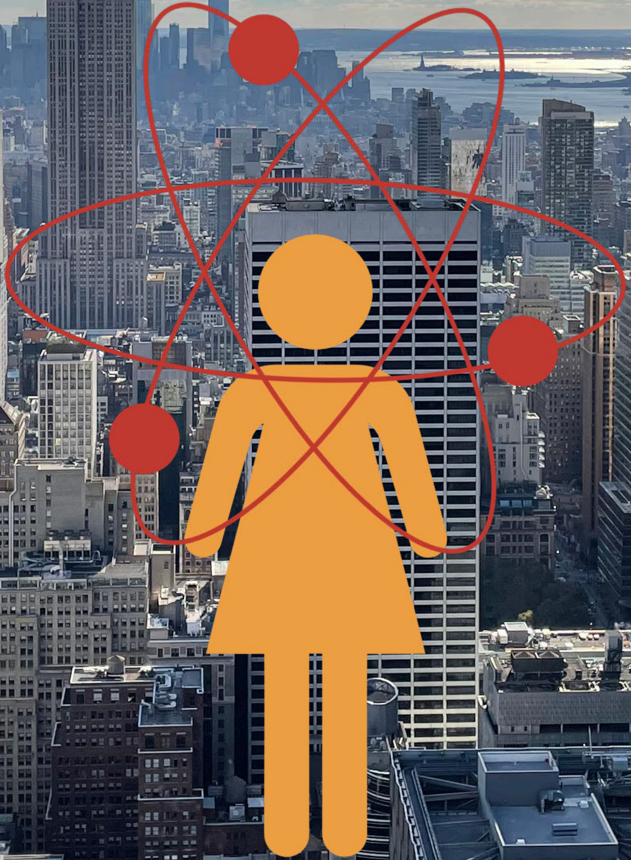
DISEASE DETECTION AND EXPOSURE ASSESSMENT: HOW METAL STABLE ISOTOPES OFFER UNIQUE INSIGHTS



Kathrin Schilling, PhD
ks3759@columbia.edu

WHEN YOU THINK ABOUT AN ELEMENT

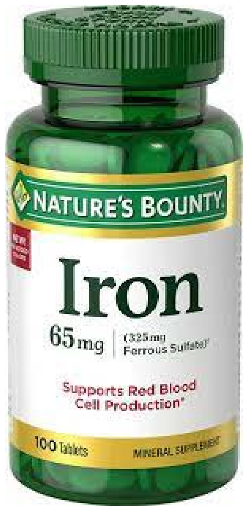
Zinc-64
49.17%

Zinc-66
27.73%

Zinc-67
4.04%

Zinc-68
18.45%

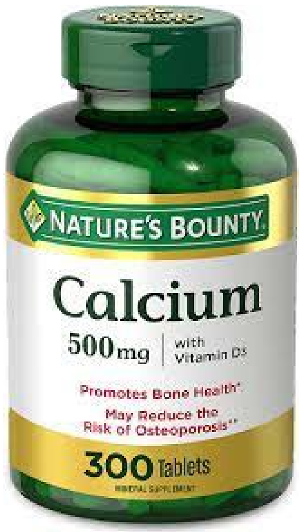
Zinc-70
0.6%



Iron-56
91.75%

Iron-57
2.12%

Iron-58
0.28%



Calcium-40
96.9%

Calcium-42
0.65%

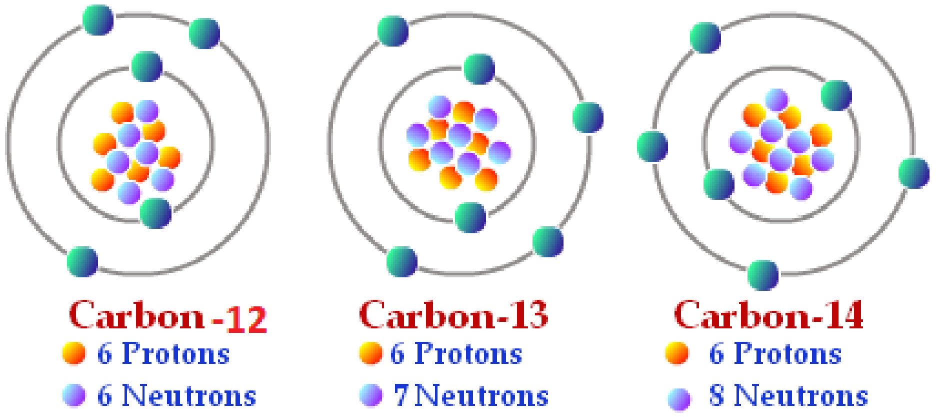
Calcium-43
0.14%

Calcium-44
2.1%

WHEN an isotope chemist thinks about an element

WHAT ARE ISOTOPES?

- **Same atomic number**
  - Same number of protons in their nuclei
  - Same number of electrons in their shells
- **Different mass**
  - Different number of neutrons in their nuclei
- **Different chemical behavior**




Frederick Soddy


Margarete Todd


J.J. Thompson


Francis Aston

Columbia University faculty pioneered isotope geochemistry

NOBEL AWARD GOES TO PROFESSOR UREY

Columbia Scientist Gets the 1934 Chemistry Prize for Discovering 'Heavy Water.'

ACHIEVEMENT WAS HAILED

Seen as of Especial Value in Cancer Study—Has Proved Great Spur to Research.

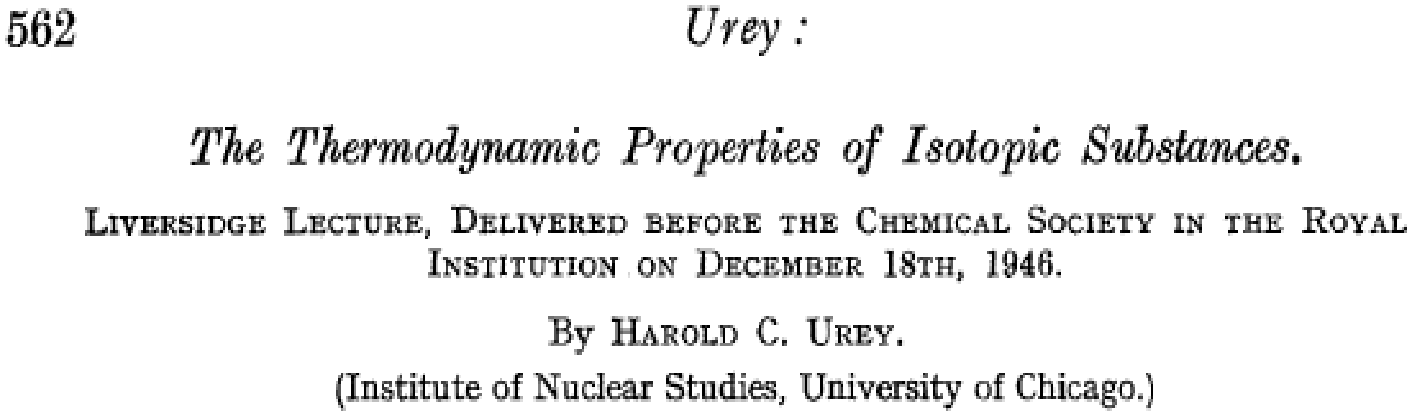
Wireless to THE NEW YORK TIMES.

STOCKHOLM, Nov. 15.—The Nobel Prize in Chemistry for 1934 was awarded today to Professor Harold C. Urey of Columbia University because of his discovery of "heavy water."

The chemistry prize for 1933 will not be awarded. It was also announced that there would be no prize in physics for this year.

Ossip Garber Studios.

WINS NOBEL PRIZE.
Professor Harold Urey.



562 Urey :

The Thermodynamic Properties of Isotopic Substances.

LIVERSIDGE LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY IN THE ROYAL INSTITUTION ON DECEMBER 18TH, 1946.

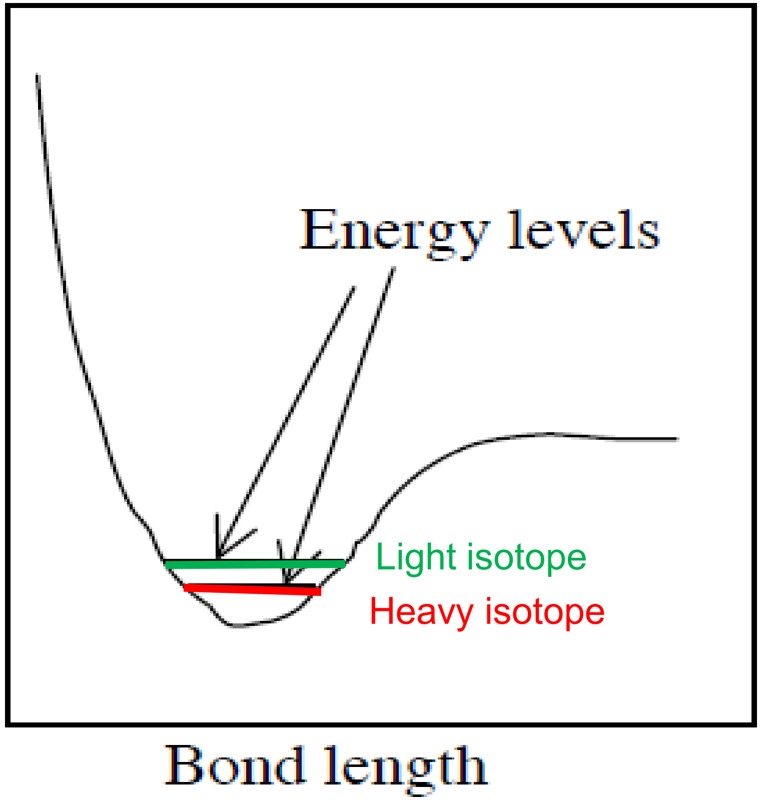
By HAROLD C. UREY.

(Institute of Nuclear Studies, University of Chicago.)

"Before the discovery of isotopes, it was generally assumed that all atoms of an element were identical in all respects. …reviewed in this paper, we know that **isotopes and isotopic compounds differ in their thermodynamic properties**. … **These small differences make possible** the concentration and **separation of the isotopes of some of the elements** … important applications as a means of determining the temperatures at geological formations were laid down."

Why do isotope fractionate?

ISOTOPE FRACTIONATION is a natural process when stable isotopes of an element are being partitioned between two materials, phases …

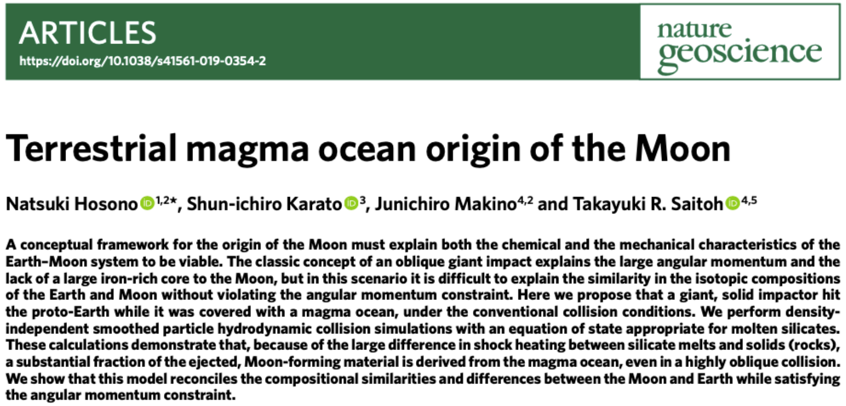


RULES OF THUMB

- The lighter of two isotopes react faster
- The heavier of two isotopes prefer the strongest bonds
- Isotope fractionation is larger for light elements
- Isotope fractionation is larger for elements with various oxidation states

Metal isotopes are powerful tools in Earth Sciences

Every object is defined by its elemental and **ISOTOPIC** composition



ARTICLES
https://doi.org/10.1038/s41561-019-0354-2

nature geoscience

Terrestrial magma ocean origin of the Moon

Natsuki Hosono[1,2*], Shun-ichiro Karato[3], Junichiro Makino[4,2] and Takayuki R. Saitoh[4,5]

A conceptual framework for the origin of the Moon must explain both the chemical and the mechanical characteristics of the Earth–Moon system to be viable. The classic concept of an oblique giant impact explains the large angular momentum and the lack of a large iron-rich core to the Moon, but in this scenario it is difficult to explain the similarity in the isotopic compositions of the Earth and Moon without violating the angular momentum constraint. Here we propose that a giant, solid impactor hit the proto-Earth while it was covered with a magma ocean, under the conventional collision conditions. We perform density-independent smoothed particle hydrodynamic collision simulations with an equation of state appropriate for molten silicates. These calculations demonstrate that, because of the large difference in shock heating between silicate melts and solids (rocks), a substantial fraction of the ejected, Moon-forming material is derived from the magma ocean, even in a highly oblique collision. We show that this model reconciles the compositional similarities and differences between the Moon and Earth while satisfying the angular momentum constraint.

HOME > SCIENCE > VOL. 346, NO. 6209 > LOW MID-PROTEROZOIC ATMOSPHERIC OXYGEN LEVELS AND THE DELAYED RISE OF ANIMALS

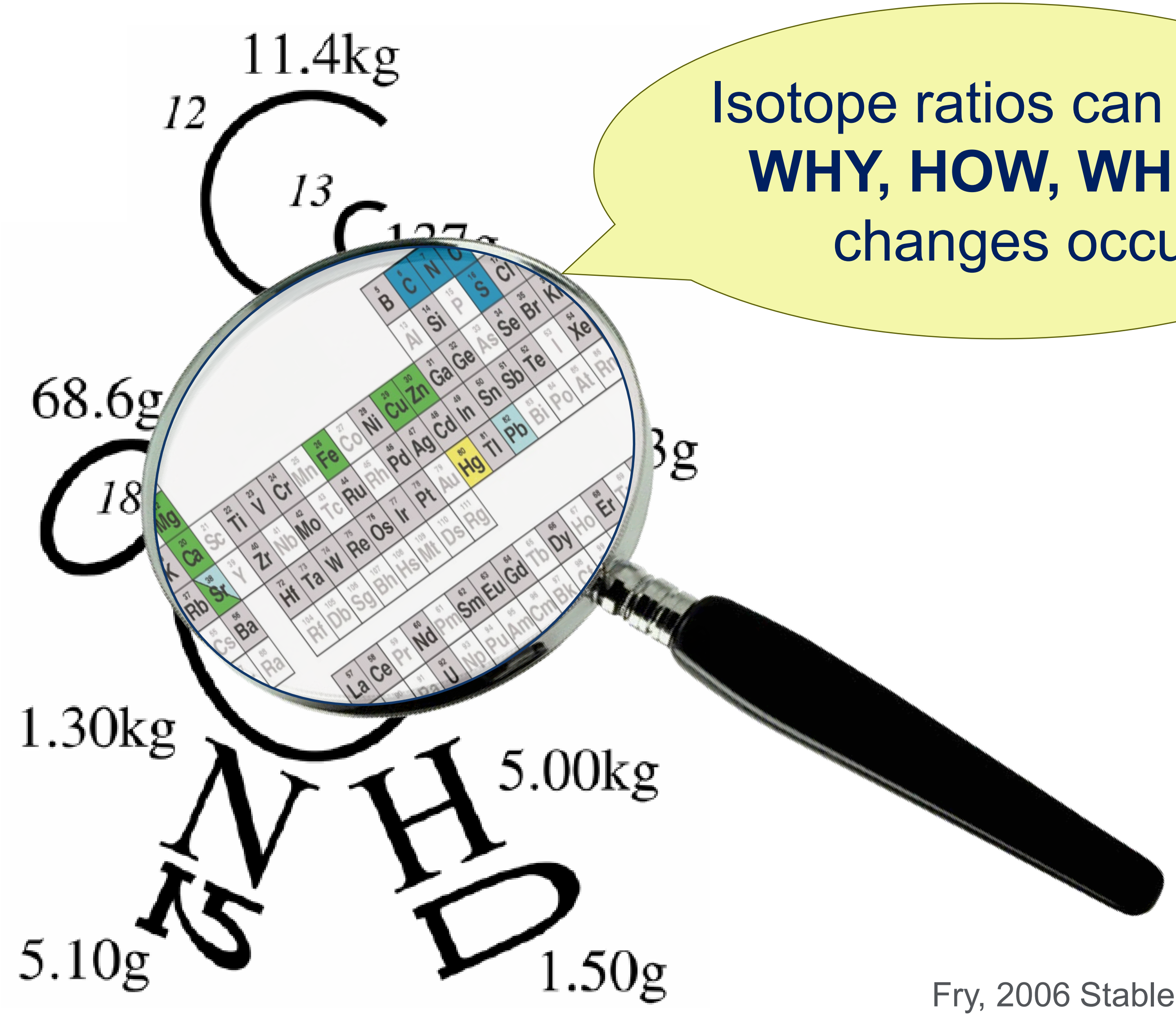
REPORT

Low Mid-Proterozoic atmospheric oxygen levels and the delayed rise of animals

NOAH J. PLANAVSKY , CHRISTOPHER T. REINHARD, XIANGLI WANG, DANIELLE THOMSON, PETER MCGOLDRICK, ROBERT H. RAINBIRD, THOMAS JOHNSON, WOODWARD W. FISCHER, AND TIMOTHY W. LYONS Authors Info & Affiliations

SCIENCE • 31 Oct 2014 • Vol 346, Issue 6209 • pp. 635-638 • DOI: 10.1126/science.1258410

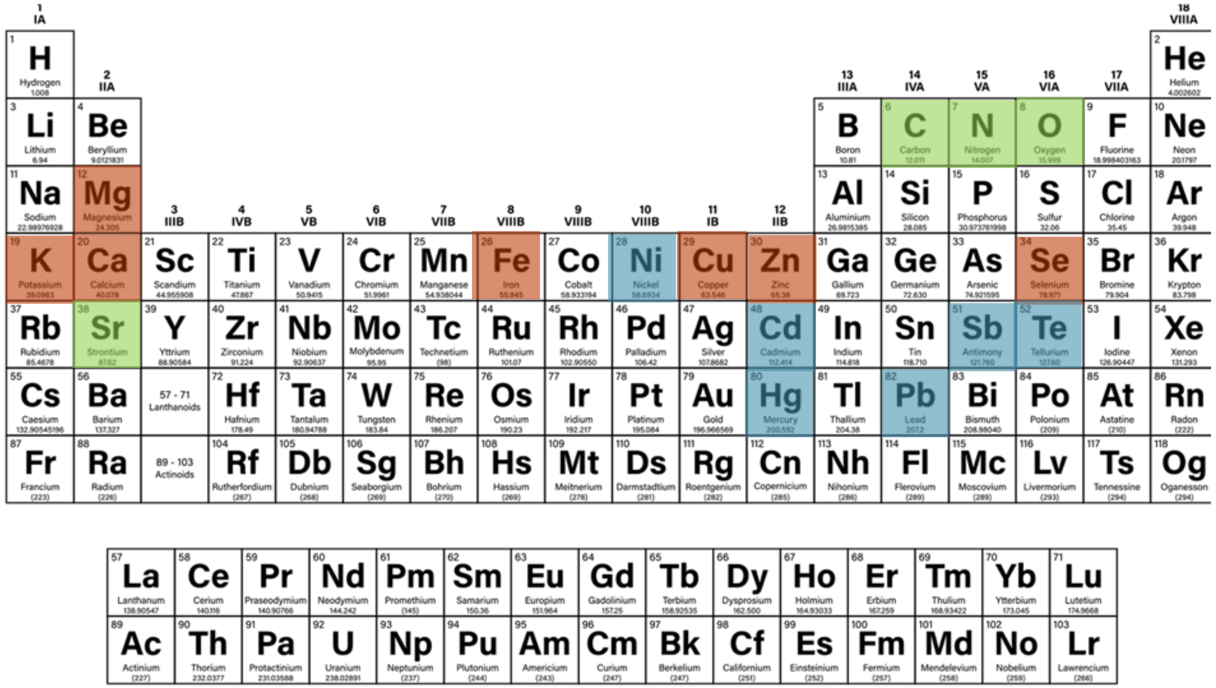
We are made of ISOTOPES!

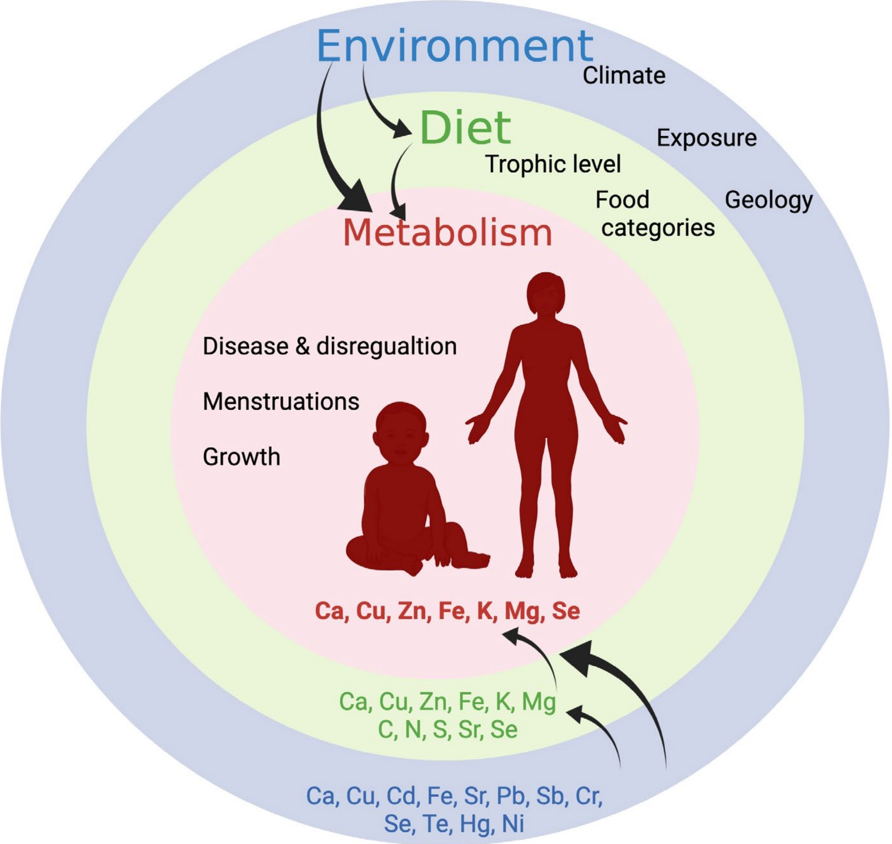


Isotope ratios can tell us
WHY, HOW, WHERE
changes occur

Fry, 2006 Stable Isotope Ecology

Isotope metallomics’ extraordinary potential

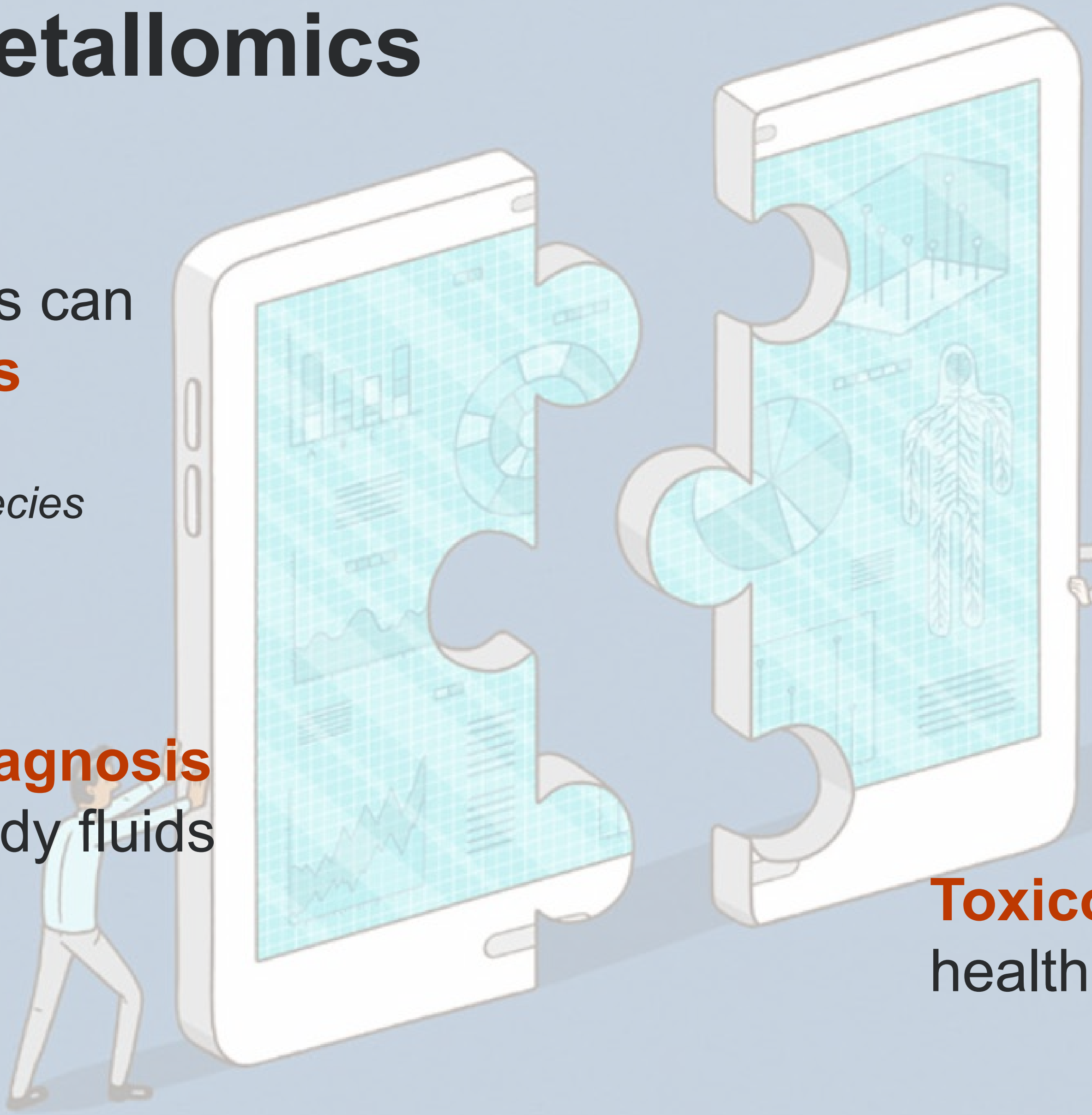




The body must ensure that elements are correctly distributed between organs, across tissues, and within cells

Isotope metallomics

Environmental Health Sciences



Biological samples can be analyzed **years after sampling**

organic biomarkers/ species degrade with time

Unravel **human metabolism & diagnosis of diseases** in body fluids or tissues

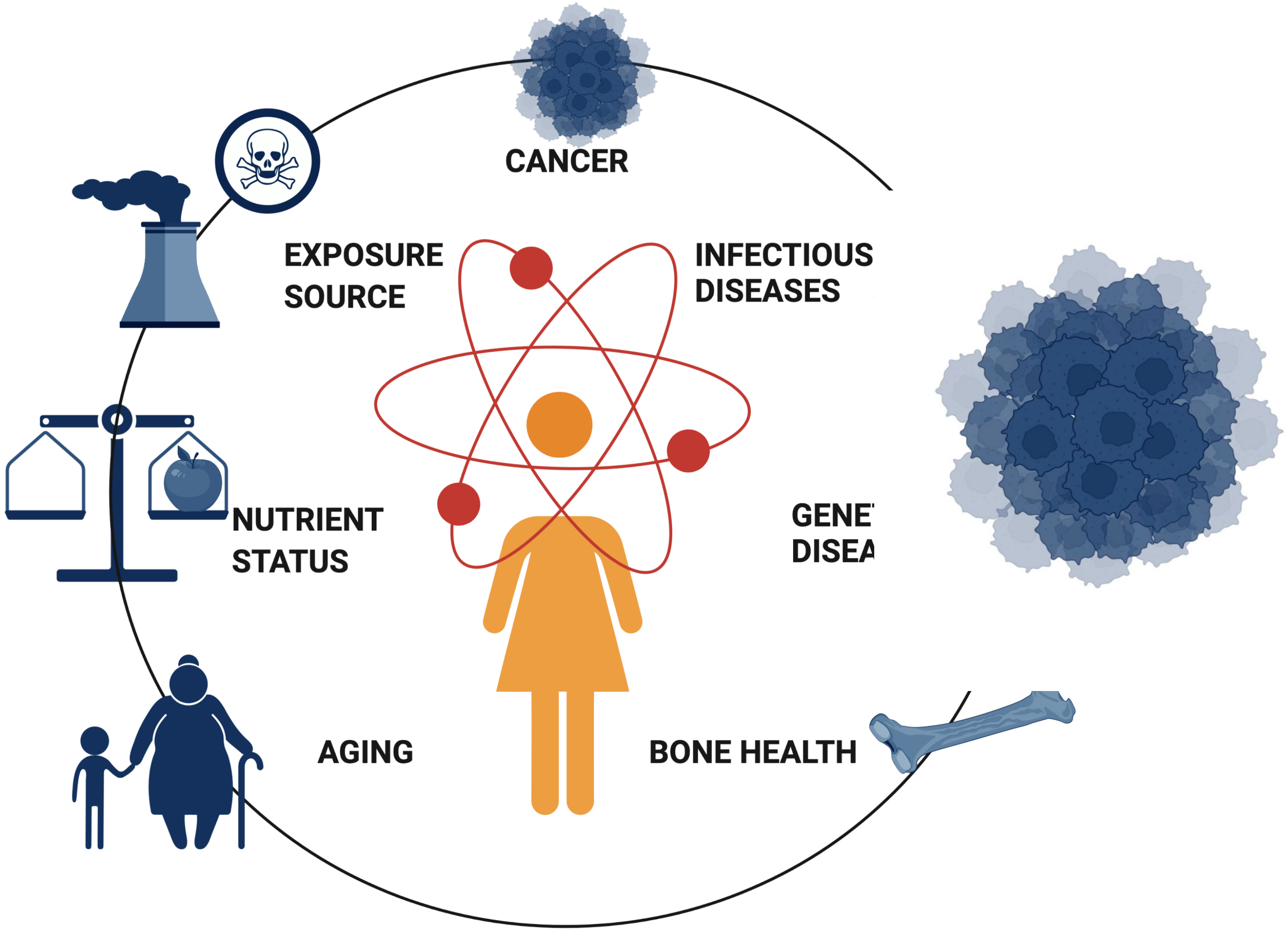
Provide extra information about **biological processes** (e.g. redox reaction, metal-protein binding)

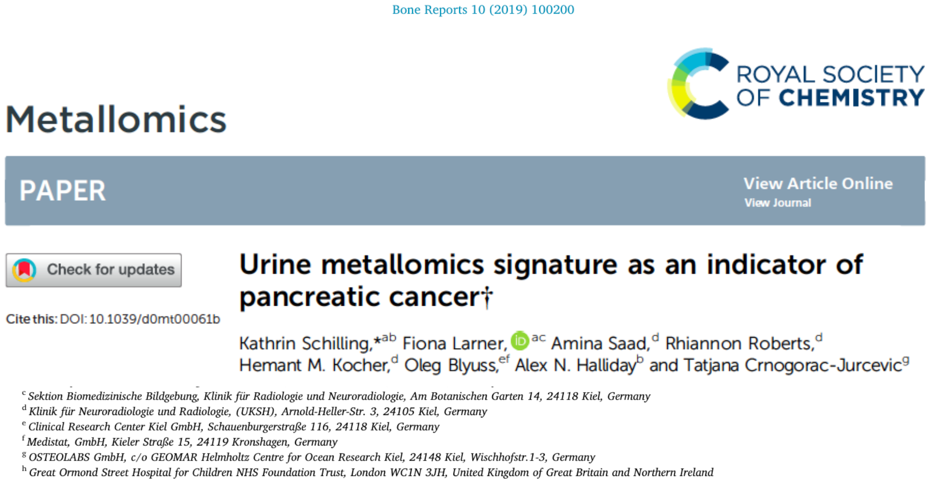
Fast-responding biomarkers in environmental epidemiological studies

Toxicological mechanisms and health risks by exposure

Photo: https://www.elsevier.com/

Isotope metallomics




Bone Reports 10 (2019) 100200

Metallomics

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Check for updates

Cite this: DOI: 10.1039/d0mt00061b

Urine metallomics signature as an indicator of pancreatic cancer†

Kathrin Schilling,*[ab] Fiona Larner,[ac] Amina Saad,[d] Rhiannon Roberts,[d] Hemant M. Kocher,[d] Oleg Blyuss,[ef] Alex N. Halliday[b] and Tatjana Crnogorac-Jurcevic[g]

[c] *Sektion Biomedizinische Bildgebung, Klinik für Radiologie und Neuroradiologie, Am Botanischen Garten 14, 24118 Kiel, Germany*
[d] *Klinik für Neuroradiologie und Radiologie, (UKSH), Arnold-Heller-Str. 3, 24105 Kiel, Germany*
[e] *Clinical Research Center Kiel GmbH, Schauenburgerstraße 116, 24118 Kiel, Germany*
[f] *Medistat, GmbH, Kieler Straße 15, 24119 Kronshagen, Germany*
[g] *OSTEOLABS GmbH, c/o GEOMAR Helmholtz Centre for Ocean Research Kiel, 24148 Kiel, Wischhofstr.1-3, Germany*
[h] *Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, United Kingdom of Great Britain and Northern Ireland*

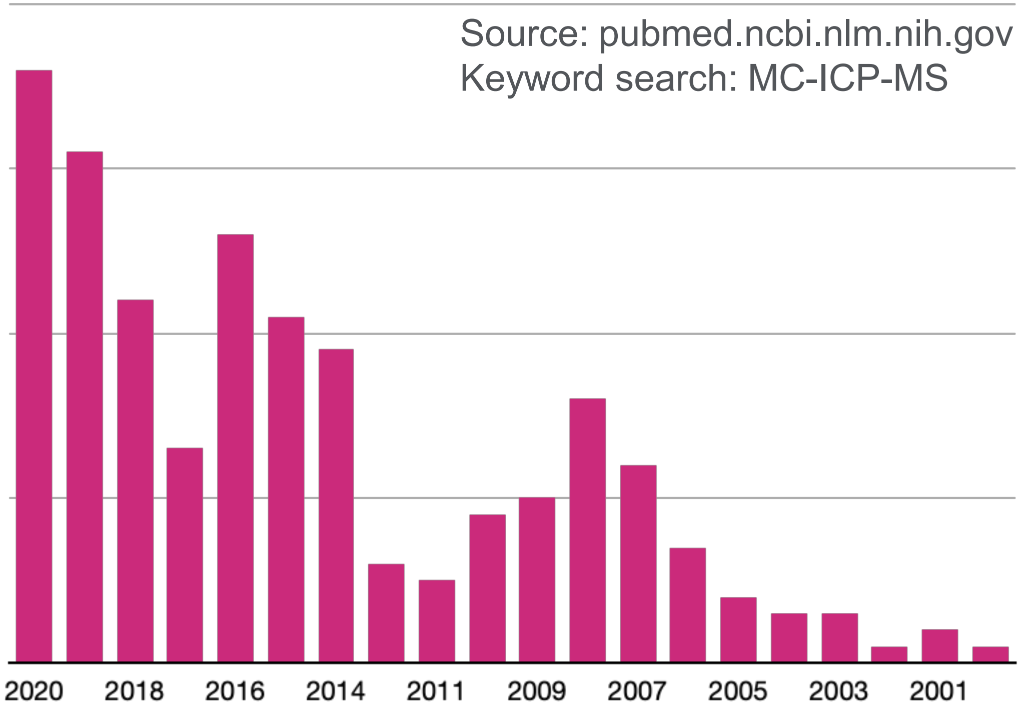

OXFORD

Metallomics, 13, 2021, mfab027
DOI: 10.1093/mtomcs/mfab027
Advance access publication date: 10 May 2021
Paper

Zinc stable isotope analysis reveals Zn dyshomeostasis in benign tumours, breast cancer, and adjacent histologically normal tissue

Kaj V. Sullivan[1,2,*], Rebekah E. T. Moore[2], Miles S. Capper[2], Kathrin Schilling[3], Kate Goddard[4], Charlotte Ion[4], Daniel Layton-Matthews[1], Matthew I. Leybourne[1,5], Barry Coles[2], Katharina Kreissig[2], Olga Antsygina[6,7], R. Charles Coombes[4], Fiona Larner[8,9,10] and Mark Rehkämper[2]

Multicollector-ICP-MS
High-precision isotope measurements



Source: pubmed.ncbi.nlm.nih.gov
Keyword search: MC-ICP-MS

Isotope ratios can be measured to **±0.005%** – c.f. ±0.5% via ordinary concentration analyses

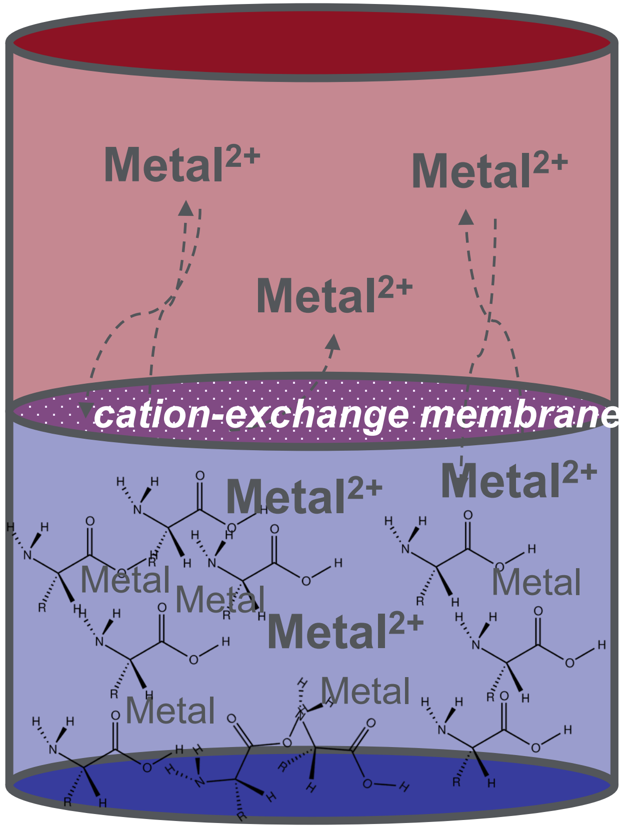
Uncertainty = 0.05‰

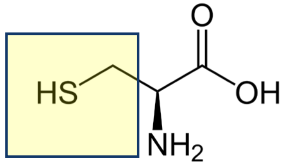
Isotope metallomics

Application

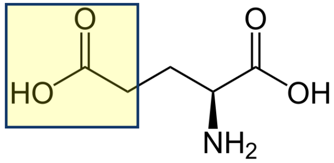
Metal isotope can tell us about **molecular binding**

Rutgers University

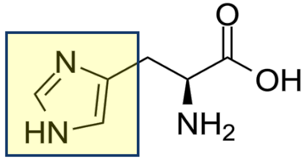




Cysteine (Cys)



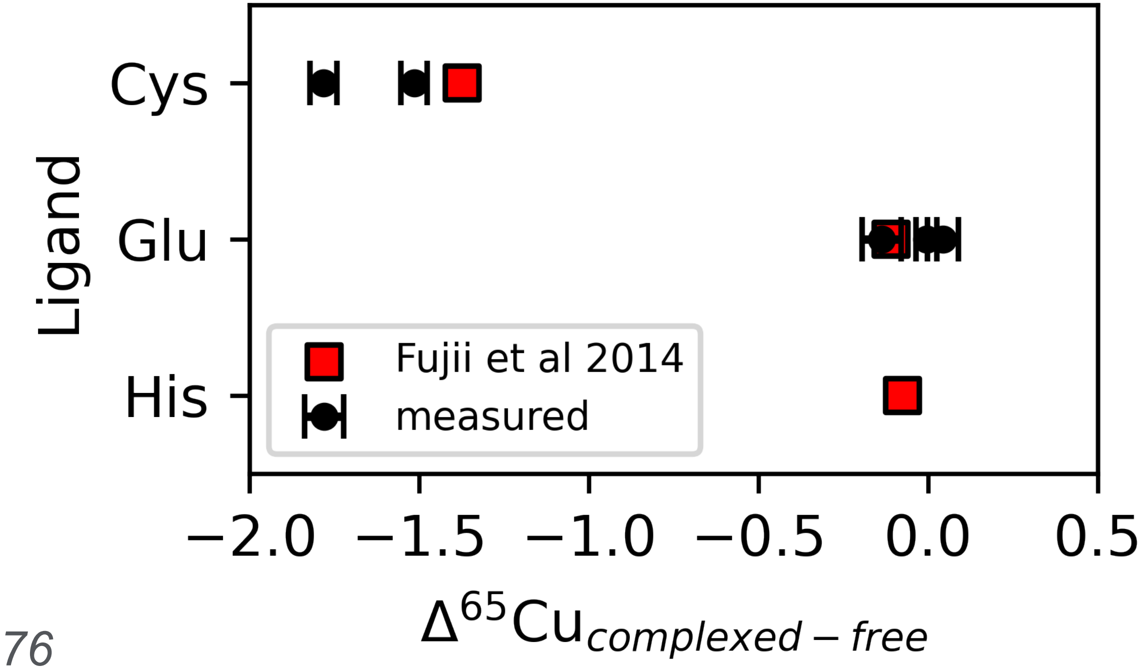
Glutamic acid (Glu)



Histidine (His)

Corday Selden

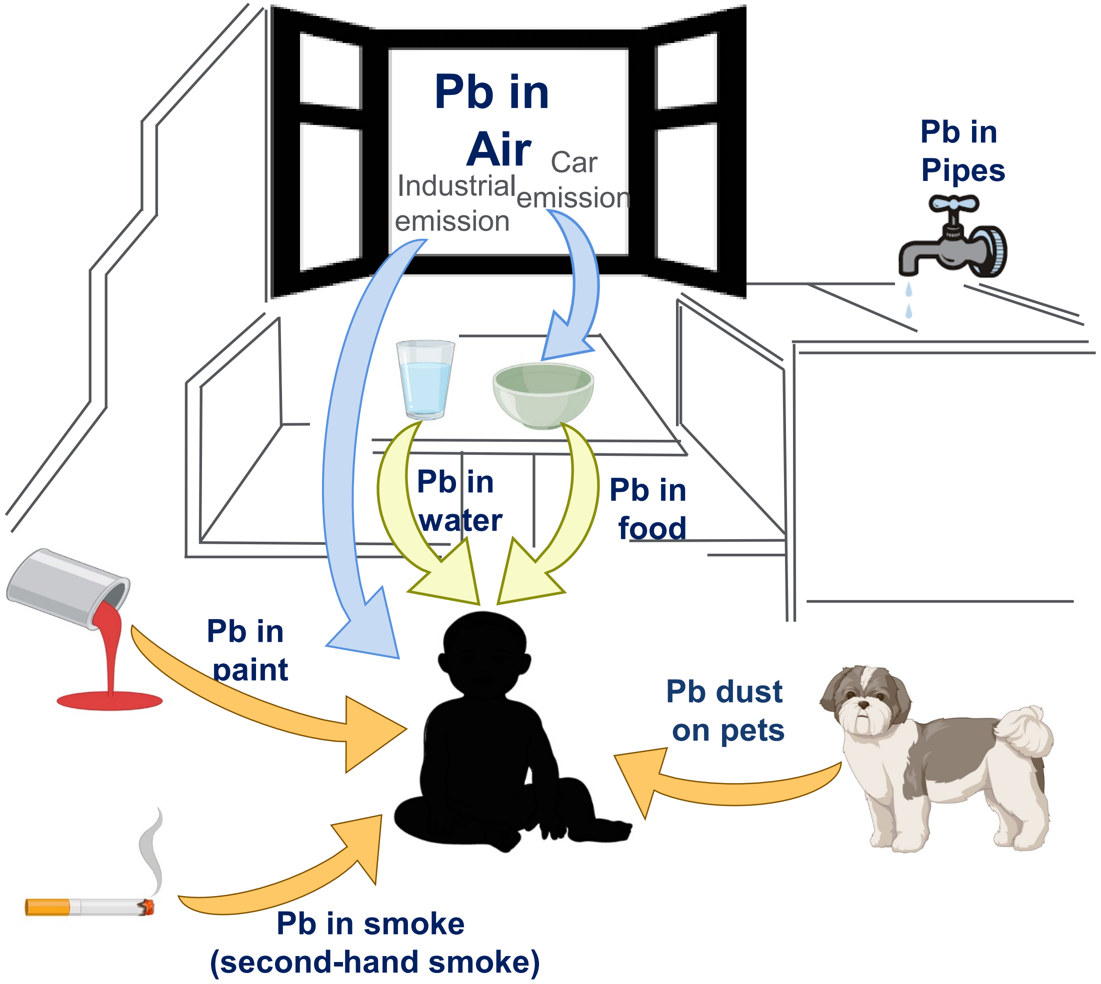
Nathan Yee

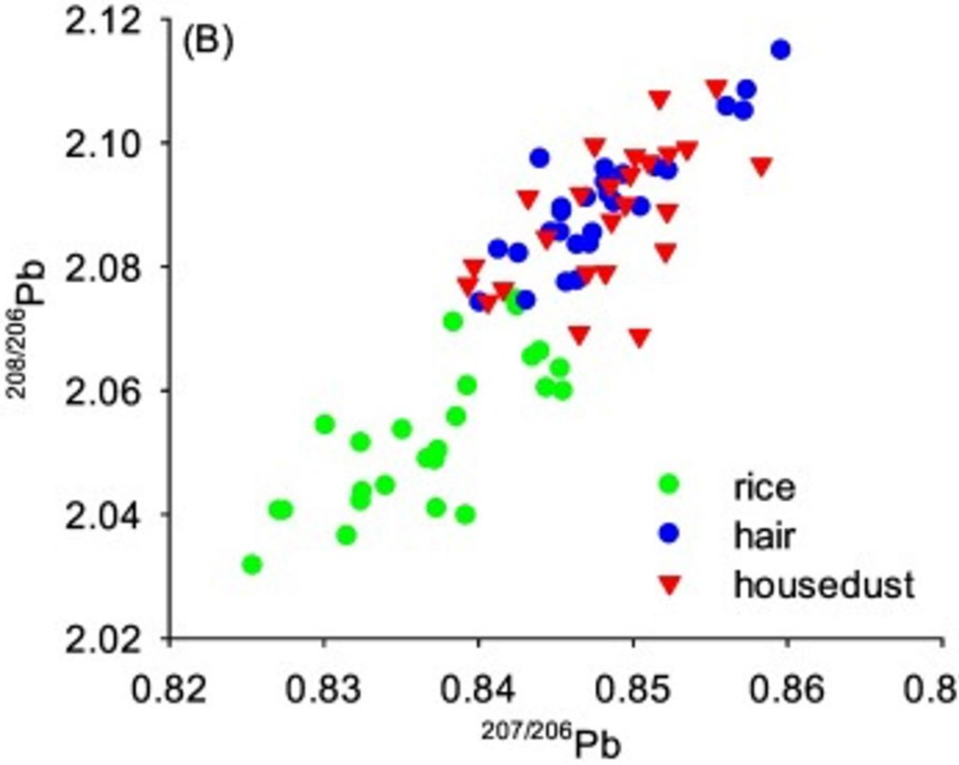


Selden et al. (in prep)

$\Delta^{65}Cu_{complexed-free} = \delta^{65}Cu_{complexed} - \delta^{65}Cu_{free}$ *relative to NIST-976*

Source fingerprinting of metal exposure





Zhao et al., 2018, Environ. Intern. 120, 563-571

Promising markers to elucidate the influences of environmental pollution on the human health

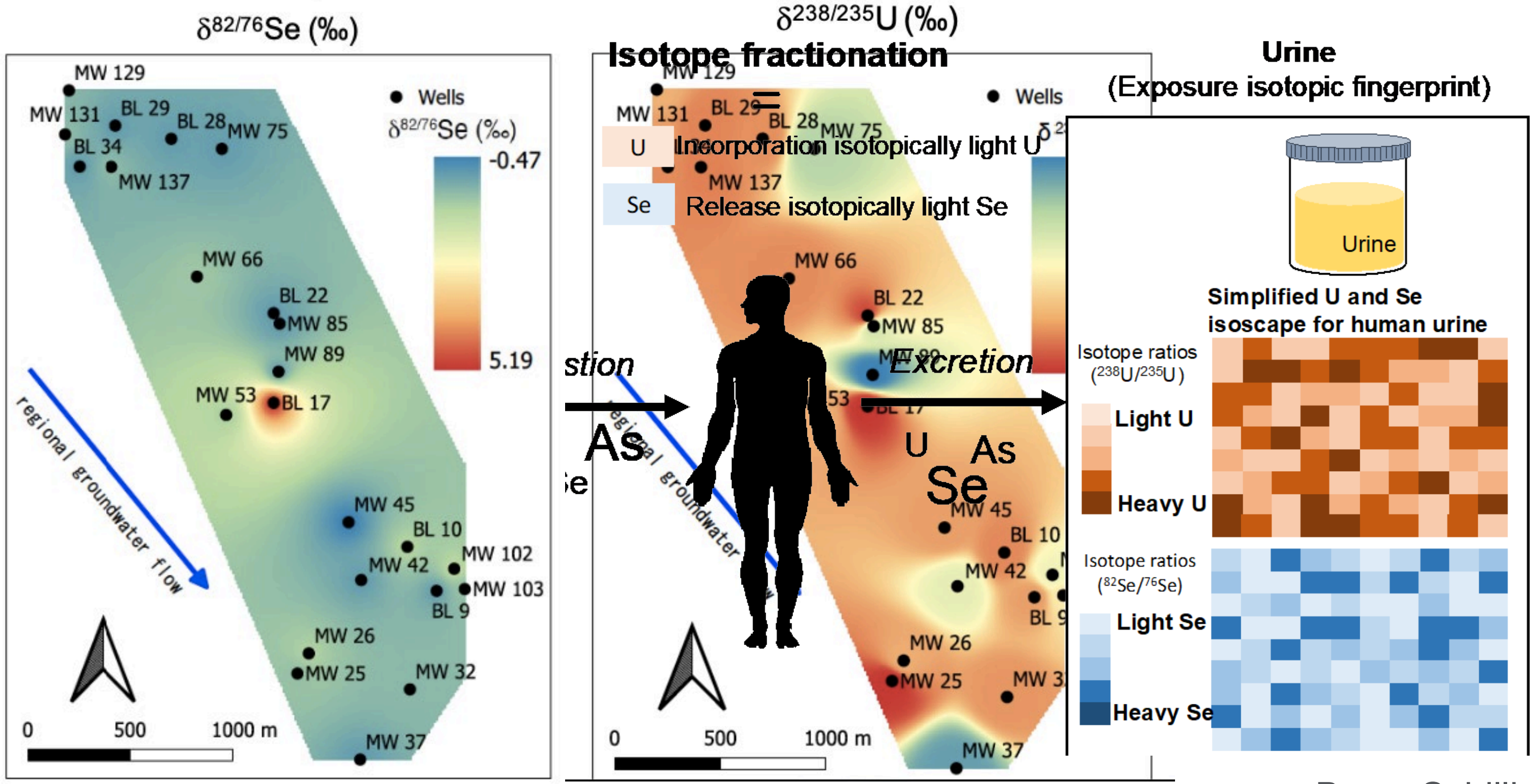
Metal isotopes and exposure

Proposed project: NIEHS Superfund 2021

Ana Navas-Acien

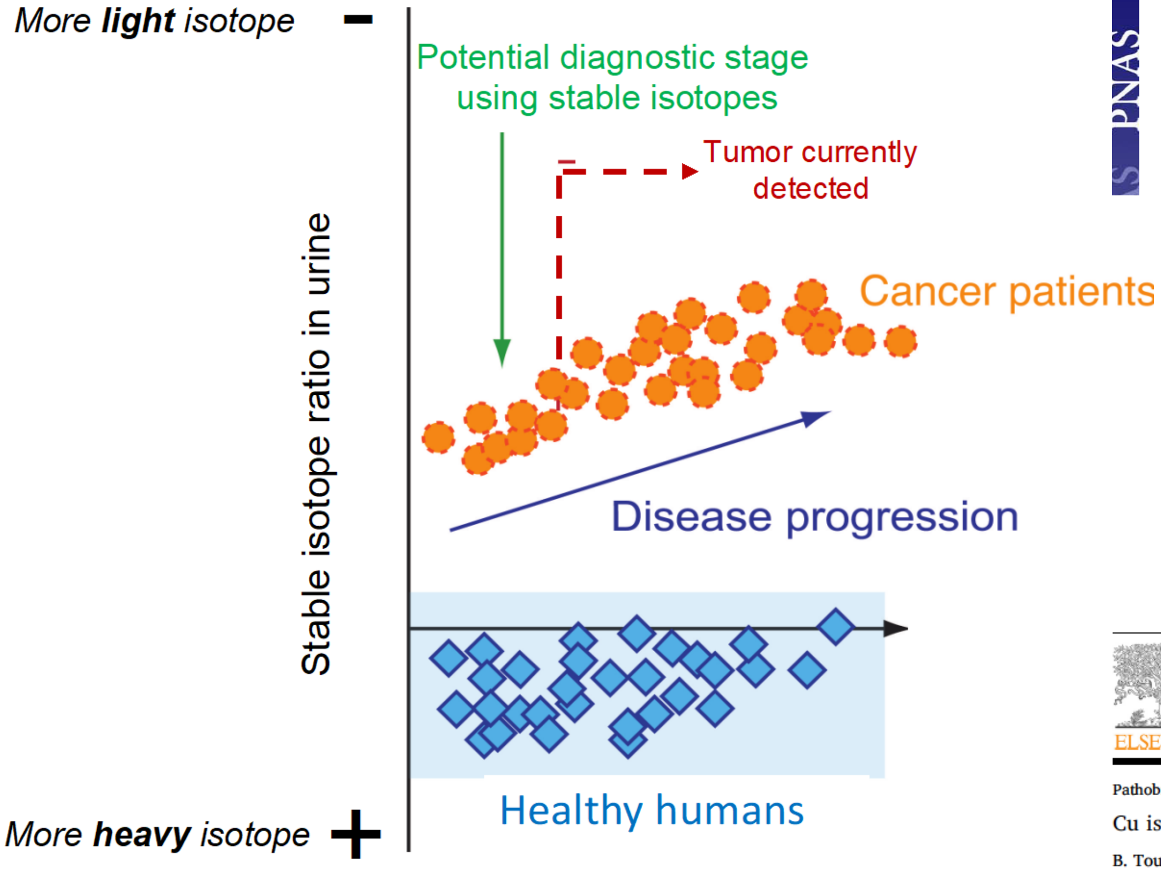
Alex Halliday

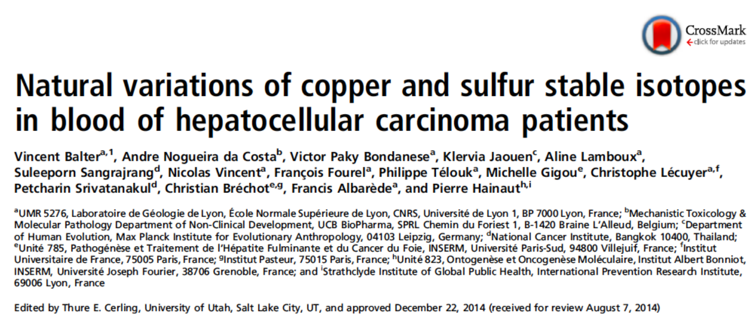
Anirban Basu



Basu, Schilling et al., 2016 (ES&T)

Metal stable isotopes as disease marker



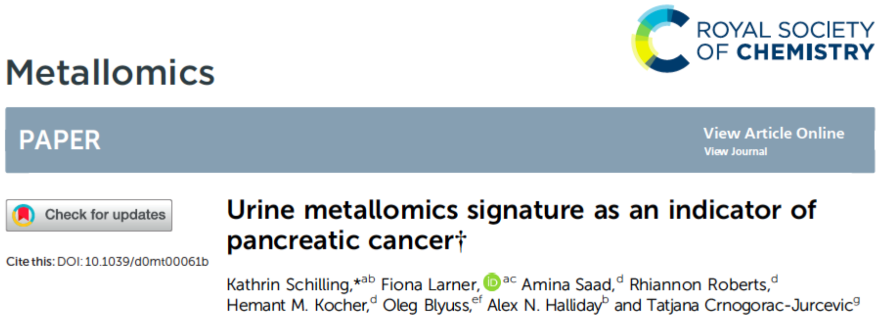


Natural variations of copper and sulfur stable isotopes in blood of hepatocellular carcinoma patients

Vincent Balter[a,1], Andre Nogueira da Costa[b], Victor Paky Bondanese[a], Klervia Jaouen[c], Aline Lamboux[a], Suleeporn Sangrajrang[d], Nicolas Vincent[a], François Fourel[a], Philippe Télouk[a], Michelle Gigou[e], Christophe Lécuyer[a,f], Petcharin Srivatanakul[d], Christian Bréchot[e,g], Francis Albarède[a], and Pierre Hainaut[h,i]

[a]UMR 5276, Laboratoire de Géologie de Lyon, École Normale Supérieure de Lyon, CNRS, Université de Lyon 1, BP 7000 Lyon, France; [b]Mechanistic Toxicology & Molecular Pathology Department of Non-Clinical Development, UCB BioPharma, SPRL Chemin du Foriest 1, B-1420 Braine L'Alleud, Belgium; [c]Department of Human Evolution, Max Planck Institute for Evolutionary Anthropology, 04103 Leipzig, Germany; [d]National Cancer Institute, Bangkok 10400, Thailand; [e]Unité 785, Pathogénèse et Traitement de l'Hépatite Fulminante et du Cancer du Foie, INSERM, Université Paris-Sud, 94800 Villejuif, France; [f]Institut Universitaire de France, 75005 Paris, France; [g]Institut Pasteur, 75015 Paris, France; [h]Unité 823, Ontogenèse et Oncogenèse Moléculaire, Institut Albert Bonniot, INSERM, Université Joseph Fourier, 38706 Grenoble, France; and [i]Strathclyde Institute of Global Public Health, International Prevention Research Institute, 69006 Lyon, France

Edited by Thure E. Cerling, University of Utah, Salt Lake City, UT, and approved December 22, 2014 (received for review August 7, 2014)



Metallomics

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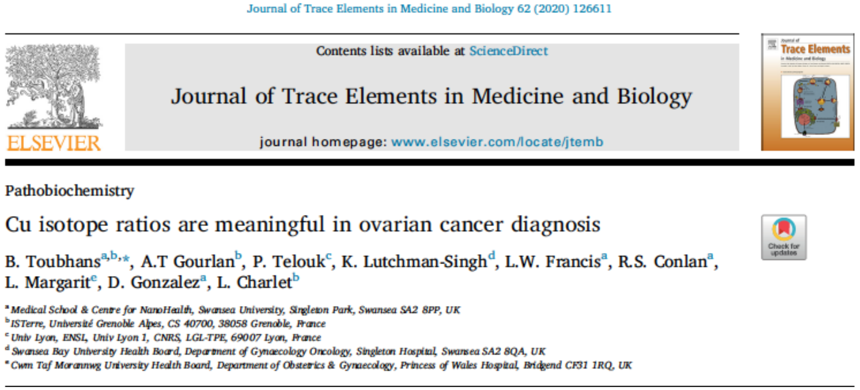
Cite this: DOI: 10.1039/d0mt00061b

Urine metallomics signature as an indicator of pancreatic cancer†

Kathrin Schilling,*[ab] Fiona Larner,[ac] Amina Saad,[d] Rhiannon Roberts,[d] Hemant M. Kocher,[d] Oleg Blyuss,[ef] Alex N. Halliday[b] and Tatjana Crnogorac-Jurcevic[g]



Journal of Trace Elements in Medicine and Biology 62 (2020) 126611

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Pathobiochemistry

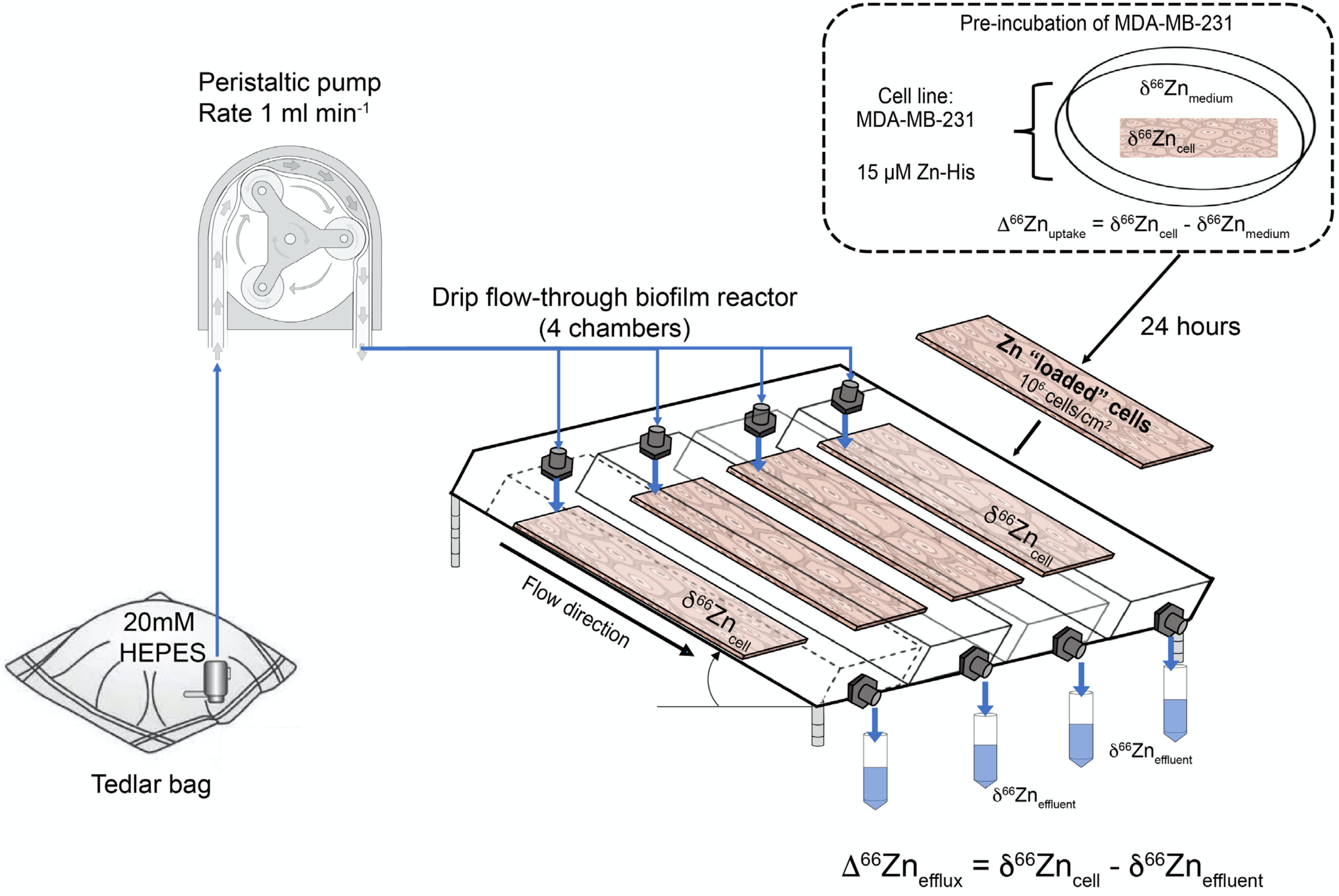
Cu isotope ratios are meaningful in ovarian cancer diagnosis

B. Toubhans[a,b,*], A.T Gourlan[b], P. Telouk[c], K. Lutchman-Singh[d], L.W. Francis[a], R.S. Conlan[a], L. Margarit[e], D. Gonzalez[a], L. Charlet[b]

[a] *Medical School & Centre for NanoHealth, Swansea University, Singleton Park, Swansea SA2 8PP, UK*
[b] *ISTerre, Université Grenoble Alpes, CS 40700, 38058 Grenoble, France*
[c] *Univ Lyon, ENSL, Univ Lyon 1, CNRS, LGL-TPE, 69007 Lyon, France*
[d] *Swansea Bay University Health Board, Department of Gynaecology Oncology, Singleton Hospital, Swansea SA2 8QA, UK*
[e] *Cwm Taf Morannwg University Health Board, Department of Obstetrics & Gynaecology, Princess of Wales Hospital, Bridgend CF31 1RQ, UK*

Metal isotope fractionation: Cellular level

In vitro with cancer cell lines



Oxford University

Adrian Harris

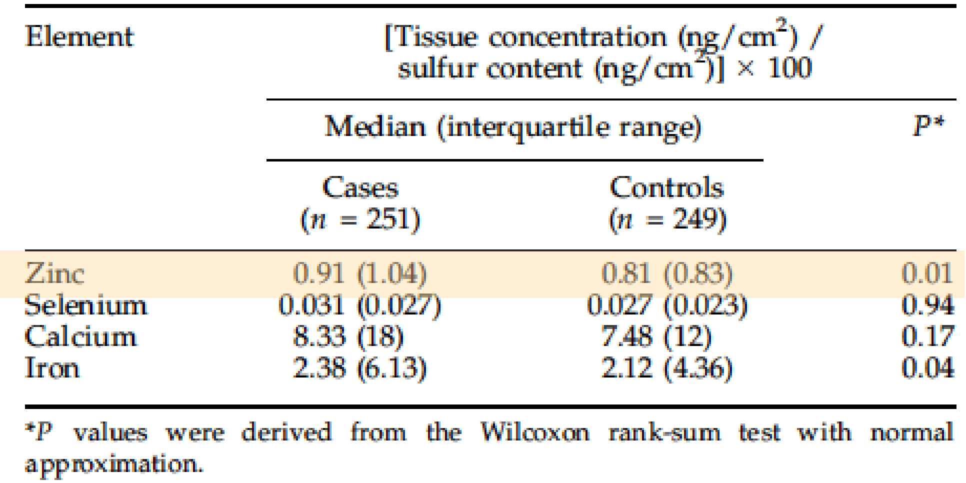
Fiona Larner

Chris Schoefield

Schilling et al. 2022, Frontiers in Medicine (doi: 10.3389/fmed.2021.746532)

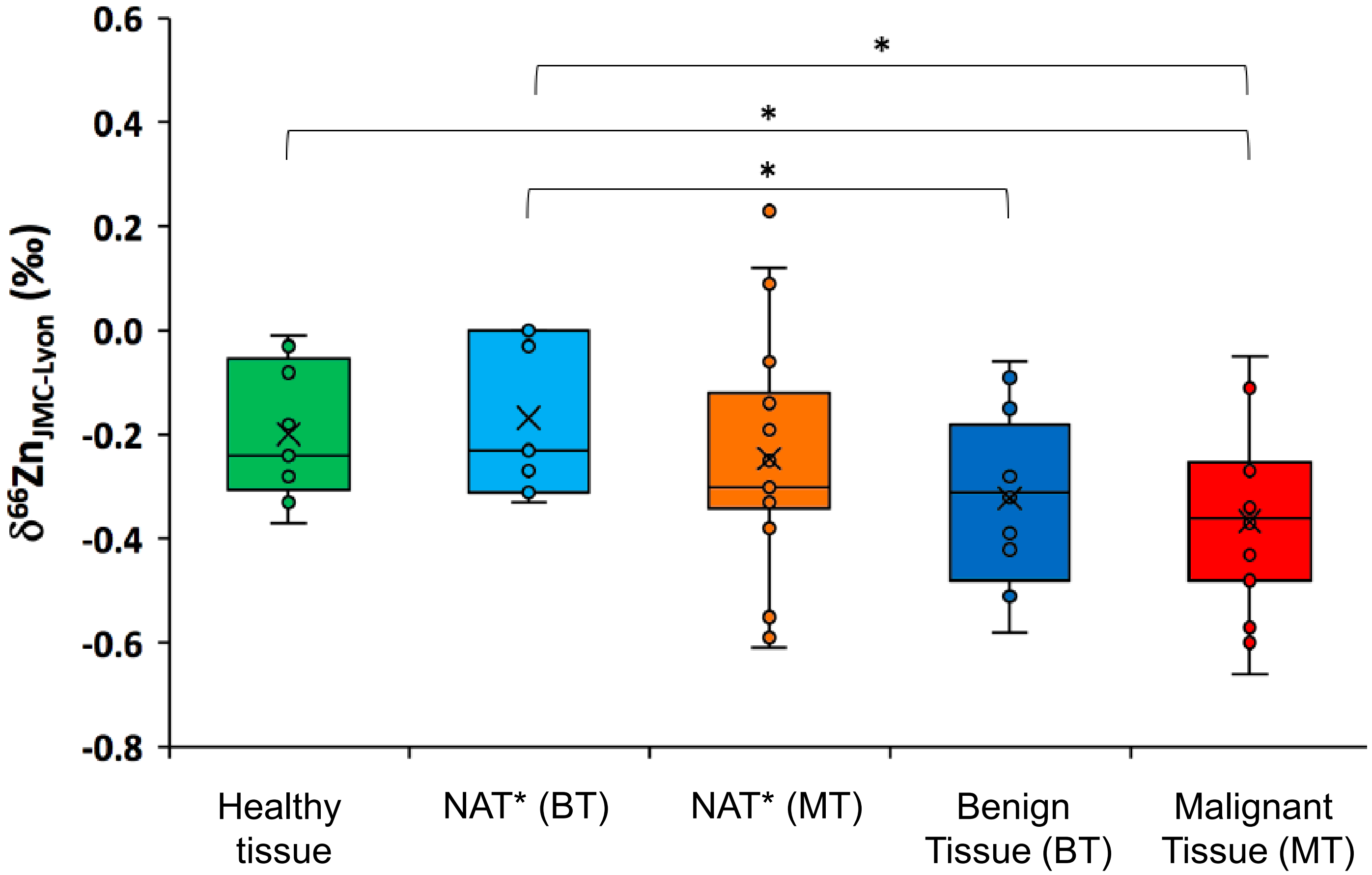
Zinc isotopes and breast cancer

Specimen: Tissue



Element	[Tissue concentration (ng/cm^2) / sulfur content (ng/cm^2)] × 100		
	Median (interquartile range)		P*
	Cases (n = 251)	Controls (n = 249)	
Zinc	0.91 (1.04)	0.81 (0.83)	0.01
Selenium	0.031 (0.027)	0.027 (0.023)	0.94
Calcium	8.33 (18)	7.48 (12)	0.17
Iron	2.38 (6.13)	2.12 (4.36)	0.04

*P values were derived from the Wilcoxon rank-sum test with normal approximation.



*Histologically normal tissue adjacent MT or BT

Sullivan, Moore, Schilling et al., 2021 (Metallomics)

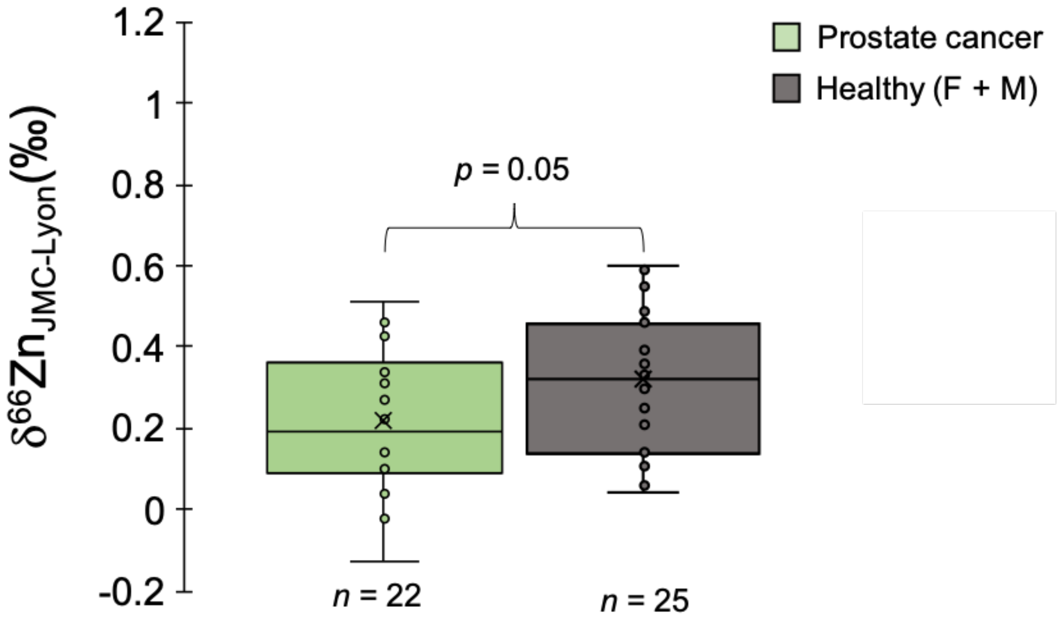
Zinc isotopes as prognostic tool for prostate cancer
Specimen: Urine

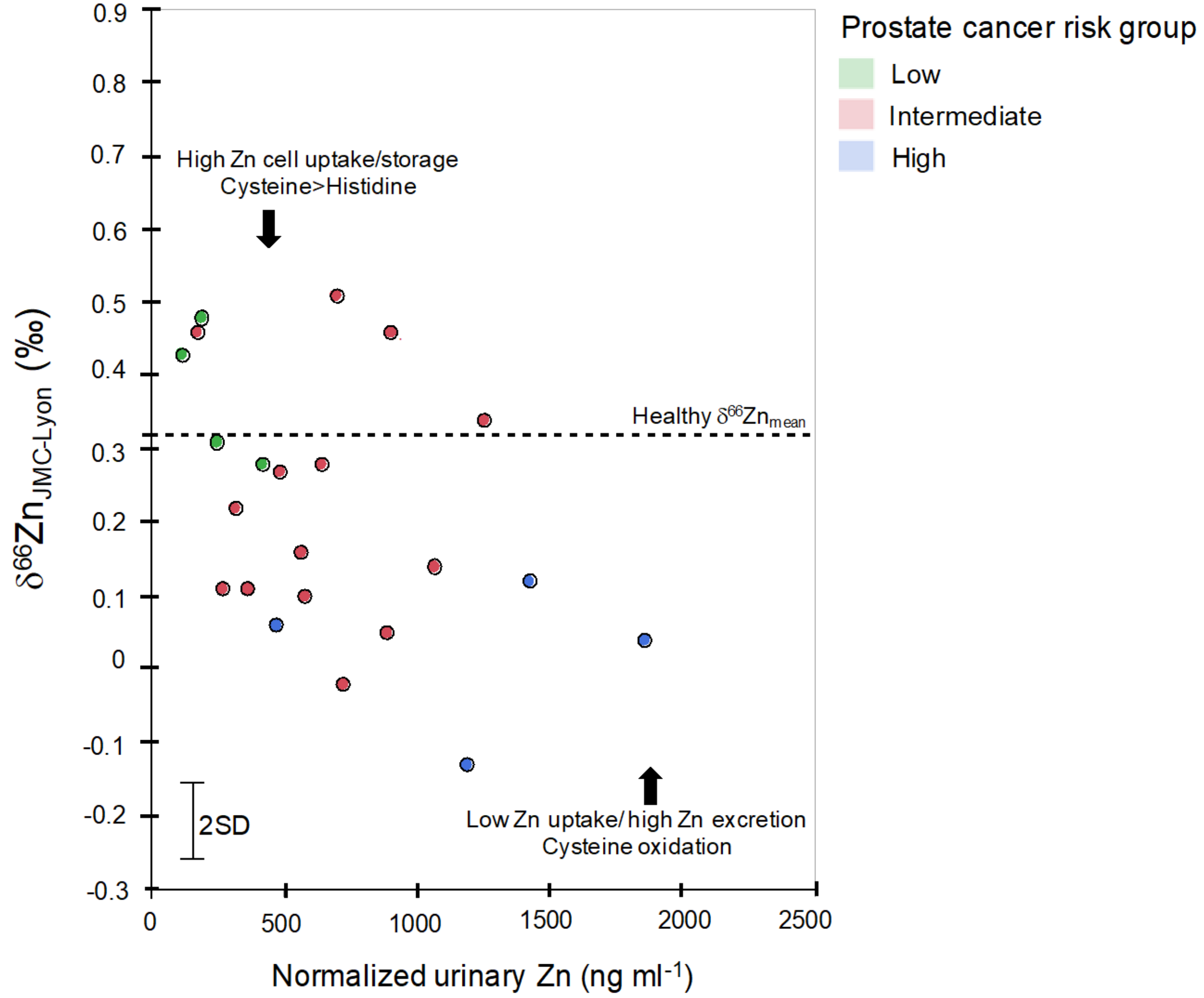
Metallomics, 13, 2021, mfab020
DOI: 10.1093/mtomcs/mfab020
Advance access publication date: 20 April 2021
Paper

Zinc stable isotopes in urine as diagnostic for cancer of secretory organs

Kathrin Schilling[1,*], Rebekah E.T. Moore[2], Kaj V. Sullivan[3], Miles S. Capper[2], Mark Rehkämper[2], Kate Goddard[4], Charlotte Ion[4], R. Charles Coombes[4], Lois Vesty-Edwards[5], Alastair D. Lamb[5], Alex N. Halliday[6] and Fiona Larner[7,8]

[1]Lamont-Doherty Earth Observatory, Columbia University, Palisades, NY, USA, [2]Department of Earth Science and Engineering, Imperial College London, London, UK, [3]Department of Renewable Resources, University of Alberta, Alberta, Canada, [4]Imperial College Healthcare NHS Trust, London, UK, [5]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, [6]Earth Institute, Columbia University, New York, NY, USA, [7]Department of Earth Sciences, University of Oxford, South Parks Road, Oxford, UK and [8]St Catherine's College, University of Oxford, Manor Road, Oxford, UK
*__Correspondence__: Lamont-Doherty Earth Observatory, Columbia University, 435 Comer Bldg, 61 Rte 9W, Palisades, NY 10964, USA. E-mail: ks3759@columbia.edu

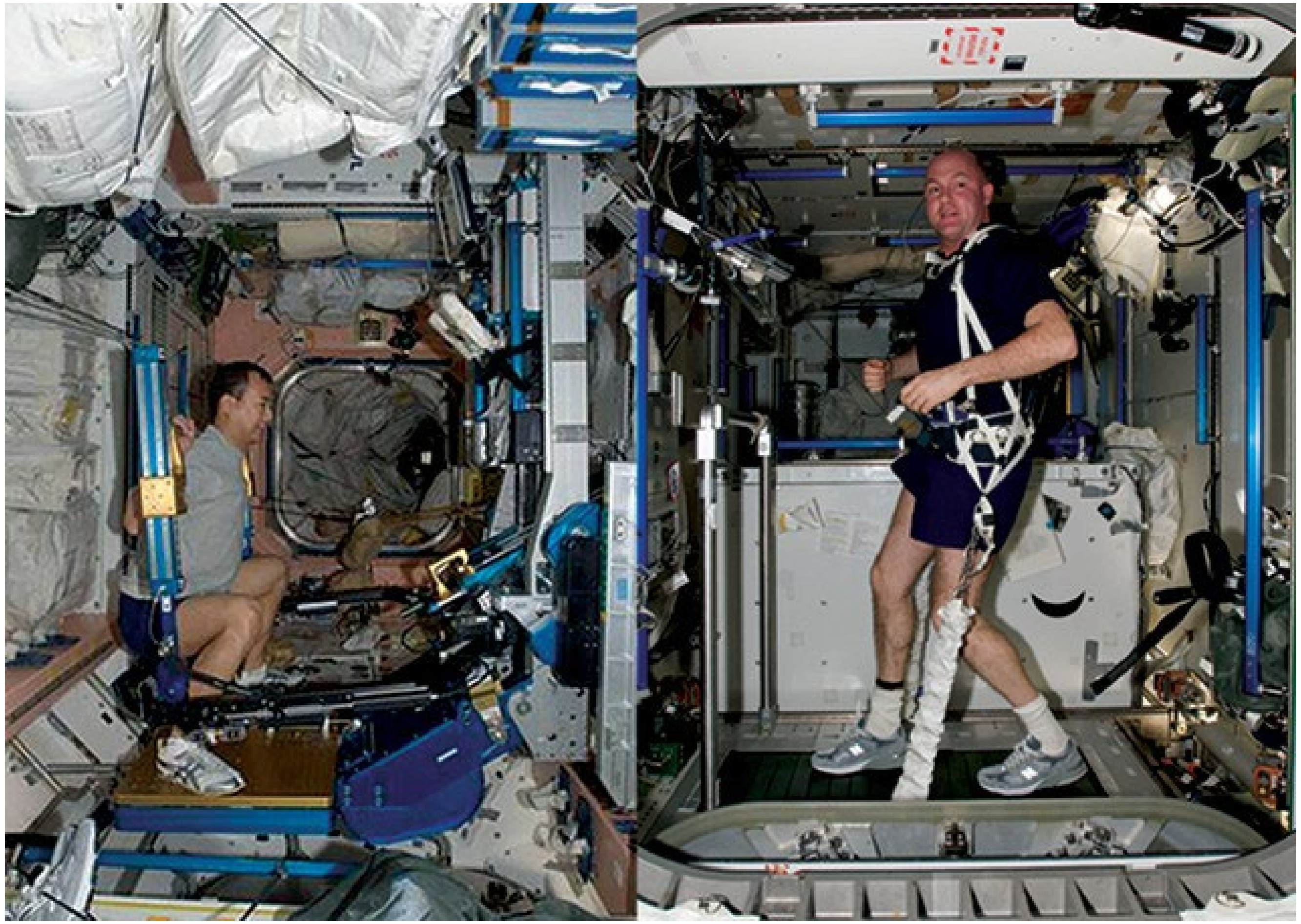




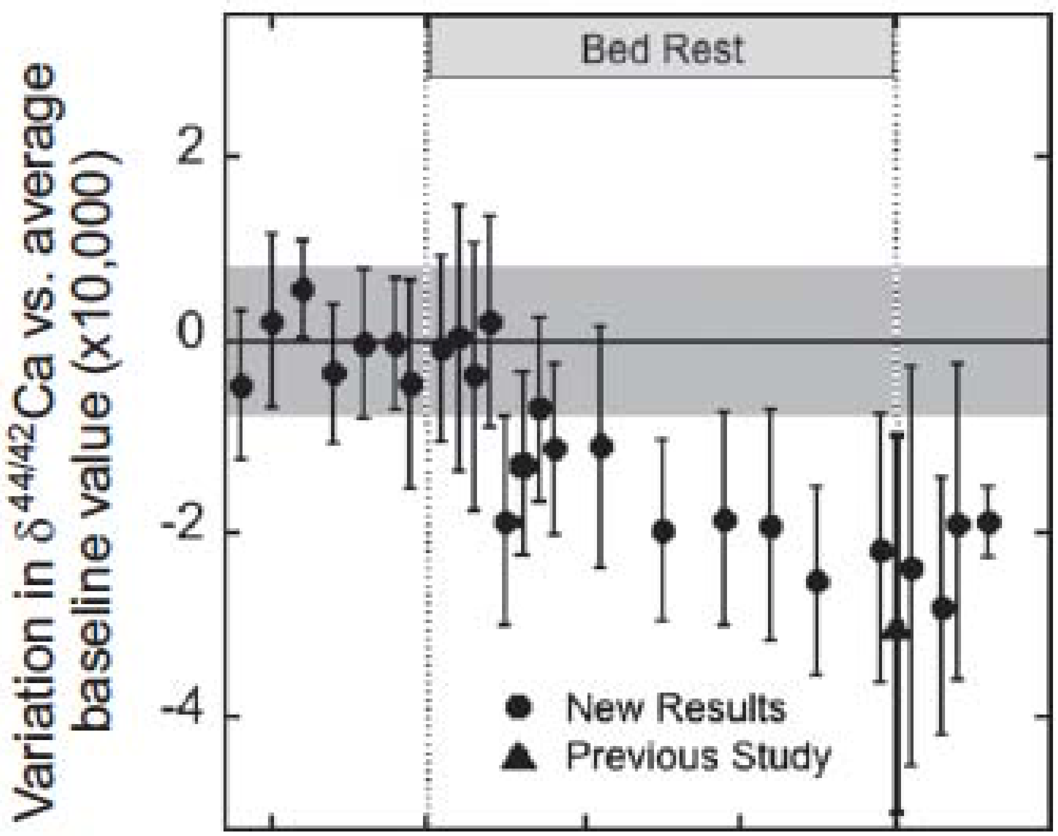
Schilling et al., 2021, Metallomics

Calcium isotopes show bone loss earlier than densitometry

Specimen: Urine

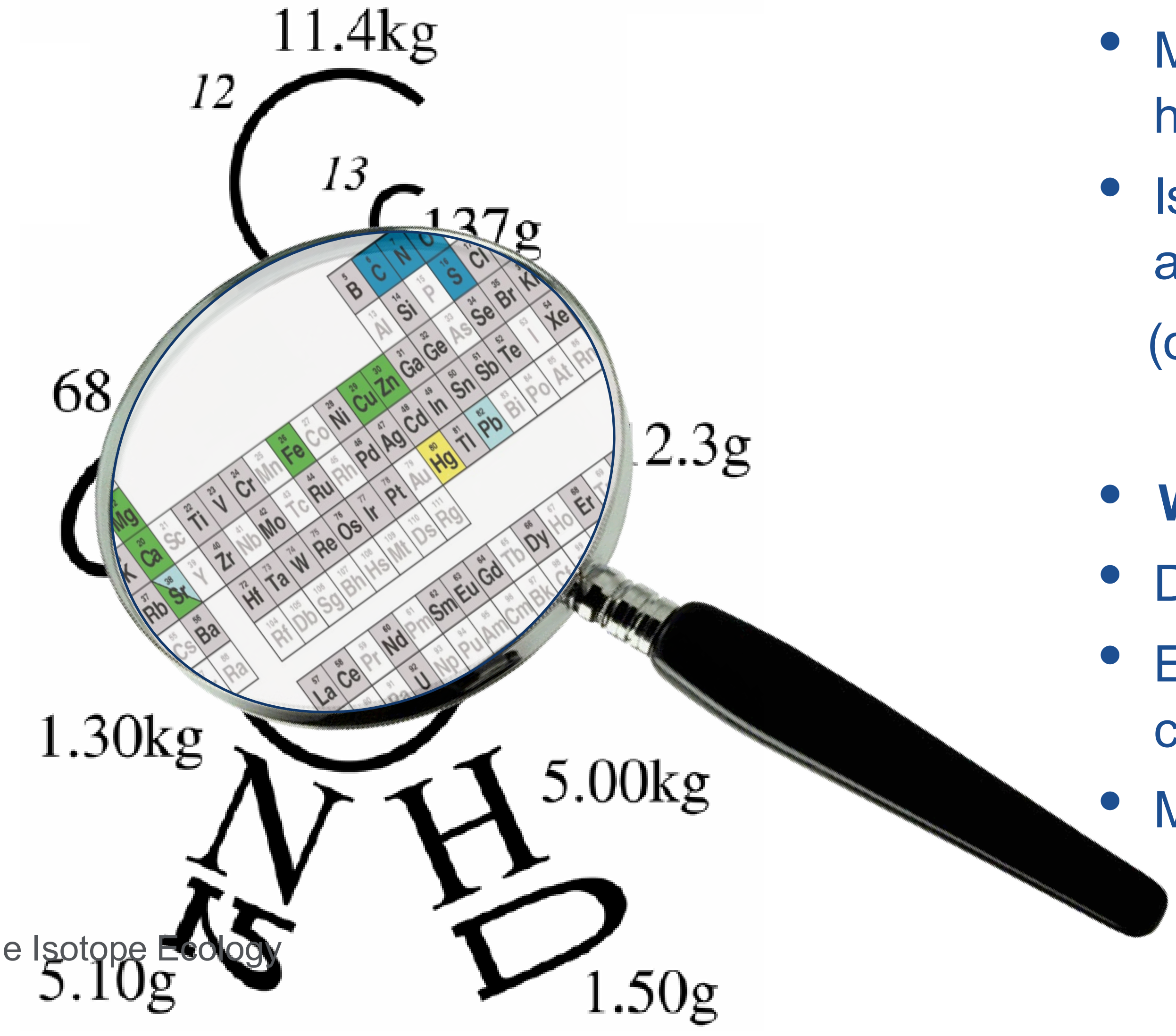


Source: NASA



Morgan et al., 2012, FASEB journal, 26: 244.

OUTLOOK: Future field in EHS



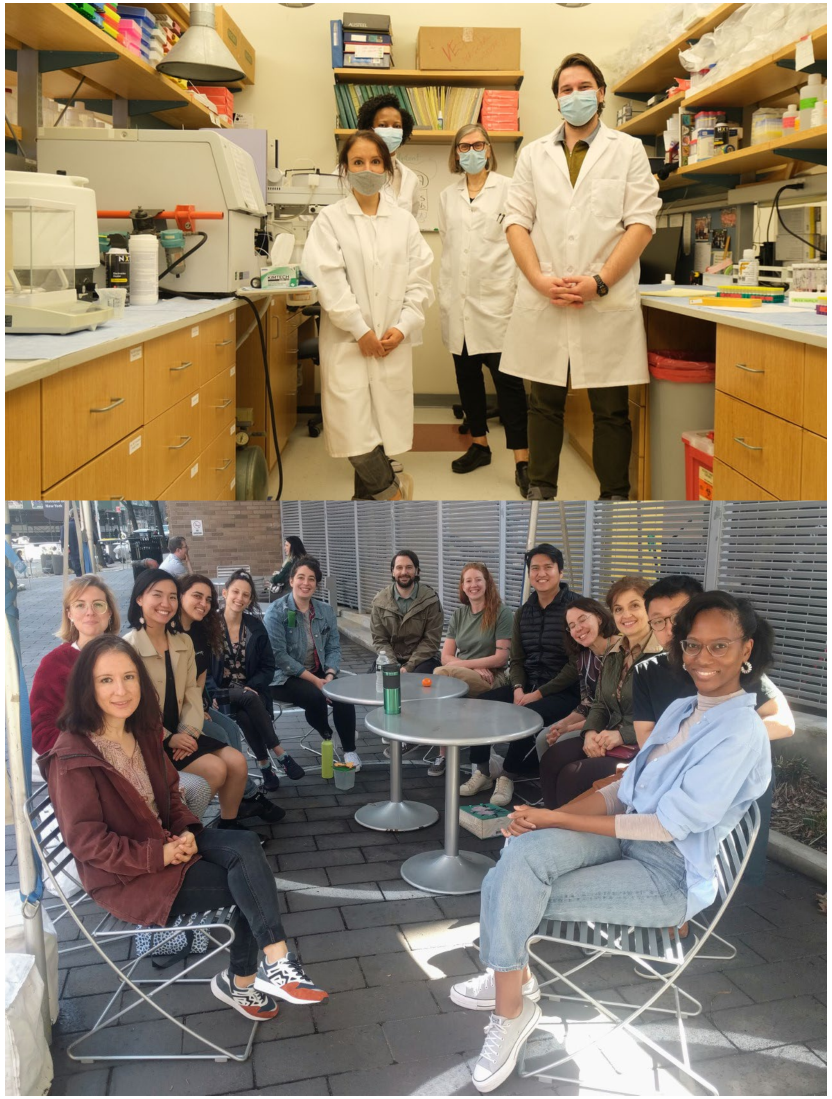
06 Stable Isotope Ecology

- More systematic approach involving a substantially higher number of patients
- Isotope ratios are more “robust” than concentrations and even tiny differences

  (of the order of 0.0005%)

- **Widespread applications**
- Disease marker (early diagnostic or prognostic tool)
- Exposure marker (source fingerprinting and contribution of different sources)
- Metabolic maker

Future success of isotope metallomics defined by united efforts of **medical and isotope (geo)scientists**



Thank you

As

NIH

NIEHS

Center for Environmental Health in Northern Manhattan