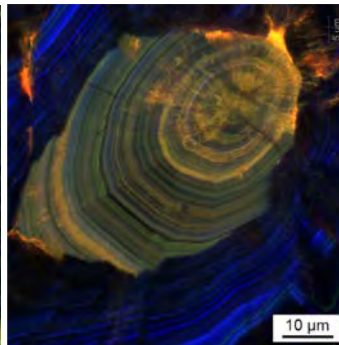
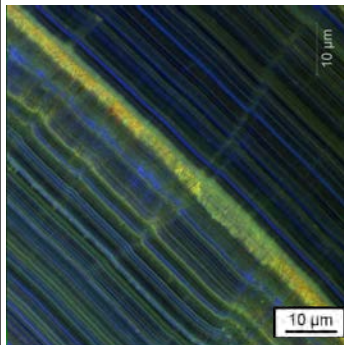




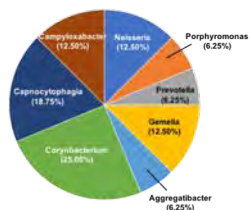




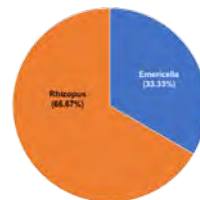
Organic Matter Characterization

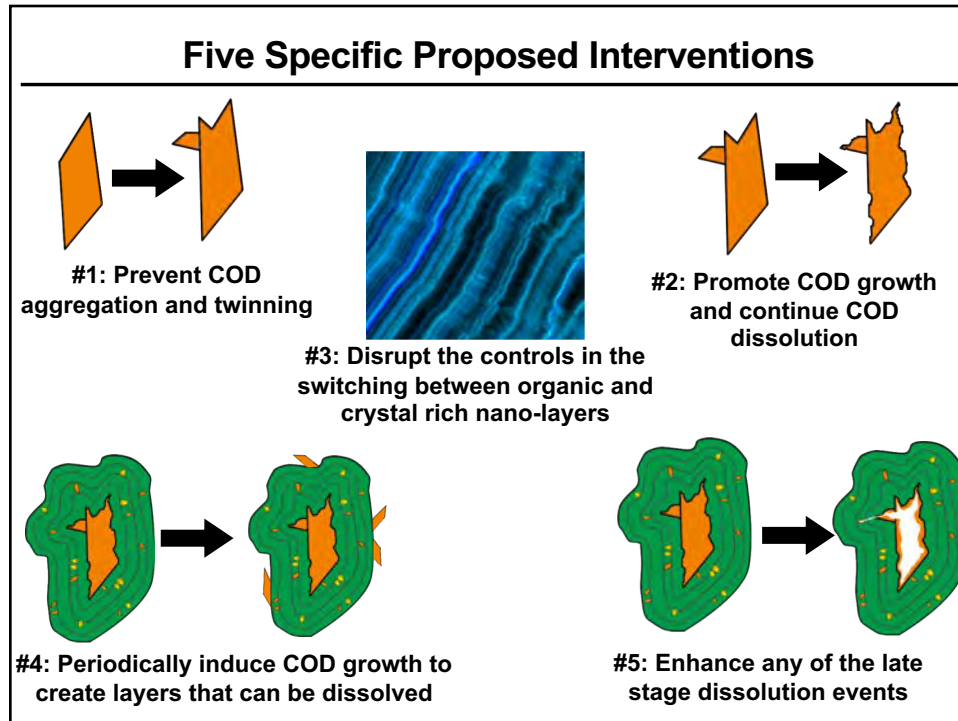


Bacterial (V1-V3 Region)



Fungal (ITS3-4 Region)





nature REVIEWS COMMENT

GeoBioMed sheds new light on human kidney stone crystallization and dissolution

Sivaguru et al (2020)
Nature Reviews Urology
Cover Image Award 2020

Migueli Sivaguru¹, John C. Lieske¹, Anja E. Koenig^{1,2} and Bruce W. Froese^{1,3,4}

<https://www.nature.com/articles/s41585-019-0256-5>

Key Results to Date

GeoBioMed integrates:

- 1) All Patient History
- 2) All Human and Microbiome Omics
- 3) All Urine Biochemistry and Hydrology
- 4) All Geobiology Data and Imaging
- 5) All Histology Data and Imaging
- 6) Requires **Microscopy-to-Omics**

CaOx = Calcium Oxalate (CaC₂O₄)
COD = Calcium Oxalate Dihydrate (•2H₂O)
COM = Calcium Oxalate Monohydrate (•H₂O)

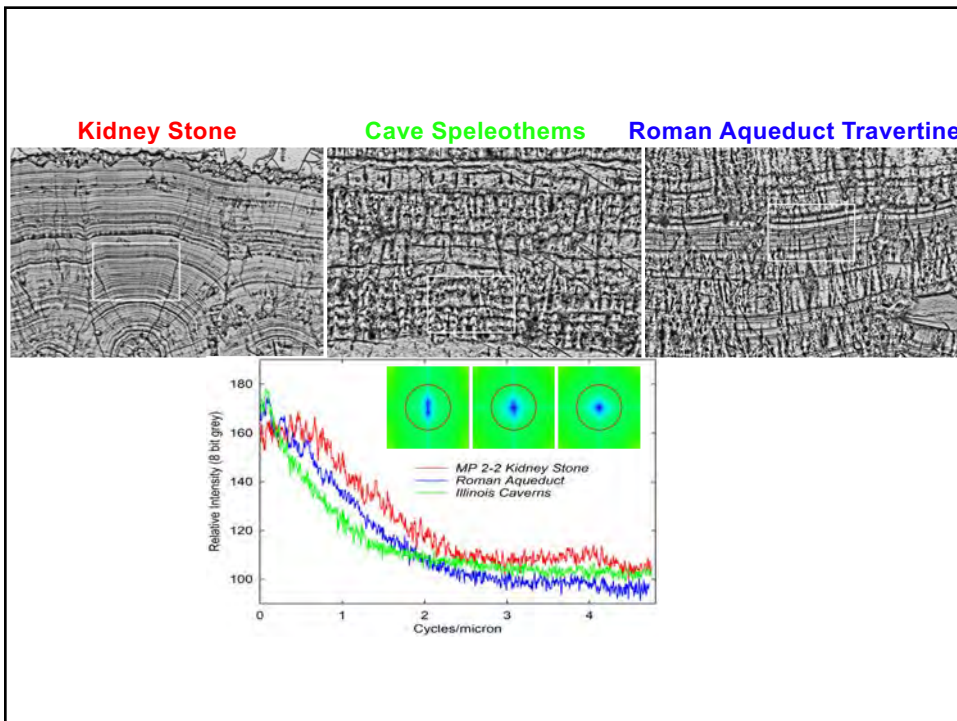
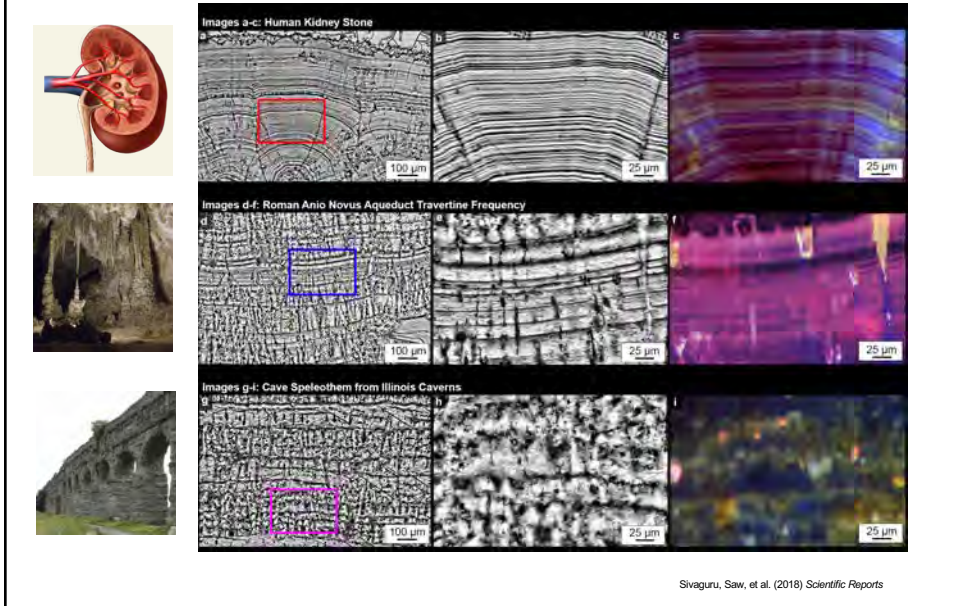
GeoBioMed has identified multiple unexpected therapeutic targets and interventions to:

- 1) prevent COD and COM crystallization
- 2) promote and maintain COD growth
- 3) continue COD surface dissolution
- 4) fully dissolve COD prior to COM
- 5) induce COD growth
- 6) disrupt crystal and urine biochemistry
- 7) control organic matter and crystal layers

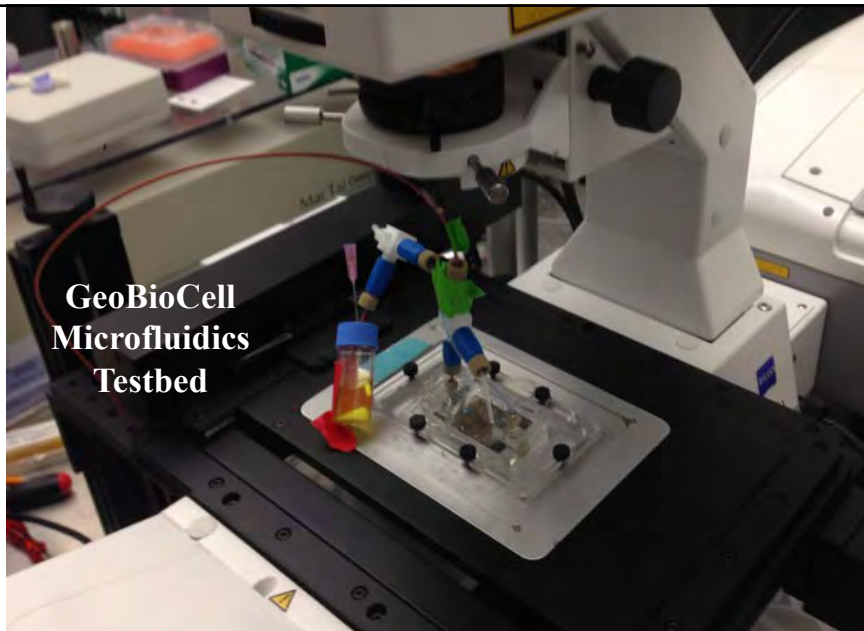
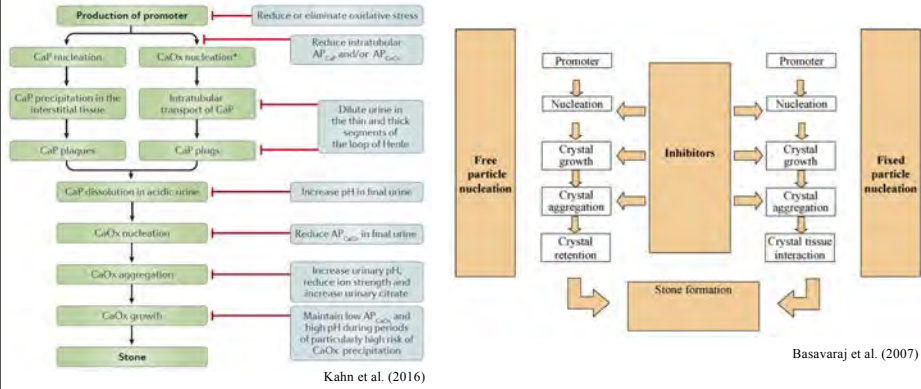
Develop clinical tools to rapidly read crystalline architecture of kidney stones to guide treatment.

Funding: Mayo Clinic – Illinois Alliance; Mayo Clinic O'Brien Urology Research Center; NASA Astrobiology Institute

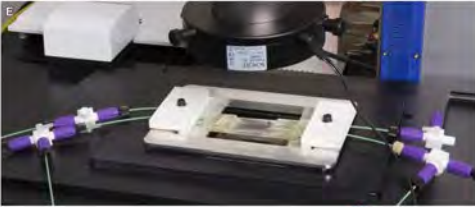
Layering is a result of Crystal Growth/Dissolution Rate and Layering Frequency
 Life-Water-Mineral "Biomarkers" on the Modern and Ancient Earth and throughout the Cosmos



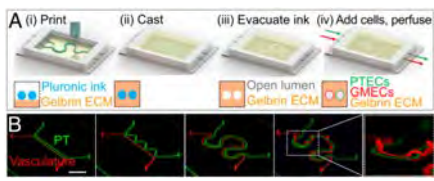
GeoBioCell will be used to Test Paragenetic Sequence and Metabolic Controls



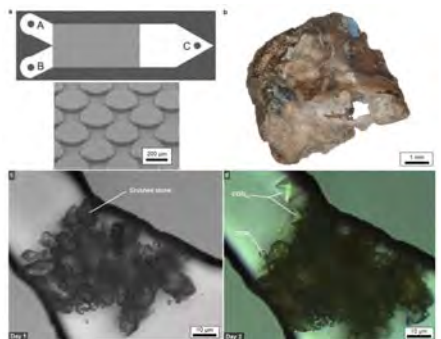
GeoBioCell: Microfluidic Flow-Through Testbed



Sivaguru et al. (in preparation)



Lin et al. (2018)

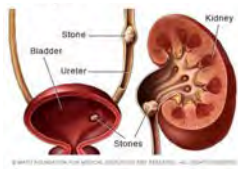


Sivaguru et al. (in preparation)

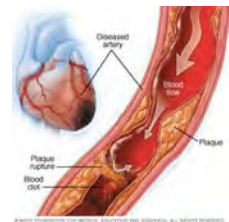
Promoting factors	Inhibiting factors
Calcium	Hexamer
Sodium	Citrate
Oxalate	Magnesium
Glucose	Pyrophosphate
Cytosine	Oxalate
Low urine pH	Tactin-Hordal protein
Tissue Inhibitor of metalloproteinases	Urokinase-type plasminogen activator
Low urine flow	Prostate Inhibitor-1 (PI-1)
	Oxalate
	Glycosaminoglycans
	Osteopontin (OPN)
	Renal osteodystrophy
	Other factors, Calcitonin
	High urine flow

Basavaraj et al. (2007)

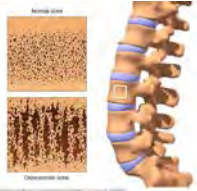
GeoBioMed: Future Applications



Concretions from fluid-containing cavities
Kidney and bladder stones
Gallstones
Gout



Pathologic calcifications
Atherosclerosis
Aortic valve calcification
Psammoma bodies



Bone disease
Osteoporosis
Renal osteodystrophy
Paget's disease

Images courtesy of Mayo Clinic