Shoumen Palit Austin Datta

How to transform SOFT ideas into HARD reality

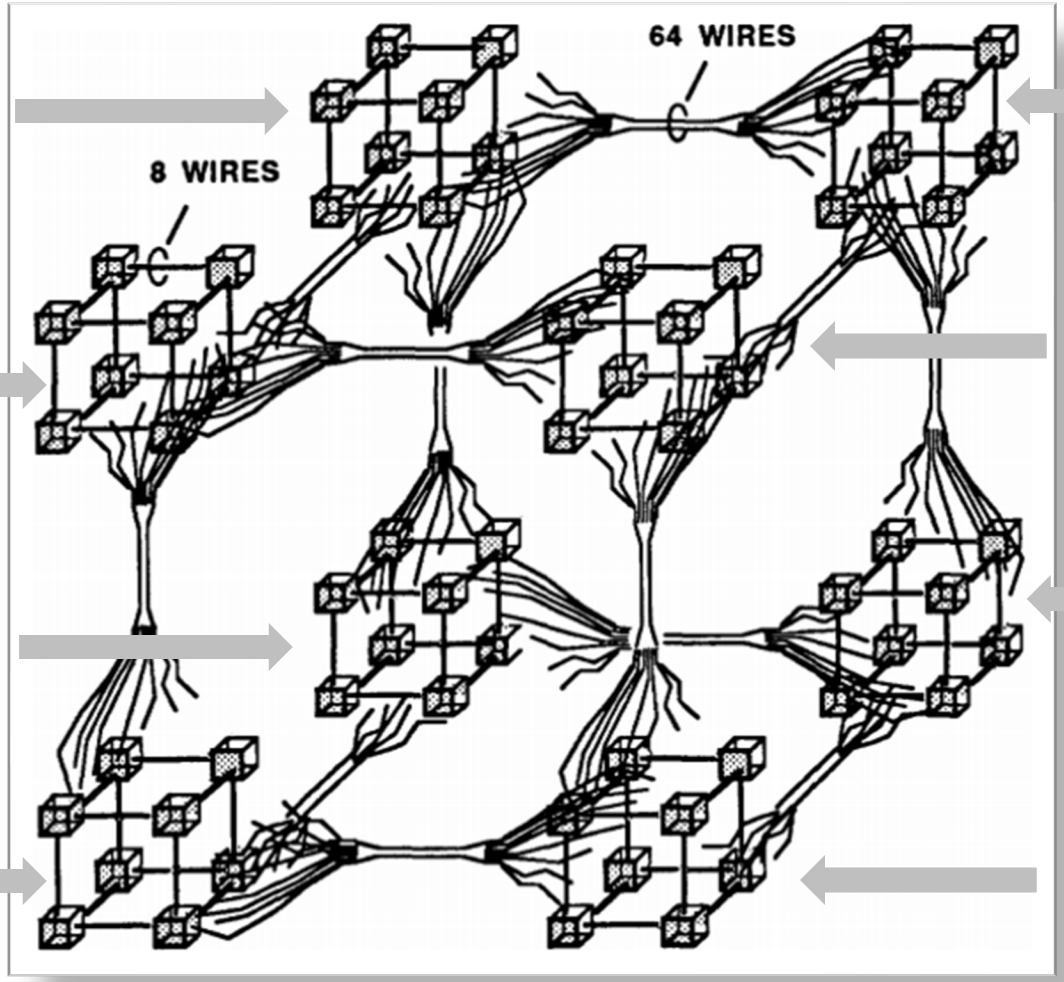
CONVERGENCE OF A SPECTRUM OF NODES TO INFORM AND INFLUENCE KEY PERFORMANCE INDICATORS (KPI)

SCIENCE & SCIENTISTS

GRANTS & DONORS

WORKFORCE DEVELOPMENT

RESEARCH & CREDIBILITY



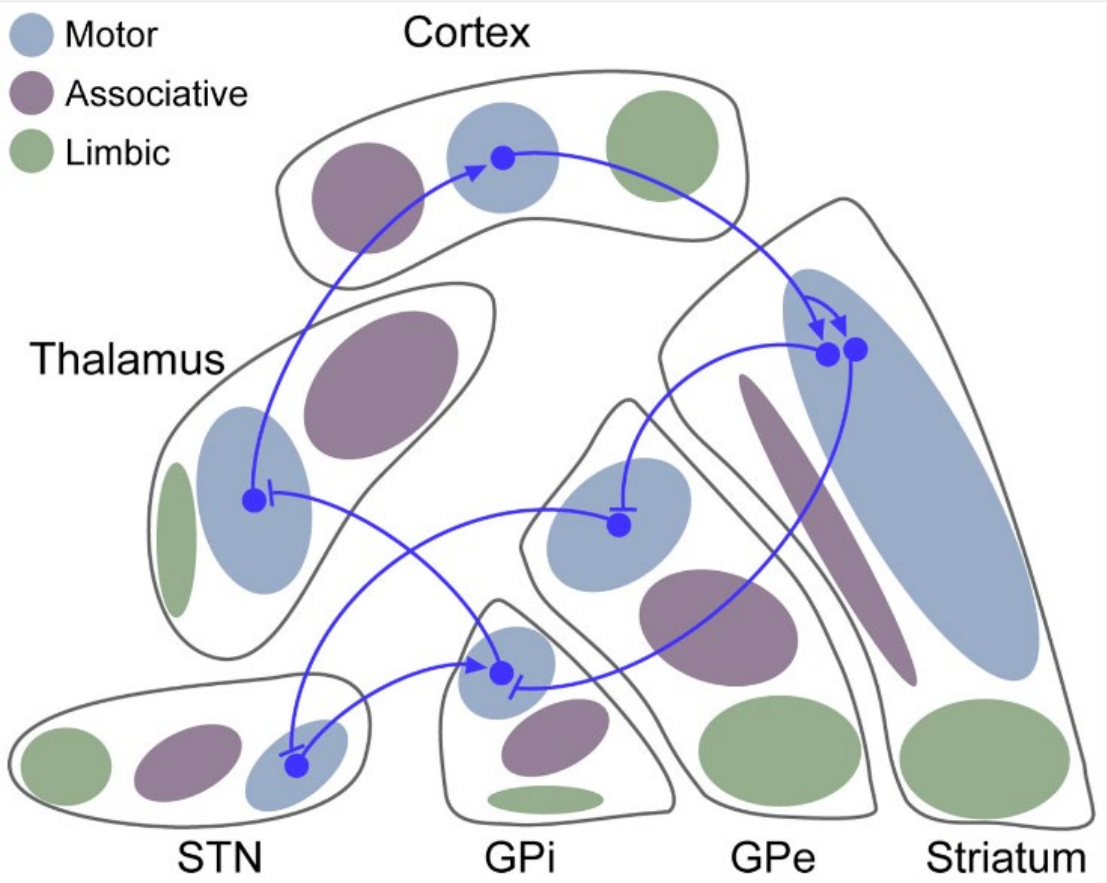
EQUIPMENT & REPOSITORIES

BUSINESS DEVELOPMENT

PRODUCTS & MARKETING

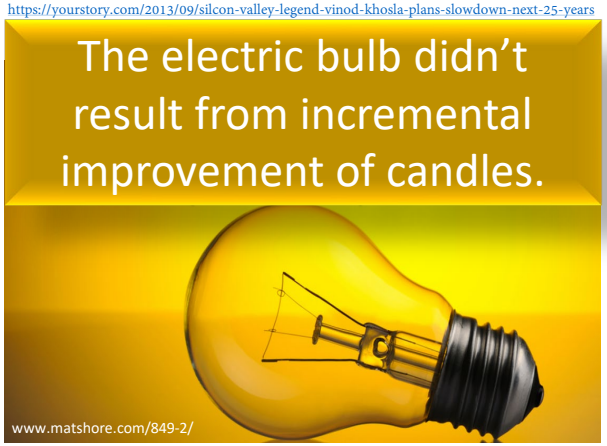
GOVERNMENT LIAISON & PR

Explore Parts 3, 2 and 1 – here - https://dspace.mit.edu/handle/1721.1/153283


Motor
Associative
Limbic
Cortex
Thalamus
STN
GPi
GPe
Striatum

Outsiders innovate ??

https://yourstory.com/2013/09/silcon-valley-legend-vinod-khosla-plans-slowdown-next-25-years



NBC didn't change media. YouTube did. NASA didn't reinvent space exploration. SpaceX did. GM didn't innovate electric car. Tesla did. AT&T didn't create smart phones. Apple did. Walmart could not innovate retail. Amazon did.

SENSE OF FUTURE THINKING

SOFT

for

HARD

Healthcare-Associated Research & Development

Outsiders innovate ??

Blood Bank Digital

https://hbr.org/2011/08/henry-ford-never-said-the-fast

Harvard Business Review

"If I had asked people what they wanted, they would have said faster horses."

Digital Health Hematology Services (DHHS in the near-future)

Shoumen Palit Austin Datta

MIT Auto-ID Labs, Senior Member, Research Affiliate, Department of Mechanical Engineering, Massachusetts Institute of Technology ▪ shoumen@mit.edu

Senior Scientist, MDPnP Lab, Cybersecurity Program and SaAMS, Massachusetts General Hospital, Harvard Medical School ▪ sdatta8@mgh.harvard.edu

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Anahita Dua, M.D., M.B.A., M.S.C., F.A.C.S., Vascular Surgeon, Associate Professor of Surgery, HMS Director, Vascular Lab; Co-Director, PADC/LEAPP; Assoc Director, Wound Care Center, Massachusetts General Hospital, Harvard Medical School www.massgeneral.org/doctors/20714/anahita-dua https://vascular.org/news-advocacy/articles-press-releases/dr-anahita-dua-named-presidential-leadership-scholar

Sheela Magge M.D., M.S.C.E., Professor of Pediatrics, Lawson Wilkins Endowed Chair of Pediatric Endocrinology and Director, Division of Pediatric Endocrinology
Johns Hopkins University School of Medicine
https://profiles.hopkinsmedicine.org/provider/Sheela+Magge/2700667
https://clinicalconnection.hopkinsmedicine.org/participant/sheela-natesh-magge-md-msce
www.niddk.nih.gov/-/media/Files/News/Meetings/Magge_Bio_508.pdf

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Anesthesia, Critical Care and Pain Medicine, MGH Research Institute
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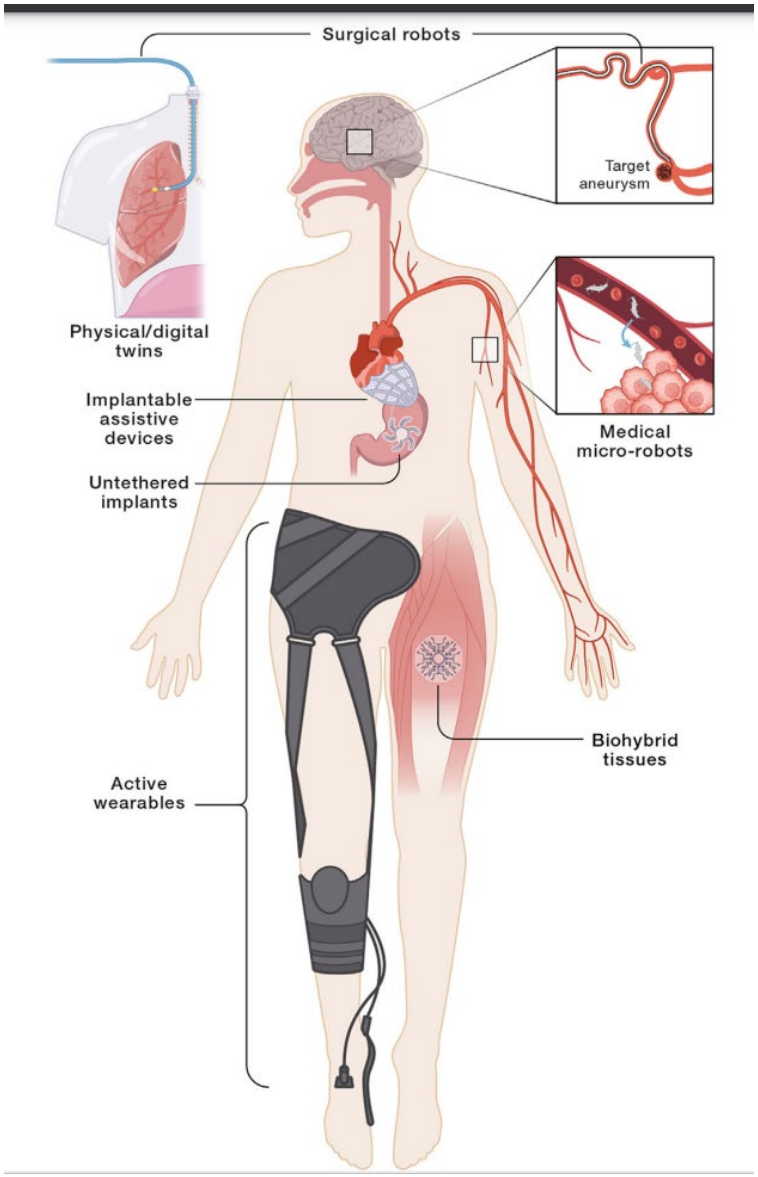
https://researchers.mgh.harvard.edu/profile/6264601/Thomas-McCoy

https://meche.mit.edu/people/faculty/ritur%40mit.edu



Therapeutic interventions *in vivo* to provide longitudinal health monitoring & modulation

Soft robotics for human health

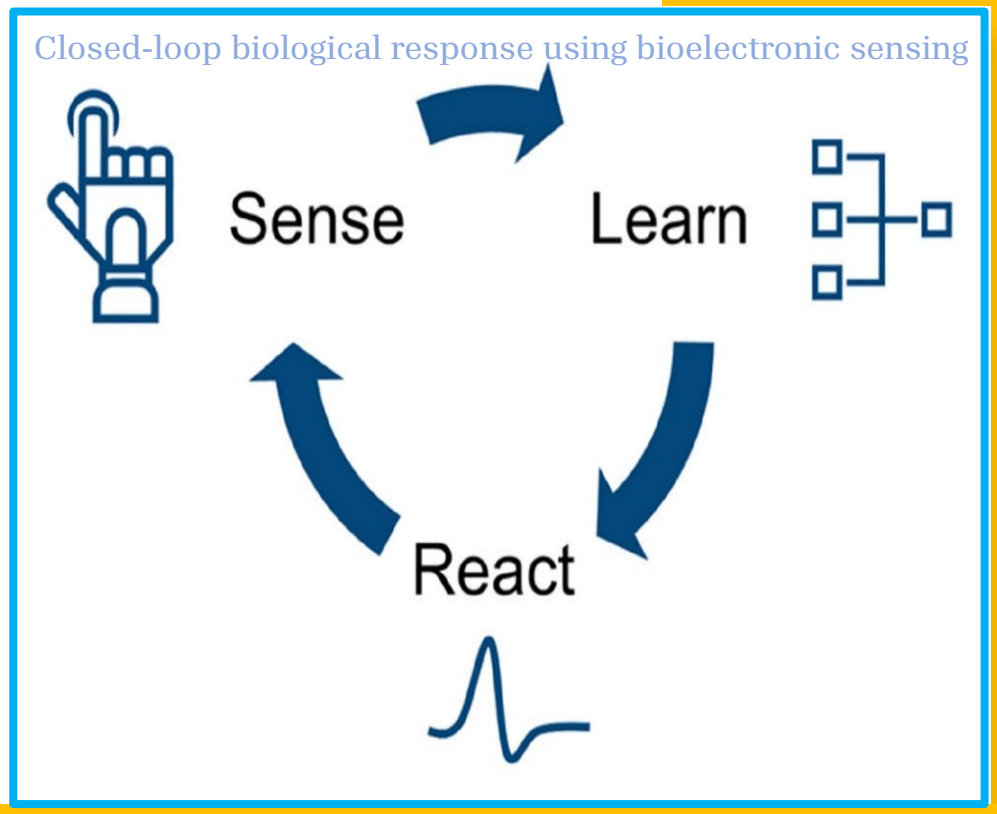
Ritu Raman[1,*] and Cecilia Laschi[2,*]

[1]Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA
[2]Department of Mechanical Engineering, National University of Singapore, Singapore, Singapore
*Correspondence: ritur@mit.edu (R.R.), mpeclc@nus.edu.sg (C.L.)

https://doi.org/10.1016/j.device.2024.100432

SOFT

Digital Convergence of Biological Transactions



Data-Informed Decision Support (DIDS) Systems

Distributed Secure Near Real-time Mobile Digital Health Services

But, at a cost ...

Transaction Cost

The Sveriges Riksbank Prize in Economic Sciences in Memory of Alfred Nobel 1991

Ronald H. Coase

Ronald H. Coase
Facts

Photo from the Nobel Foundation archive.

Ronald H. Coase
The Sveriges Riksbank Prize in Economic Sciences in Memory of Alfred Nobel 1991

Born: 29 December 1910, Willesden, United Kingdom

Died: 2 September 2013, Chicago, IL, USA

Affiliation at the time of the award: University of Chicago, Chicago, IL, USA

Prize motivation: "for his discovery and clarification of the significance of transaction costs and property rights for the institutional structure and functioning of the economy"

https://www.nobelprize.org/prizes/economic-sciences/1991/coase/facts

BIOBANKS

Been there, done that?

UK Biobank is an intensively characterised prospective cohort of 500,000 adults aged 40–69 years, recruited between 2006 and 2010. The study was established to enable researchers worldwide to undertake health-related research in the public interest.

ELSEVIER

Health Policy and Technology

Volume 1, Issue 3, September 2012, Pages 123-126

UK Biobank: Current status and what it means for epidemiology

Naomi Allen [a b], Cathie Sudlow [a c], Paul Downey [a], Tim Peakman [a], John Danesh [d], Paul Elliott [e], John Gallacher [f], Jane Green [g], Paul Matthews [h], Jill Pell [i], Tim Sprosen [j], Rory Collins [a b], on behalf of UK Biobank [1]

Cambridge Prisms: Precision Medicine

www.cambridge.org/pcm

UK biobank: Enhanced assessment of the epidemiology and long-term impact of coronavirus disease-2019

Qi Feng[1,2], Ben Lacey[1,2], Jelena Bešević[1,2], Wemimo Omiyale[1,2], Megan Conroy[1,2], Fenella Starkey[1,2], Catherine Calvin[1,2], Howard Callen[1,2], Laura Bramley[1,2], Samantha Welsh[2], Allen Young[1,2], Mark Effingham[2], Alan Young[1,2], Rory Collins[1,2], Jo Holliday[1,2] and Naomi Allen[1,2]

[1]Oxford Population Health, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK and [2]UK Biobank, Stockport, Greater Manchester, UK

Review

Cite this article: Feng Q, Lacey B, Bešević J, Omiyale W, Conroy M, Starkey F, Calvin C, Callen H, Bramley L, Welsh S, Young A, Effingham M, Young A, Collins R, Holliday J and Allen N (2023). UK biobank: Enhanced assessment of the epidemiology and long-term impact of coronavirus disease-2019. *Cambridge Prisms: Precision Medicine*, **1**, e30, 1–9
https://doi.org/10.1017/pcm.2023.18

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Revised: 08 July 2023
Accepted: 18 July 2023

The Evolution of a Large Biobank at Mass General Brigham

Natalie T. Boutin [1], Samantha B. Schecter [1], Emma F. Perez [2], Natasha S. Tchamitchian [1], Xander R. Cerretani [1], Vivian S. Gainer [3], Matthew S. Lebo [1,2], Lisa M. Mahanta [1], Elizabeth W. Karlson [1,2,*] and Jordan W. Smoller [1,4]

[1] Mass General Brigham Personalized Medicine, Boston, MA 02115, USA
[2] Brigham and Women's Hospital, Boston, MA 02115, USA
[3] Mass General Brigham Research Information Science & Computing, Boston, MA 02115, USA
[4] Massachusetts General Hospital, Boston, MA 02114, USA
* Correspondence: ekarlson@bwh.harvard.edu; Tel.: +1-617-732-5078; Fax: +1-617-713-3030

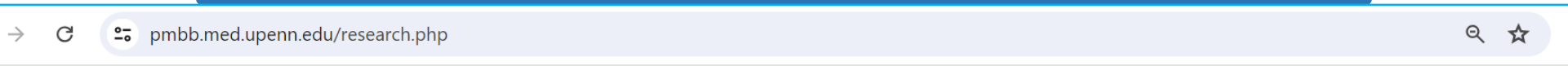
Abstract: The Mass General Brigham Biobank (formerly Partners HealthCare Biobank) is a large repository of biospecimens and data linked to extensive electronic health record data and survey data. Its objective is to support and enable translational research focused on genomic, environmental, biomarker and family history associations with disease phenotypes. The Biobank has enrolled more than 135,000 participants, generated genomic data on more than 65,000 of its participants, distributed approximately 153,000 biospecimens, and served close to 450 institutional studies with biospecimens or data. Although the Biobank has been successful, based on some measures of output, this has required substantial institutional investment. In addition, several challenges are ongoing, including: (1) developing a sustainable cost model that doesn't rely as heavily on institutional funding; (2) integrating Biobank operations into clinical workflows; and (3) building a research resource that is diverse and promotes equity in research. Here, we describe the evolution of the Biobank and highlight key lessons learned

Boutin NT, Schecter SB, Perez EF, Tchamitchian NS, Cerretani XR, Gainer VS, Lebo MS, Mahanta LM, Karlson EW, Smoller JW. Evolution of a Large Biobank at Mass General Brigham. J Personaized Medicine. 2022 August 17;12(8):1323. doi: 10.3390/jpm12081323. PMID: 36013271; PMCID: PMC9410531. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9410531/pdf/jpm-12-01323.pdf

MGB Biobank at MGH

The state-of-the-art Biobank at MGH provides researchers with access to high-quality samples to help foster research and advance the practice of medicine and our understanding of the causes of common diseases.

- Website: https://www.massgeneralbrigham.org/en/research-and-innovation/participate-in-research/biobank/for-researchers
- Mass General Brigham personalized medicine for information on how to obtain samples and how to collaborate with the Partners Biobank.



Penn Medicine BioBank Research

Revolutionizing Medicine: How Biobanks Are a Valuable Resource for Advancing Healthcare

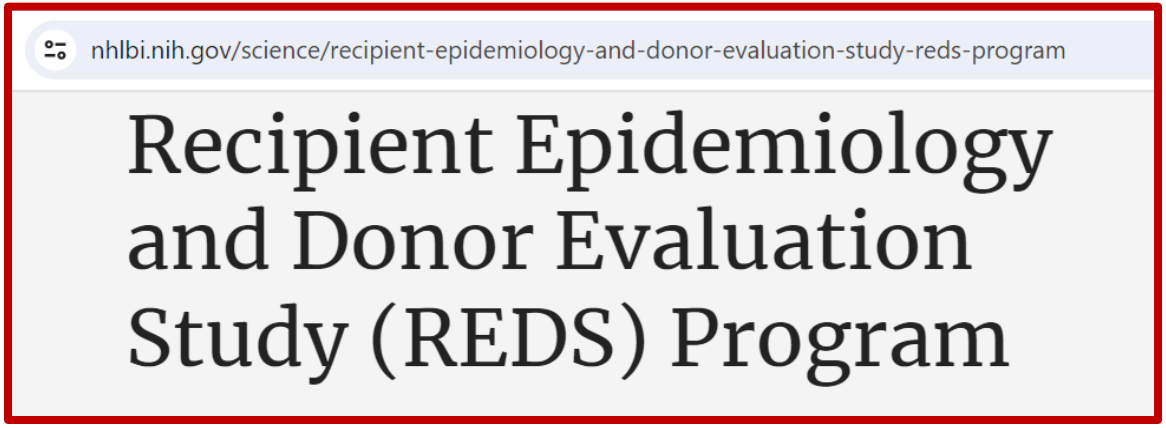
Biobanks play a pivotal role in modern healthcare. Biobanks are a warehouse of invaluable biological and genetic information that drive medical research, innovation, and personalized patient care. The Penn Medicine BioBank (PMBB) is a resource that collects and combines various health-related data, including medical records, genetic information, and lifestyle details from surveys, to aid in scientific studies and medical advancements. The PMBB is also part of a global initiative, the Global Biobank Meta-Analysis Initiative that merges genetic data from 23 biobanks worldwide, enhancing our understanding of disease and promoting drug discovery. Researchers and clinicians have developed tools to integrate genetic data and clinical data for precision medicine.

These tools have allowed researchers to:

- identify specific genes that are associated with different diseases
- identify shared genetic factors that may influence unrelated conditions, like cardiovascular disease and mental health disorders
- understand how genes impact how patients respond to certain medications
- study genes to predict the risk of developing diseases like urinary tract stones, different cancers, psychiatric disorders

What about blood bank and cord blood bank epidemiology?

Not much, yet.



What is the goal of the REDS program?

The goal of the REDS program is to evaluate and improve the safety and availability of the blood supply, as well as the safety and effectiveness of transfusion therapies. The program also works to proactively address potential emerging threats to the nation's blood supply and serves as a resource for ongoing work in transfusion research. Now in its fourth phase, the Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P) program aims primarily at improving the benefits of transfusion while reducing its risks; the REDS program also has a new focus on previously understudied populations.

Over the past 30 years, REDS has been the premier research program in blood collection and transfusion safety in the United States. **www.nhlbi.nih.gov**

Blood Bank

and

Cord Blood Bank

Epidemiology ??

www.brighamandwomens.org/obgyn/cord-blood-donation

www.dana-farber.org/how-you-can-help/get-involved/donate-bone-marrow-stem-cells

An element of DHHS ?

Blood Bank

and

Cord Blood Bank

Epidemiology

Foundation of DHHS ?

LIQUID BIOPSIES

SCALE POPULATION HEALTH USING LIQUID BIOPSIES VIA COMMUNITY BLOOD BANKS?

Angioni D, Delrieu J, Hansson O, Fillit H, Aisen P, Cummings J, Sims JR, Braunstein JB, Sabbagh M, Bittner T, Pontecorvo M, Bozeat S, Dage JL, Largent E, Mattke S, Correa O, Gutierrez Robledo LM, Baldivieso V, Willis DR, Atri A, Bateman RJ, Ousset PJ, Vellas B, Weiner M. ***Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done? A Report from the EU/US CTAD Task Force.*** J Prev Alzheimers Dis. 2022; 9(4):569-579. doi: 10.14283/jpad.2022.85. PMID: 36281661; PMCID: PMC9683846. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9683846/pdf/nihms-1846920.pdf

Castro-Giner F, Gkountela S, Donato C, Alborelli I, Quagliata L, Ng CKY, Piscuoglio S, Aceto N. ***Cancer Diagnosis Using a Liquid Biopsy: Challenges and Expectations***. Diagnostics (Basel). 2018 May 9 ;8(2):31. doi: 10.3390/diagnostics8020031. PMID: 29747380; PMCID: PMC6023445. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023445/pdf/diagnostics-08-00031.pdf

LIQUID BIOPSY (LB)

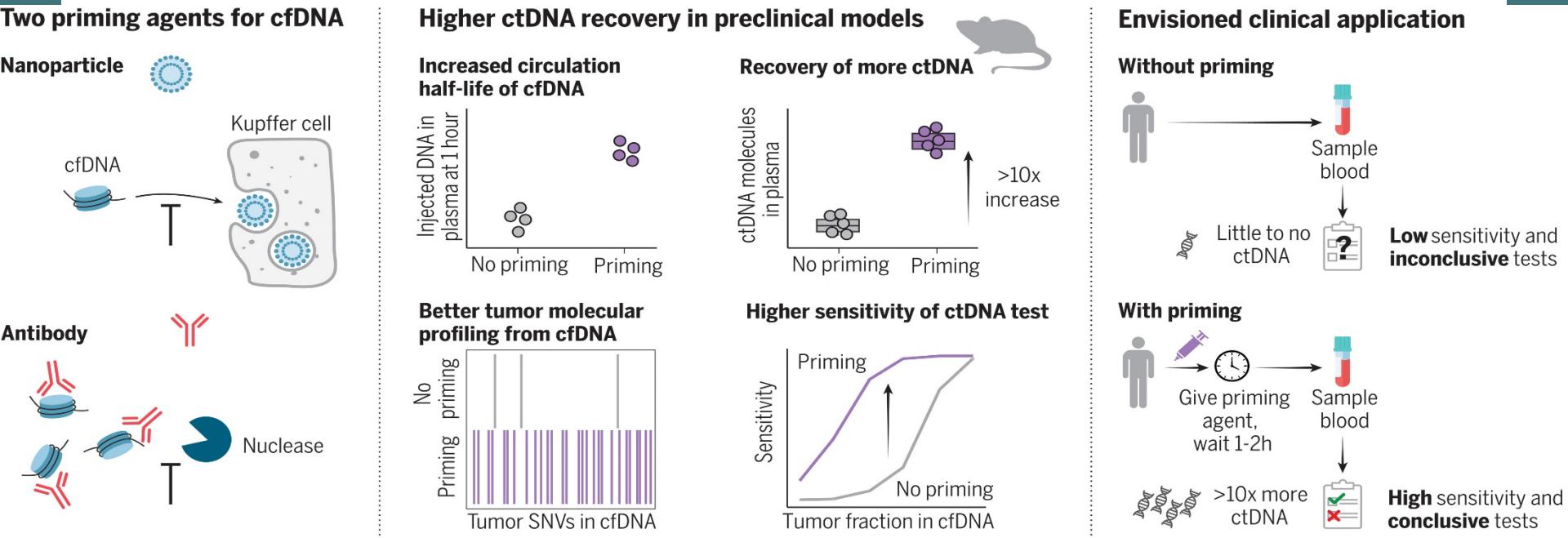
why it can scale

Liquid biopsies (LB) using blood can scale to reveal **personal** as well as **population health** signals (predictive) because blood draw in clinics and blood donation in community blood banks can be accomplished with relative ease and at a low cost even for resource constrained communities.

Key performance indicators (KPI) for liquid biopsies are sensitivity, predictive outcome (precision and accuracy). Key performance driver (KPD) is cost.

www.ncbi.nlm.nih.gov/pmc/articles/PMC9882213/

LIQUID BIOPSY - surpassing sensitivity limits by transiently augmenting the level of circulating tumor DNA (ctDNA) in blood (using nanoparticle priming agents) to attenuate clearance of cell-free DNA (cfDNA) in vivo.



https://www.science.org/doi/10.1126/science.adf2341

Priming agents (PA) reduce the clearance of cell-free (cf) DNA and enhance the sensitivity of liquid biopsies.

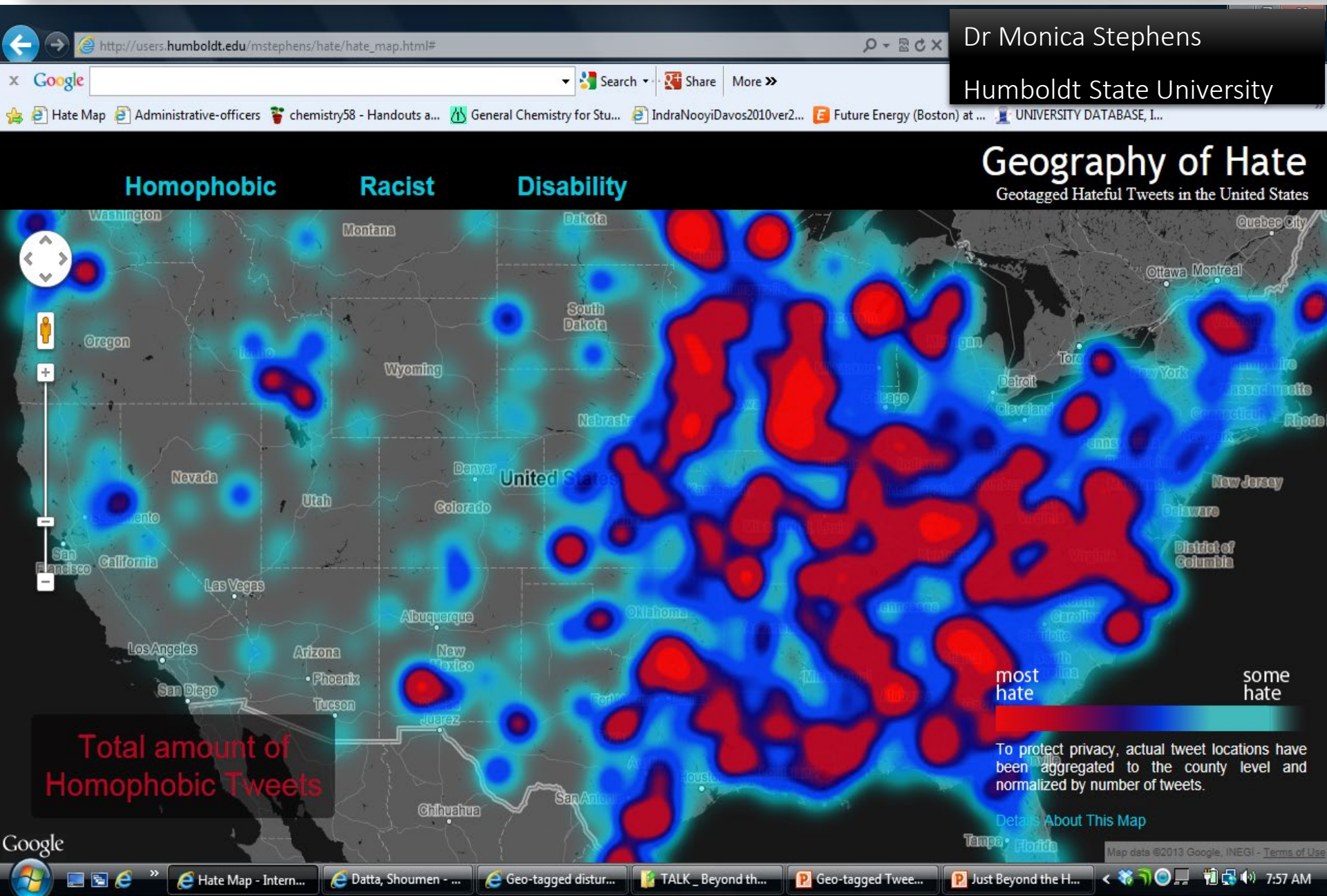
Priming agents transiently attenuate natural clearance mechanisms for cfDNA and consist of nanoparticles that act on the cells responsible for cfDNA clearance (top left) or DNA-binding antibodies that protect cfDNA from cellular uptake and enzymatic digestion (bottom left). In preclinical models, priming agents increased the half-life of cfDNA, enhanced recovery of circulating tumor (ct) DNA, and improved tumor molecular profiling from ctDNA and sensitivity of ctDNA testing (middle). PA's administered 1 to 2 hours prior to a blood draw, improves recovery of ctDNA and may boost the sensitivity of many types of liquid biopsy tests (right).

Martin-Alonso C, Tabrizi S, Xiong K, Blewett T, Patel S, An Z, Sridhar S, Bekdemir A, Shea D, Amini AP, Wang ST, Kirkpatrick J, Rhoades J, Golub TR, Love JC, Adalsteinsson VA, Bhatia SN. A nanoparticle priming agent reduces cellular uptake of cell-free DNA and enhances the sensitivity of liquid biopsies. bioRxiv [Preprint]. 2023 January 14:2023.01.13.524003. doi: 10.1101/2023.01.13.524003. PMID: 36711603

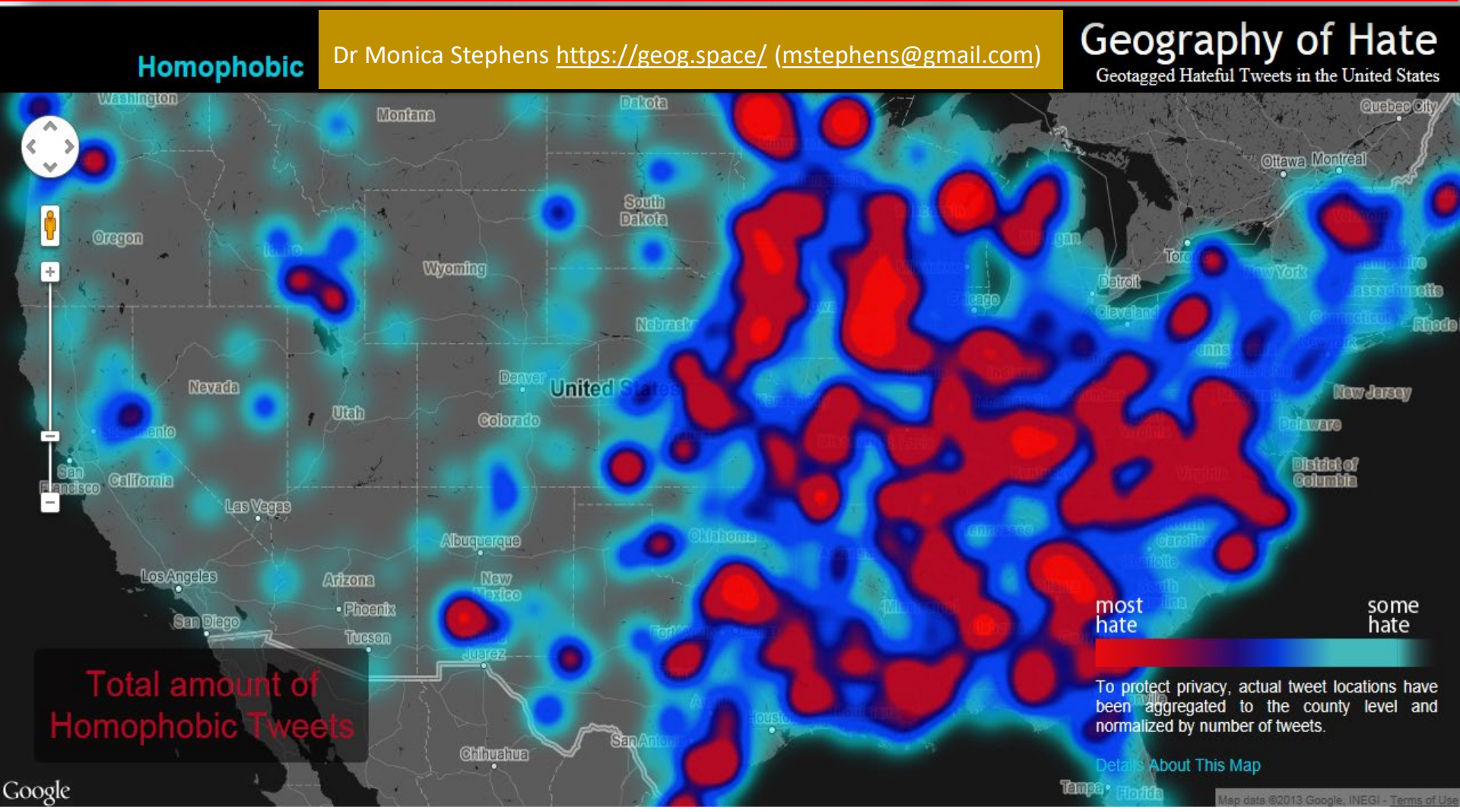
Twitter Data Analytics from Geo Tagged Social Signals

Dr Monica Stephens

Humboldt State University



Instead of mapping hate, let us map anonymized liquid biopsy data by zip code (e.g., cancer clusters?)



LIQUID BIOPSY (population genetics?) from BLOOD BANKS ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2024 VOL. 390 NO. 11

A Cell-free DNA Blood-Based Test for Colorectal Cancer Screening

Daniel C. Chung, M.D., Darrell M. Gray II, M.D., M.P.H., Harminder Singh, M.D., Rachel B. Issaka, M.D., M.A.S., Victoria M. Raymond, M.S., Craig Eagle, M.D., Sylvia Hu, Ph.D., Darya I. Chudova, Ph.D., AmirAli Talasaz, Ph.D., Joel K. Greenson, M.D., Frank A. Sinicrope, M.D., Samir Gupta, M.D., M.S.C.S., and William M. Grady, M.D.

Published March 13, 2024 ▪ N Engl J Med 2024;390:973-983 ▪ DOI: 10.1056/NEJMoa2304714

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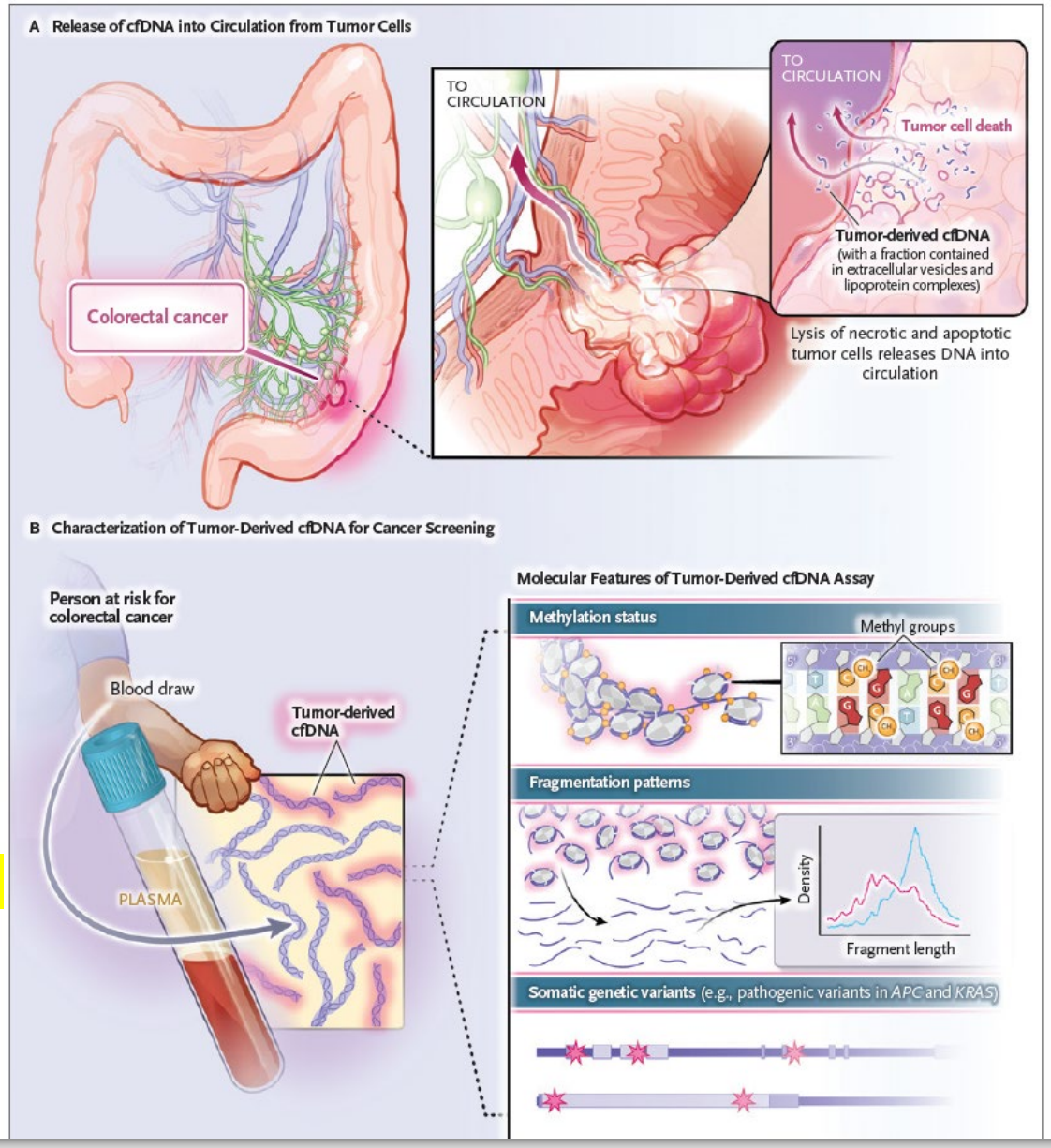
Daniel C. Chung, M.D., Darrell M. Gray II, M.D., M.P.H., Harminder Singh, M.D., Rachel B. Issaka, M.D., M.A.S., Victoria M. Raymond, M.S., Craig Eagle, M.D., Sylvia Hu, Ph.D., Darya I. Chudova, Ph.D., AmirAli Talasaz, Ph.D., Joel K. Greenson, M.D., Frank A. Sinicrope, M.D., Samir Gupta, M.D., M.S.C.S., and William M. Grady, M.D.



Chung DC, Gray DM 2nd, Singh H, Issaka RB, Raymond VM, Eagle C, Hu S, Chudova DI, Talasaz A, Greenson JK, Sinicrope FA, Gupta S, Grady WM. **A Cell-free DNA Blood-Based Test for Colorectal Cancer Screening.** N Engl J Med. 2024 March 14; 390(11):973-983. doi: 10.1056/NEJMoa2304714. PMID: 38477985.

LIQUID BIOPSY using samples from cord BLOOD BANKS

There is an **immense** (yet cryptic) potential for multi-generational epidemiologic studies to analyze bio-markers and specific precision changes in personal profiles over time and/or before/after any metabolic event (e.g., CoVID-19, CVD, COPD, PKD). The molecular metabolic signatures may be analyzed from stored blood in blood banks and pathology labs.

Proof is in the Pudding ?

FRAMINGHAM HEART STUDY

https://www.nhlbi.nih.gov/science/framingham-heart-study-fhs

FHS began in 1948. This is what was reported in 2024

Li C, Stražar M, Mohamed AMT, Pacheco JA, Walker RL, Lebar T, Zhao S, Lockart J, Dame A, Thurimella K, Jeanfavre S, Brown EM, Ang QY, Berdy B, Sergio D, Invernizzi R, Tinoco A, Pishchany G, Vasan RS, Balskus E, Huttenhower C, Vlamakis H, Clish C, Shaw SY, Plichta DR, Xavier RJ. ***Gut microbiome and metabolome profiling in Framingham heart study reveals cholesterol-metabolizing bacteria.*** Cell. 2024 March 21: S0092-8674(24)00305-2. doi: 10.1016/j.cell.2024.03.014 https://pubmed.ncbi.nlm.nih.gov/38569543/

FRAMINGHAM HEART STUDY

https://www.nhlbi.nih.gov/science/framingham-heart-study-fhs

Stool metagenomics and metabolomics from **1,429 Framingham Heart Study** participants revealed microbiome and metabolome composition. Specifically, the study found bacterial species from the *Oscillibacter* genus were associated with decreased fecal and plasma cholesterol levels. A bacterial enzyme called ismA can metabolize cholesterol into coprostanol, a lipid excreted, instead of absorbed by the body. Gut bacteria, including several *Oscillibacter* species, correlate with lower cholesterol levels in people. These bacteria could also metabolize cholesterol in lab experiments. Whether these bacteria can directly influence blood cholesterol in people needs to be confirmed. If delivered to the right place in the gut, it might lead to new treatments using bacteria to transform artery-clogging cholesterol into a more harmless form. How about direct enzyme (ismA) delivery using mRNA?

FRAMINGHAM HEART STUDY - *started in 1948 and still helpful*

Li C, Stražar M, Mohamed AMT, Pacheco JA, Walker RL, Lebar T, Zhao S, Lockart J, Dame A, Thurimella K, Jeanfavre S, Brown EM, Ang QY, Berdy B, Sergio D, Invernizzi R, Tinoco A, Pishchany G, Vasan RS, Balskus E, Huttenhower C, Vlamakis H, Clish C, Shaw SY, Plichta DR, Xavier RJ. ***Gut microbiome and metabolome profiling in Framingham heart study reveals cholesterol-metabolizing bacteria.*** Cell. 2024 March 21: S0092-8674(24)00305-2. doi: 10.1016/j.cell.2024.03.014 https://pubmed.ncbi.nlm.nih.gov/38569543/

https://www.nhlbi.nih.gov/science/framingham-heart-study-fhs

nhlbi.nih.gov/science/framingham-heart-study-fhs

What is the goal of the FHS?

The NHLBI has a long history of supporting large population and epidemiology studies that have transformed the way the public approaches heart disease. These studies involve studying the health of various populations to uncover patterns, trends, and outcomes that may be applicable to the general population. When it launched in 1948 the original goal of the Framingham Heart Study (FHS) was to identify common factors or characteristics that contribute to cardiovascular disease. Over the years, the FHS has become a successful, multigenerational study that analyzes family patterns of cardiovascular and other diseases, while gathering more genetic information from the two generations that followed the original study participants. The FHS also has expanded to include diverse populations so that risk factors in these different groups can be understood.

NIH National Heart, Lung, and Blood Institute

75 YEARS Bringing Research to Life

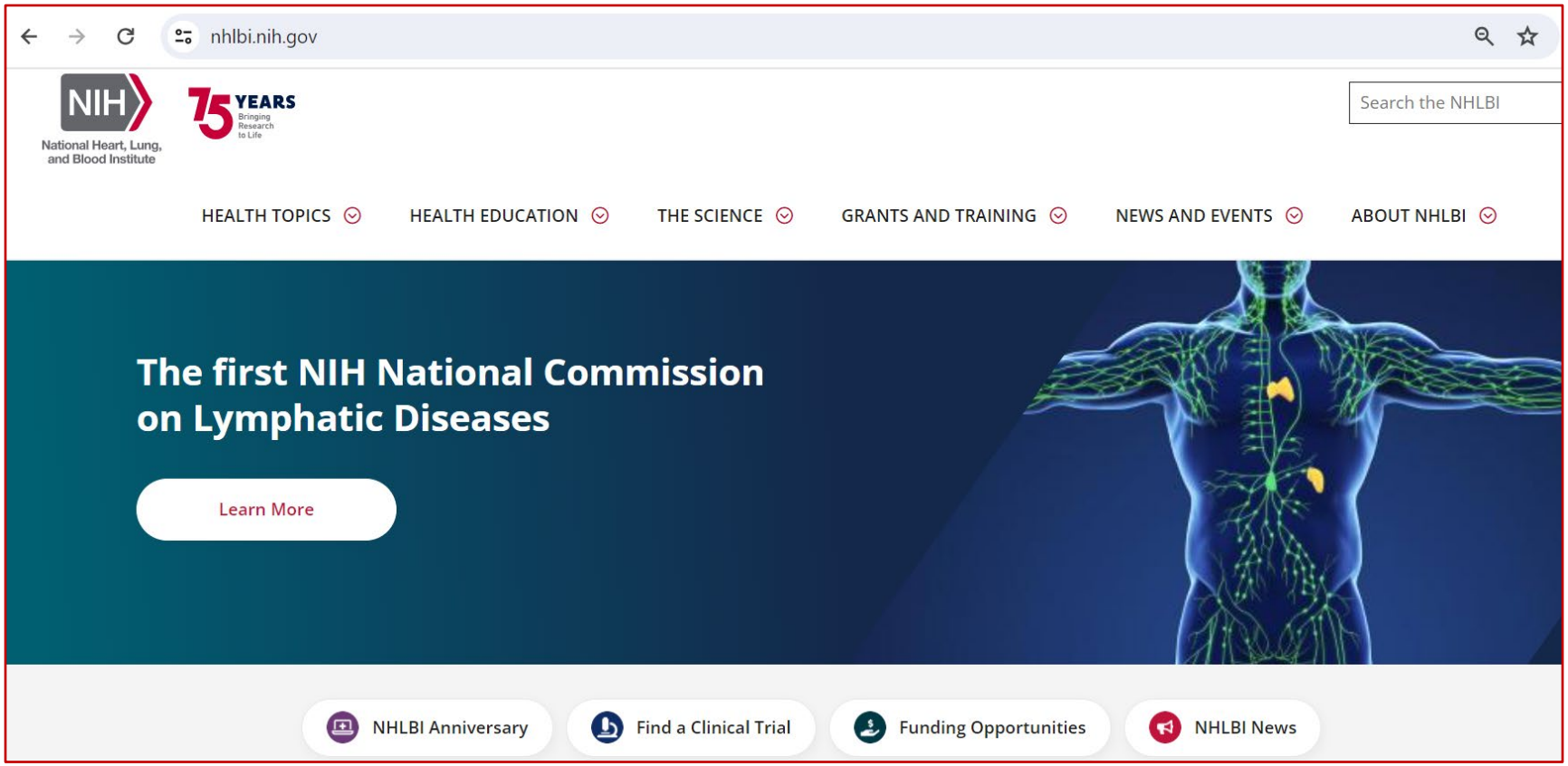
> FHS is a longitudinal study

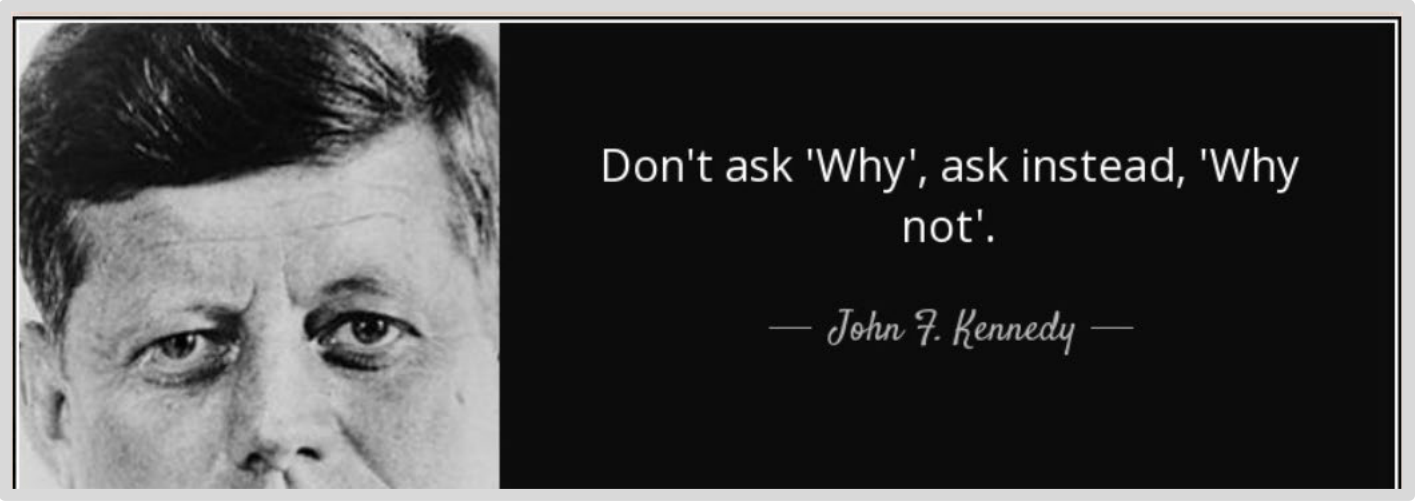
- *The FHS had over 15,000 people from three generations, including the original participants, their children, and their grandchildren at the start of each cohort.*
- *FHS findings have informed the understanding of how cardiovascular health affects the rest of the body.*
- *The study found high blood pressure and high blood cholesterol to be major risk factors for cardiovascular disease.*
- *In the past half century, the study has produced approximately 6,000 articles in leading medical journals.*
- *Data and biologic resources from the study are available for researchers to use, which continue to spur new scientific discoveries.*

What is possible using data from research on stored blood bank samples (cord blood)?

Molecular metabolomics, proteomics & genetics of diseases?

this is happening . . .





nhlbi.nih.gov

NIH National Heart, Lung, and Blood Institute

75 YEARS Bringing Research to Life

Search the NHLBI

HEALTH TOPICS | HEALTH EDUCATION | THE SCIENCE | GRANTS AND TRAINING | NEWS AND EVENTS | ABOUT NHLBI

The first NIH National Commission

Blood Bank Repositories for Research

NHLBI Anniversary | Find a Clinical Trial | Funding Opportunities | NHLBI News

Tsunami

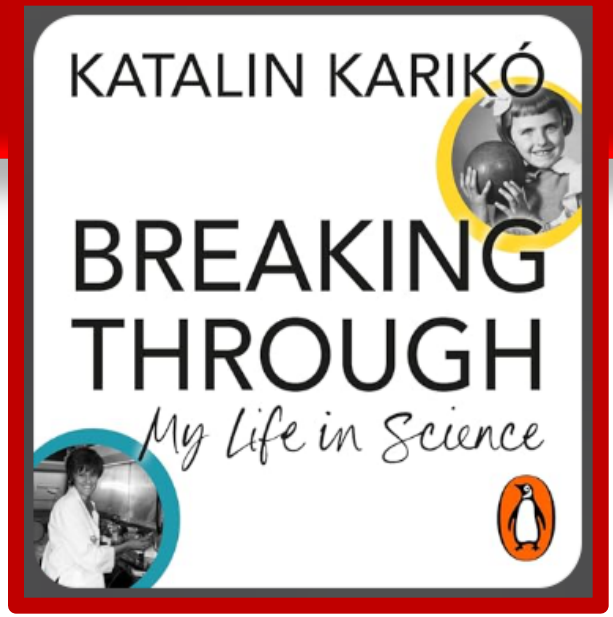
of research findings, waiting to happen!

Blood Bank Repositories for Research

Tsunami

of research findings, waiting to happen!

Tsunami needs to be triggered
Research needs leader to breakthrough



www.nobelprize.org/prizes/medicine/2023/kariko/facts

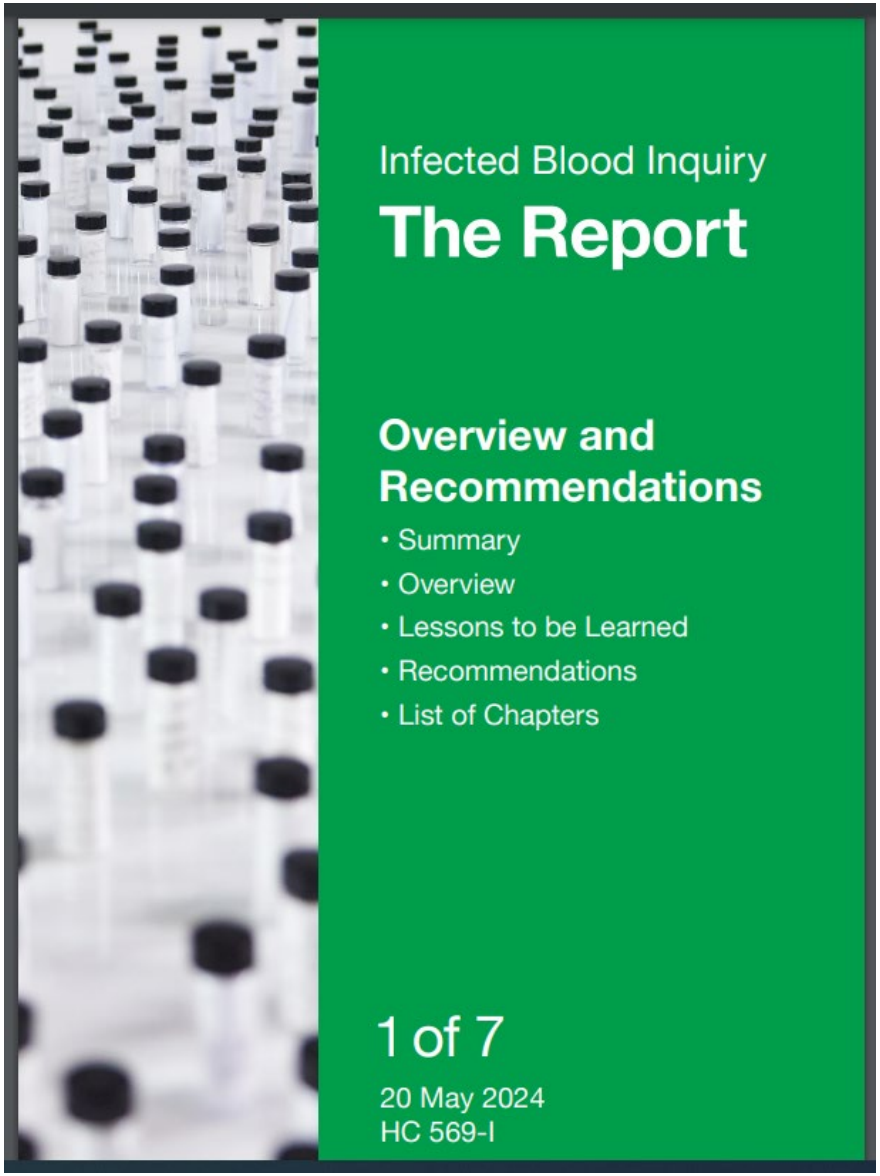
Tsunami

of research findings, waiting to happen!

Just think of one example ➔

EBV

https://www.infectedbloodinquiry.org.uk/reports/inquiry-report



Volume 1
https://www.infectedbloodinquiry.org.uk/sites/default/files/Volume_1.pdf

Volume 2
https://www.infectedbloodinquiry.org.uk/sites/default/files/Volume_2.pdf

Volume 3
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Volume 4
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Volume 5
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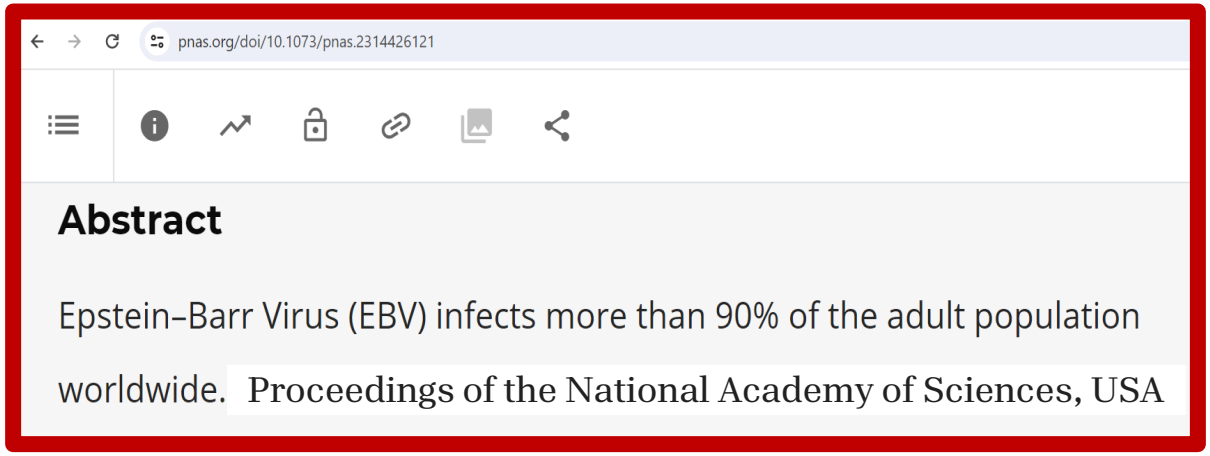
Volume 6
https://www.infectedbloodinquiry.org.uk/sites/default/files/Volume_6.pdf

Volume 7
https://www.infectedbloodinquiry.org.uk/sites/default/files/Volume_7.pdf

https://www.infectedbloodinquiry.org.uk/reports/final-report-volume-1.html



90% of the adult population is infected with Epstein-Barr Virus (EBV), worldwide.

Maroui MA, Odongo GA, Mundo L, Manara F, Mure F, Fusil F, Jay A, Gheit T, Michailidis TM, Ferrara D, Leoncini L, Murray P, Manet E, Ohlmann T, De Boevre M, De Saeger S, Cosset FL, Lazzi S, Accardi R, Herceg Z, Gruffat H, Khoueiry R. (2024) ***Aflatoxin B1 and Epstein-Barr virus-induced CCL22 expression stimulates B cell infection.*** Proceedings of the National Academy of Sciences U S A. 2024 April 16; 121(16):e2314426121. doi: 10.1073/pnas.2314426121. Epub 2024 April 4. PMID: 38574017 https://pubmed.ncbi.nlm.nih.gov/38574017/

Data

from cross-sectional research, still chained in blood banks and labs?

Can we detect EBV in stored blood samples?

Yes

?

Gulley ML. ***Molecular diagnosis of Epstein-Barr virus-related diseases.*** J Mol Diagn. 2001 Feb; 3(1):1-10. doi: 10.1016/S1525-1578(10)60642-3. PMID: 11227065; PMCID: PMC1907346.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1907346/pdf/0043.pdf

Ayee R, Ofori MEO, Wright E, Quaye O. (2020) ***Epstein Barr Virus Associated Lymphomas and Epithelia Cancers in Humans.*** J Cancer 2020; 11(7):1737-1750. doi:10.7150/jca.37282. https://www.jcancer.org/v11p1737.htm

Establishment of latent infection by EBV has been implicated in several malignancies [30] due to the expression of limited sets of latent proteins, shown to play various biological roles discussed in Table 1.

Table 1

Biological activities of Epstein Barr virus latency stage gene products and associated cancers

EBV associated cancers

EBV latency protein	Type of latency	Biological activity	Associated cancers[d]
EBNA-1[a]	Latency I, II, III	Segregation of viral genome in progenies, DNA replication, inhibition of MHC class I, enhances p53 degradation	Burkitt lymphoma, Gastric cancer, Breast cancer
EBNA-2	Latency III	Upregulation of host and viral proteins (transactivation), facilitate B cell immortalization	Posttransplant lymphoproliferative disorder
EBNA-3	Latency III	Transcription transactivation of both host and viral proteins, immortalization of B cell	Posttransplant lymphoproliferative disorder
EBNA-LP[b]	Latency III	Transactivation of EBNA-2 to inactivate tumor suppressors, essential for immortalization of B cells	Posttransplant lymphoproliferative disorder
LMP-1/2[c]	Latency II/III	B cell survival, upregulation of antiapoptotic proteins, mimics CD 40 ligand associated signaling, constitutively activate growth and cell survival promoting signaling pathways	Hodgkin lymphoma, Nasopharyngeal cancer, Posttransplant lymphoproliferative disorder, T/NK cell lymphoma, Breast cancer
EBV-Micro RNAs	Latency I, II, III	Target host mRNAs involved in apoptosis, proliferation and transformation. Suppress antigen presentation and activation of immune cells	Gastric cancer, T/NK cell lymphoma, nasopharyngeal cancer

[a] EBNA-1 is expressed and detected in all EBV associated malignancies. [b] EBNA-LP is also known as EBNA-5. [c] LMP-1/2 are both involved in epithelia and B cell tumors, however, LMP 2 is frequently detected in a majority of all tumors as compared to LMP-1. [d] The associated tumors are not only limited to the ones discussed in this review.

Transmission of EBV through transplantation and blood transfusion has been reported. EBV establishes latent infection in B lymphocytes where it expresses limited sets of proteins (ETPs, EBNAs, LMP) and EBER. Hematopoietic cell derived tumors include but not limited to Burkitt's lymphoma, Hodgkin lymphoma, post-transplant lymphoproliferative disorders, and natural killer (NK)/T cell lymphoma. EBV also causes epithelia derived malignancies such as nasopharyngeal cancer, gastric cancer, and breast cancer.

Information

from research findings just from one virus may save millions of lives.

If we can't detect, we can't treat, we can't cure

Blood Banks ?

Real potential for cross-sectional data to feed and morph into longitudinal epidemiologic study.

60 YEARS AGO

› Lancet. 1964 Mar 28;1(7335):702-3. doi: 10.1016/s0140-6736(64)91524-7.

VIRUS PARTICLES IN CULTURED LYMPHOBLASTS FROM BURKITT'S LYMPHOMA

M A EPSTEIN, B G ACHONG, Y M BARR

PMID: 14107961 DOI: 10.1016/s0140-6736(64)91524-7

That's why it is called Epstein-Barr Virus.

90% of 8 billion people are infected with EBV

Sir Michael Anthony Epstein (1921–2024)

Codiscoverer of the Epstein-Barr virus

RICHARD F. AMBINDER AND RENA R. XIAN Authors Info & Affiliations

SCIENCE · 18 Apr 2024 · Vol 384, Issue 6693 · p. 274 · DOI: 10.1126/science.adp2961

Lancet. 1964 Mar 28;1(7335):702-3. doi: 10.1016/s0140-6736(64)91524-7.

VIRUS PARTICLES IN CULTURED LYMPHOBLASTS FROM BURKITT'S LYMPHOMA

M A EPSTEIN, B G ACHONG, Y M BARR

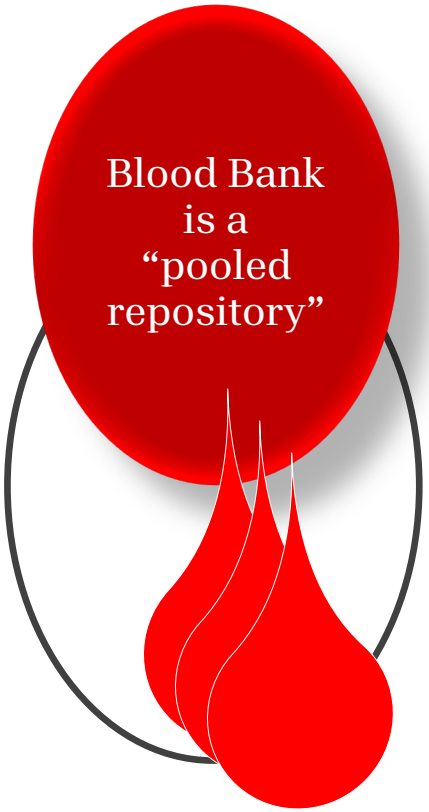
PMID: 14107961 DOI: 10.1016/s0140-6736(64)91524-7

Sir Michael Anthony Epstein, pathologist who identified the first known human cancer–causing virus, died on **6 February 2024** at the age of 102. His team's pioneering work investigating primary tumor tissue and cultured tumor specimens from Ugandan children with jaw tumors identified the virus that now bears his name: the Epstein-Barr virus (EBV). EBV is associated with the tumor Epstein was studying, now known as Burkitt lymphoma, as well as a variety of other cancers and illnesses, including infectious mononucleosis and multiple sclerosis.

https://doi.org/10.1126/science.adp2961

Born in London, England, on 18 May 1921, Epstein studied medicine at Trinity College at the University of Cambridge and Middlesex Hospital Medical School in London. After national service with the Royal Army Medical Corps in India, he returned to the Middlesex Hospital, where there was interest in, as he wrote in his chapter of *Epstein Barr Virus Volume 1*, "the then deeply unfashionable chicken cancer viruses." In 1911, Peyton Rous had characterized a virus in chickens that led to cancer, but there had been little interest in the implications. In 1956, Epstein spent a year studying electron microscopy with George Palade at the Rockefeller Institute in New York City. Palade convinced Epstein that viruses could be categorized on the basis of how they looked. Epstein again returned to the Middlesex Hospital, where he investigated the morphology of Rous sarcoma virus with electron microscopy and showed that it was an RNA virus.

Epstein was thus familiar with both cancer-causing viruses and electron microscopy when he happened to attend a lunchtime lecture by Denis Burkitt on a cancer prevalent in African children. Burkitt was a British Colonial Service medical officer based in Uganda, on leave in the UK. He described a tumor that typically arose in the jaw and quickly led to death, but what most interested Epstein was Burkitt's data showing that the geographical distribution of the tumor in Africa depended on temperature and rainfall. This suggested to Epstein that, as he wrote later, "a biological agent must play a part in causation," and he immediately "postulated a climate-dependent arthropod vector spreading a cancer-causing virus." Epstein decided to halt his current work and look for a virus in the lymphoma. He obtained funding from the British Empire Cancer Campaign (later Cancer Research UK) to travel to Uganda to, as he wrote, "work out how a regular supply of lymphoma samples" could be flown to his laboratory in London for testing.



ncbi.nlm.nih.gov/pmc/articles/PMC5618724/

Journal Article

T1-mapping using the Shortened Modified Look-Locker Inversion Recovery (ShMOLLI) technique has been validated in single- and multi-center clinical studies for a variety of cardiovascular diseases [17–28, 30–41]. It is also used in the UK Biobank (over 10,000 datasets acquired; projected total: 100’000, [42, 43]), and the ongoing multi-centre Hypertrophic Cardiomyopathy Registry study (HCMR; 2750 patients, [42–44]). We have a large resource of clinical and research scans with T1-mapping accumulated from pooled evidence from the past 7 years [18, 19, 23, 24, 26, 28, 30, 31, 34, 35, 39, 45]. In this study of 1291 subjects, we characterized commonly encountered clinical myocardial conditions using T1-mapping, derived native T1 ranges, and produced sample-size calculations to guide future clinical studies and trials.

Liu *et al. Journal of Cardiovascular Magnetic Resonance* (2017) 19:74
DOI 10.1186/s12968-017-0386-y

Journal of Cardiovascular Magnetic Resonance

RESEARCH Open Access

Measurement of myocardial native T1 in cardiovascular diseases and norm in 1291 subjects

Joanna M. Liu[1], Alexander Liu[1], Joana Leal[1], Fiona McMillan[1], Jane Francis[1], Andreas Greiser[2], Oliver J. Rider[1], Saul Myerson[1], Stefan Neubauer[1], Vanessa M. Ferreira[1] and Stefan K. Piechnik[1*]

Liu JM, Liu A, Leal J, McMillan F, Francis J, Greiser A, Rider OJ, Myerson S, Neubauer S, Ferreira VM, Piechnik SK. ***Measurement of myocardial native T1 in cardiovascular diseases and norm in 1291 subjects.*** J Cardiovasc Magn Reson. 2017 September 28;19(1):74. doi: 10.1186/s12968-017-0386-y https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5618724/pdf/12968_2017_Article_386.pdf

ncbi.nlm.nih.gov/pmc/articles/PMC6861460/table/T1/?report=objectonly

https://doi.org/10.1182/blood-2016-06-721688

Table I

Delobel J, Rubin O, Prudent M, Crettaz D, Tissot JD, Lion N. (2010) ***Biomarker analysis of stored blood products: emphasis on pre-analytical issues.*** Int J Mol Sci. 2010 November 17;11(11):4601-4617. doi: 10.3390/ijms11114601. www.ncbi.nlm.nih.gov/pmc/articles/PMC3000103/pdf/ijms-11-04601.pdf

Parameters	Day 0	Day 3	Day 7	Day 14	Day 28	P value
Sodium	152.8 ± 4.01	150.1 ± 2.89	147.9 ± 1.41	143.1 ± 1.97	141.9± 3.99	<0.001
Potassium	4.33±1.29	6.73±2.43	9.93±2.97	14.16±4.56	19.89±4.01	<0.001
Chloride	86.32±1.96	89.55±2.05	93.91±2.44	96.83±2.19	91.34±1.09	<0.001
Calcium	0.06+0.007	0.062±0.005	0.063±0.004	0.0067±0.001	0.0066±0.021	NS
Urea	27.71±3.99	25.19±2.70	26.11±3.18	24.32±2.45	24.17±2.56	NS
Creatinine	0.99±0.04	1.02±0.02	1.07±0.04	1.01±0.06	1.02±0.01	NS
AST (mg/dl)	21.95 ± 4.91	23.54±6.32	28.43±3.22	38.26±9.90	44.31±8.55	<0.001
ALT (mg/dl)	40.65±13.65	40.43±18.89	39.54±23.66	44.87±13.76	46.32±10.87	0.487
LDH (mg/dl)	202.54±17.87	289.21±23.98	487.91±97.93	523.65±113.54	643.32±187.8	<0.001
Proteins (g/dl)	6.76±0.77	6.43±0.76	5.99±0.11	6.87±0.3	6.7±0.88	NS
PH	7.22±0.18	7.01±0.33	6.91±0.44	6.89±0.23	6.77±0.54	<0.001

Will protein bio-markers suffer from storage lesions?

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6861460/pdf/PJMS-35-1697.pdf

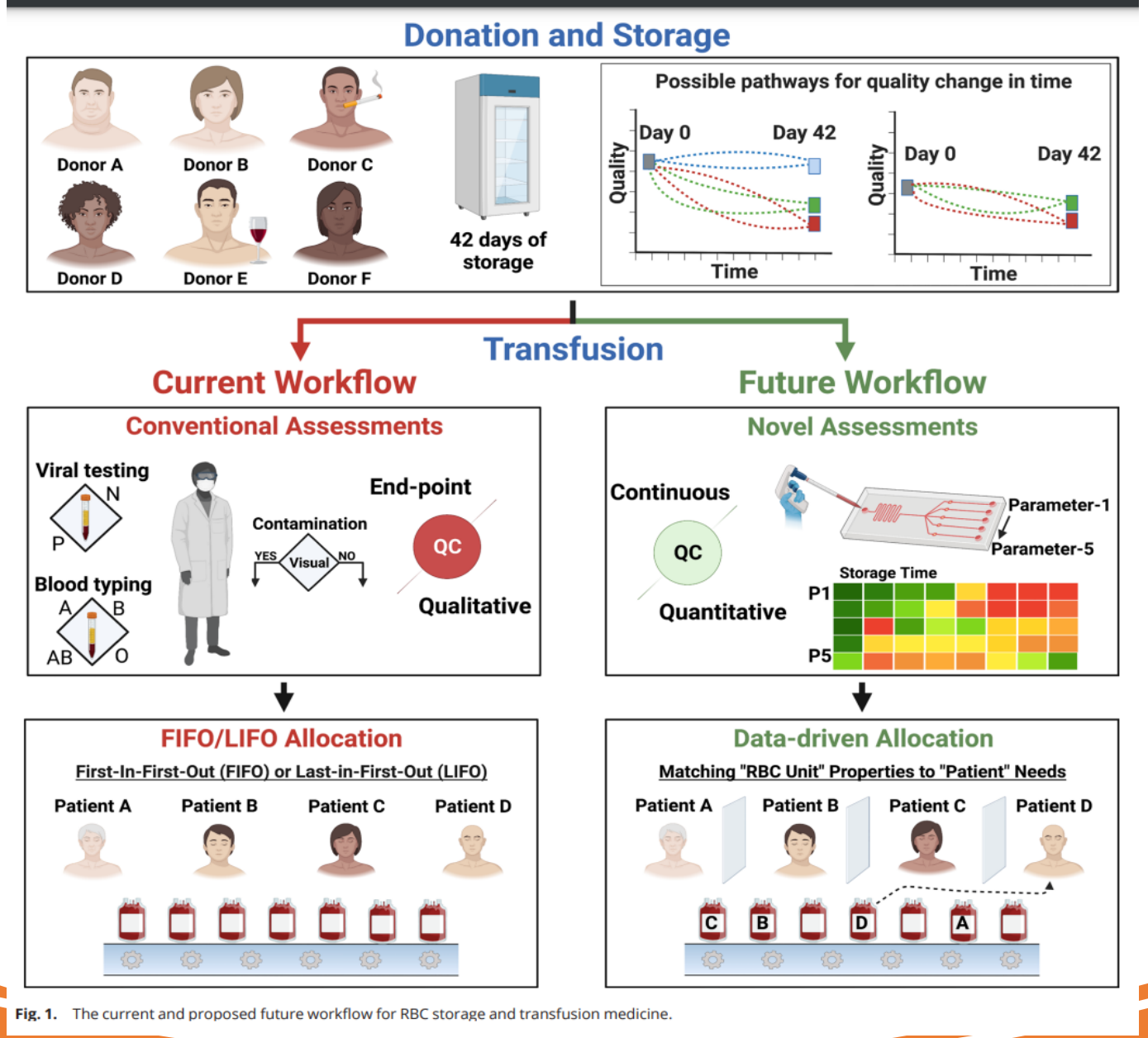


Fig. 1. The current and proposed future workflow for RBC storage and transfusion medicine.

Isiksacan Z, D'Alessandro A, Wolf SM, McKenna DH, Tessier SN, Kucukal E, Gokaltun AA, William N, Sandlin RD, Bischof J, Mohandas N, Busch MP, Elbuken C, Gurkan UA, Toner M, Acker JP, Yarmush ML, Usta OB. ***Assessment of stored red blood cells through lab-on-a-chip technologies for precision transfusion medicine.*** Proc Natl Acad Sci U S A. 2023 August 8; 120(32):e2115616120. doi: 10.1073/pnas.2115616120 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10410732/pdf/pnas.202115616.pdf

blood®

Volume 143, Issue 5, 1 February 2024, Pages 456-472

TRANSFUSION MEDICINE

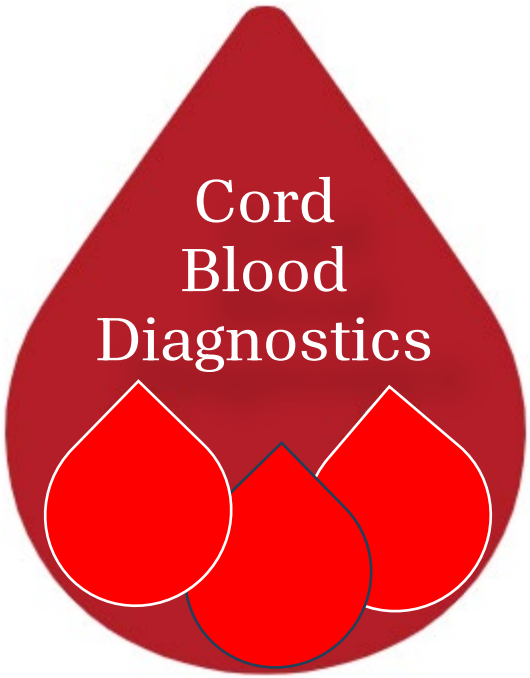
Regulation of kynurenine metabolism by blood donor genetics and biology impacts red cell hemolysis invitro and invivo

Travis Nemkov [*1,2], Daniel Stephenson [*1], Christopher Erickson [1], Monika Dzieciatkowska [1], Alicia Key [1], Amy Moore [3], Eric J. Earley [3], Grier P. Page [3], Ian S. Lacroix [1], Mars Stone [4,5], Xutao Deng [4,5], Thomas Raife [6], Steven Kleinman [7], James C. Zimring [8], Nareg Roubinian [4,5,9], Kirk C. Hansen [1], Michael P. Busch [4,5], Philip J. Norris [4,5], Angelo D'Alessandro [1,2], Recipient Epidemiology and Donor Evaluation Study-IV-P

Not only proteomic biomarkers but also genetic sign-posts using microarrays?

Kynurenine is a marker of osmotic fragility, and its levels are reproducible within a donor across donations. Polymorphisms in SLC7A5, ATXN2 are associated with kynurenine levels in stored RBCs, Hgb increments, and in vivo hemolysis upon transfusion. https://doi.org/10.1182/blood.2023022052

Data analyses from cord blood are a cross-sectional study with potential for longitudinal research.



Bio-markers on-a-chip may lead to predictive/prognostic clues for personalized risk mitigation clinical strategies.

Guibert N, Pradines A, Favre G, Mazieres J. ***Current and future applications of liquid biopsy in non-small cell lung cancer from early to advanced stages.*** Eur Respir Rev. 2020 February 12; 29(155):190052. doi: 10.1183/16000617.0052-2019. PMID: 32051167; PMCID: PMC9488537. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9488537/pdf/ERR-0052-2019.pdf

Šutić M, Vukić A, Baranašić J, Försti A, Džubur F, Samaržija M, Jakopović M, Brčić L, Knežević J. (2021) ***Diagnostic, Predictive, and Prognostic Biomarkers in Non-Small Cell Lung Cancer (NSCLC) Management.*** J Pers Med. 2021 October 27;11(11):1102. doi: 10.3390/jpm11111102. PMID: 34834454; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8624402/pdf/jpm-11-01102.pdf

Imagine the treasure trove of data hiding in stored blood samples in blood banks

What epidemiology of blood donors can reveal about population public health

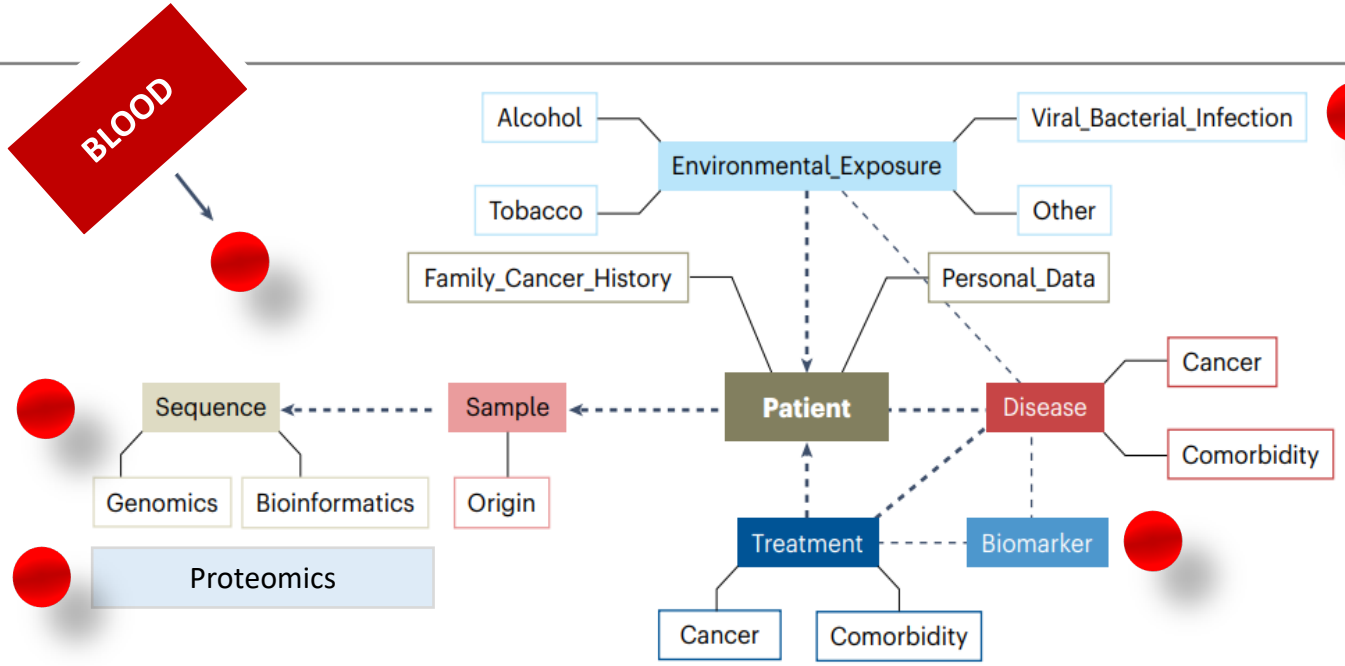


Fig. 1 | The 1+MG-MDC structure. Illustration of the 1+MG-MDC structure, comprising eight conceptual domains and related subdomains. Thick dotted lines indicate connections between domains, in some instances an additional arrowhead denotes directionality. Thin dotted lines indicate potential relationships between domains. Adapted from ref. 6.

https://www.nature.com/articles/s41588-024-01721-x.pdf

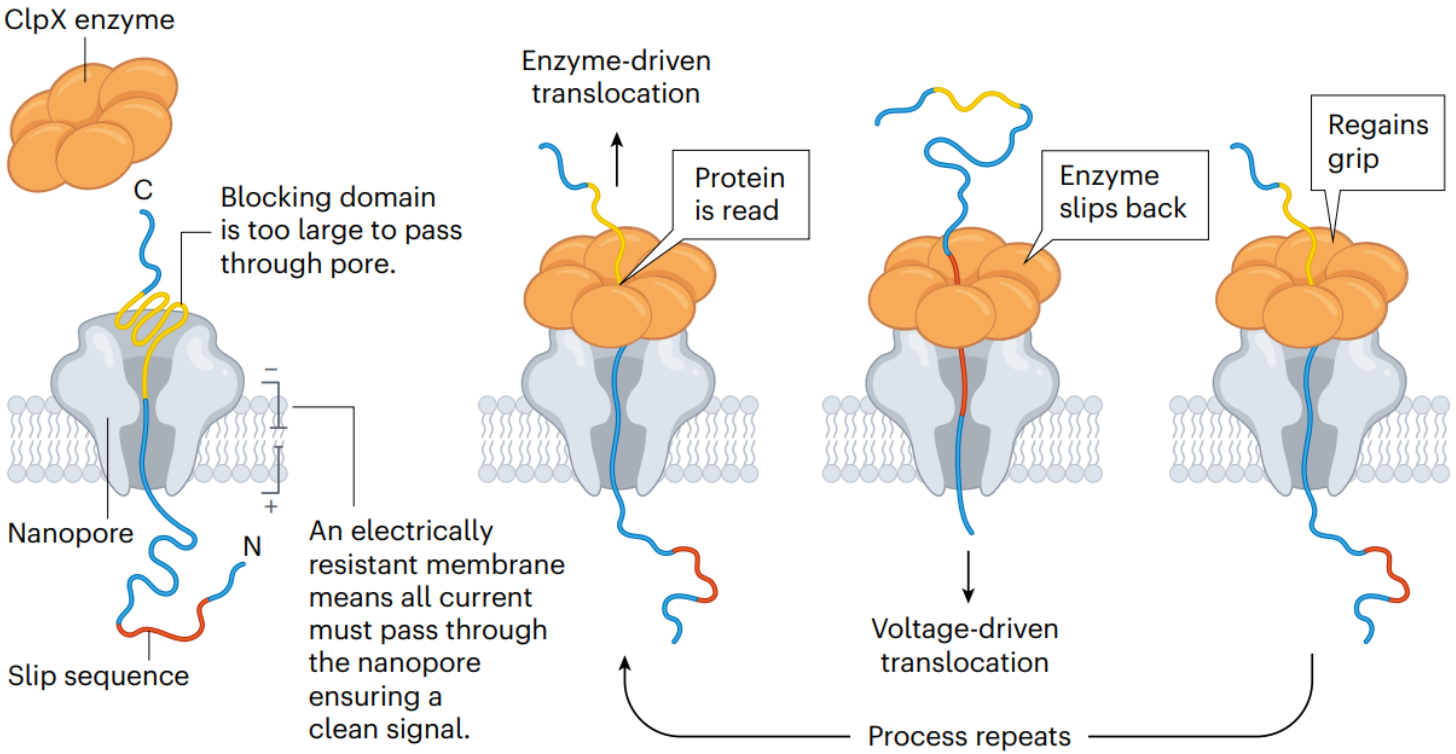
Riba M, Sala C, Culhane AC, Flobak Å, Patocs A, Boye K, Plevova K, Pospíšilová Š, Gandolfi G, Morelli MJ, Bucci G, Edsjö A, Lassen U, Al-Shahrour F, Lopez-Bigas N, Hovland R, Cuppen E, Valencia A, Poirel HA, Rosenquist R, Scollen S, Arenas Marquez J, Belien J, De Nicolo A, De Maria R, Torrents D, Tonon G. **The 1+Million Genomes Minimal Dataset for Cancer.** Nat Genet. 2024 May 3. doi: 10.1038/s41588-024-01721-x

Genomics (genotype) is not necessarily phenotype (proteomics)

https://media.nature.com/original/magazine-assets/d41586-024-01280-5/d41586-024-01280-5.pdf

READ AND REPEAT

One nanopore-based protein-sequencing strategy uses the push and pull of an electric field, the ClpX enzyme (orange) and a 'slip sequence' to move a protein back and forth across a membrane, providing multiple views of the protein sequence and increasing accuracy.



A nanopore sequencing device is typically used for sequencing DNA and RNA.

NANOPORE SEQUENCING COMES FOR PROTEINS

l'humanité a besoin de rêveurs

Will there be bumps on the road to success? Undoubtedly.

Humanity needs dreamers

https://pccm.princeton.edu/events/humanity-needs-dreamers-visit-marie-curie-1

https://www.cambridgema.gov/cpl/calendarofevents/2018/04/19/humanityneedsdreamersavisitwithmariecurie

www.colorado.edu/cuwizards/2020/11/14/december-5-2020-humanity-needs-dreamers-visit-marie-curie-susan-marie-frontczak

Article | Separation Sample Preparation 26 November 2012

Blood bank bias: Protein biomarkers of stored red blood cells

Overview

Several biomarkers of degradation in stored red blood cells have been identified in a proteomics study, providing an opportunity to estimate deterioration during storage as well as blood doping in sports.

Storage-induced changes of the cytosolic red blood cell proteome analyzed by 2D DIGE and high-resolution/high-accuracy MS.

Walpurgis K [1], Kohler M , Thomas A , Wenzel F , Geyer H , Schänzer W , Thevis M

Author information

Proteomics, 09 Oct 2012, 12(21):3263-3272
https://doi.org/10.1002/pmic.201200280 PMID: 22965759

BUT

If only 1% of the global population (~8 billion people) use diagnostics & treatment, imagine the business potential of research results!

If ethical profitability of social businesses can help improve healthcare for even 10% of the global population, then we helped ~800 million more!

Leukapheresis to enrich for T (CAR-T) lymphocytes for non-affluent nations?

CUTTING-EDGE CANCER THERAPY IS MADE IN INDIA — AT ONE-TENTH THE COST

The treatment, called NexCAR19, raises hopes that a transformative class of medicine will become more readily available in low- and middle-income countries.

By Smriti Mallapaty

A small Indian biotechnology company is producing a home-grown version of a cutting-edge cancer treatment known as chimeric antigen receptor (CAR) T-cell therapy that was pioneered in the United States. CAR-T therapies are used mainly to treat blood cancers and have burgeoned in the past few years. The Indian CAR-T therapy costs one-tenth that of comparable commercial products available globally.

A single treatment of NexCAR19, manufactured by Mumbai-based ImmunoACT, costs between US$30,000 and $40,000. The first CAR-T therapy was approved in the United States in 2017, and commercial CAR-T therapies currently cost between $370,000 and $530,000, not including hospital fees and drugs to treat side effects. These treatments have also shown promise in treating autoimmune diseases and brain cancer.

India's drug regulator approved NexCAR19 for therapeutic use in India in October. By December, ImmunoACT was administering the therapy to paying patients, and it is now treating some two-dozen people a month in hospitals across the country.

"It's a dream come true," says Alka Dwivedi, an immunologist who helped to develop NexCAR19 and is now at the US National Cancer Institute (NCI) in Bethesda, Maryland. Her voice becomes tender as she describes seeing the first patient's cancer go into remission. These are people for whom all other treatments have failed, says Dwivedi.

https://www.nature.com/articles/d41586-024-00809-y.pdf

The social business of medicine guided by ethical profitability for for-profit ventures? **Model for non-affluent non-OECD nations?**

COST IN USA

$530,000

NEWS | 21 March 2024 https://www.nature.com/articles/d41586-024-00809-y

Cutting-edge CAR-T cancer therapy is now made in India — at one-tenth the cost

The treatment, called NexCAR19, raises hopes that this transformative class of medicine will become more readily available in low- and middle-income countries.

COST IN INDIA

$30,000

A single treatment of NexCAR19, manufactured by Mumbai-based ImmunoACT, costs between US$30,000 and $40,000. The first CAR-T therapy was approved in the United States in 2017, and commercial CAR-T therapies in the US cost between $370,000 and $530,000, not including hospital fees and drugs to treat side effects. These treatments have also shown promise in treating autoimmune diseases and brain cancer. "It's a dream come true," says Alka Dwivedi, an immunologist who helped to develop NexCAR19 and is now at the US National Cancer Institute (NCI, NIH) in Bethesda, MD. These are people for whom all other treatments have failed, says Dwivedi. There is a "tremendous patient need", says Nirali Shah, a paediatric oncologist at NCI, NIH who is also an academic collaborator of the researchers at ImmunoACT. "It's positive news," says Renato Cunha, a haematologist at the Grupo Oncoclínicas in São Paulo, Brazil. He says the Indian product could pave the way for making advanced cellular therapies accessible to other low- and middle-income countries. "Hope is the word that comes to mind."

The potential for blood banks and blood donors as a source for CAR-T cells?

nature.com/articles/d41586-024-00470-5

NEWS | 22 February 2024 | Correction 22 February 2024

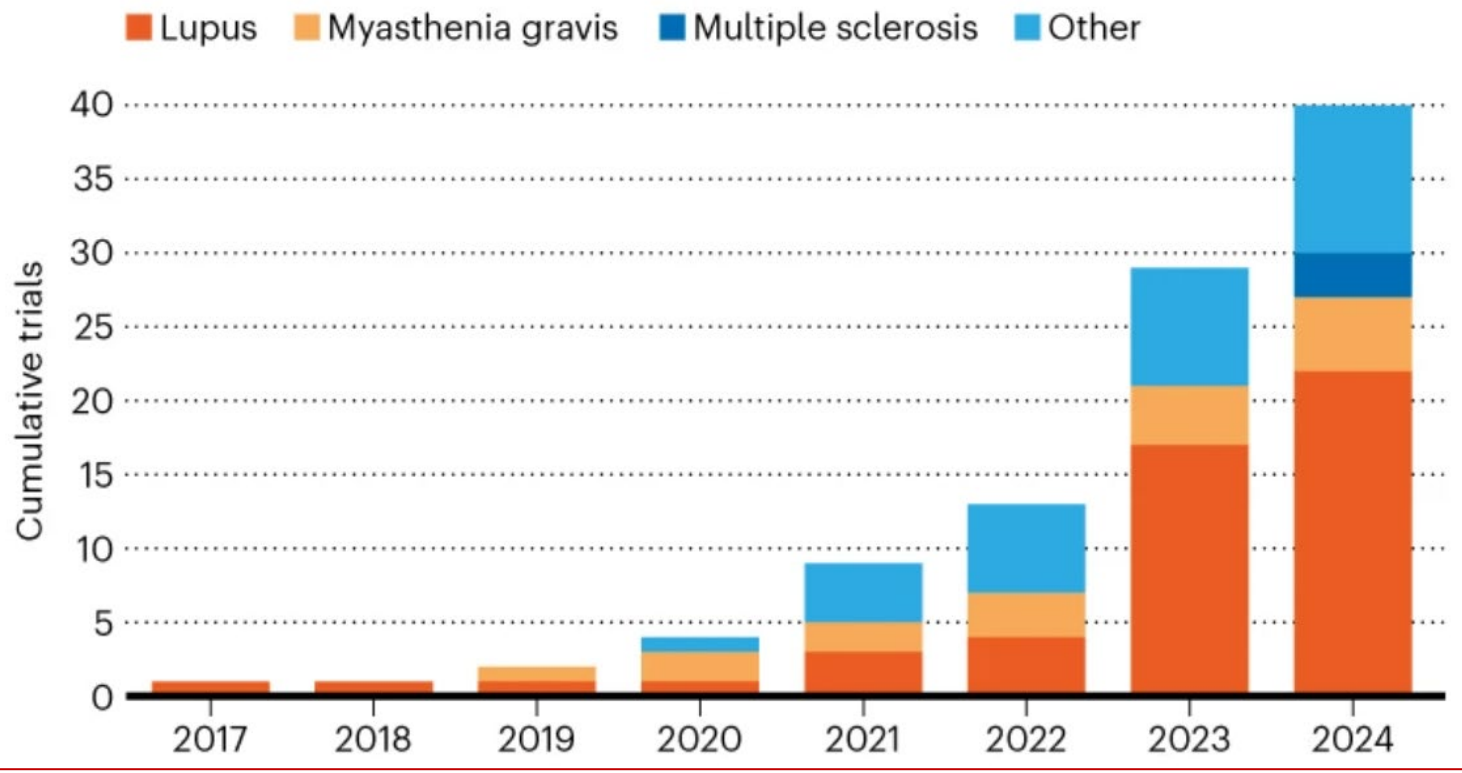
CAR-T therapy for multiple sclerosis enters US trials for first time

Hopes are high that engineered immune cells, which are already in use to treat blood cancer, will halt the progression of a degenerative autoimmune disorder.

nature.com/articles/d41586-024-00470-5 www.nature.com/articles/d41586-024-00470-5

ENLISTING IMMUNE CELLS TO TREAT AUTOIMMUNE DISEASE

The number of clinical trials of CAR T cells — engineered immune cells — used to treat autoimmune disorders has grown rapidly over the past seven years. Testing of CAR-T therapy for the autoimmune disorder lupus accounts for the bulk of the trials.



Biol Blood Marrow Transplant 21 (2015) 1188–1194

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Review

Cord Blood Banking in the Arab World: Current Status and Future Developments

Monica M. Matsumoto [1], Rana Dajani [2], Kirstin R.W. Matthews [1,*]

[1] James A. Baker III Institute for Public Policy, Science and Technology Policy Program, Rice University, Houston, Texas
[2] Department of Biology and Biotechnology, Hashemite University of Jordan, Zarqa, Jordan

http://dx.doi.org/10.1016/j.bbmt.2015.01.012 1083-8791/

Table 3
Timeline of Major CB Banking Developments in the Arab World

Year	Development
1998	First CB transplant is performed in Arab world
2003	SA: KFSH-RC begins performing CB transplants (from imported units)
	Muslim World League's Jurisprudential Council issues a *fatwa* approving CB for research and therapy
2006	UAE: DCRC opens first CB bank in the region, as a public–private hybrid model
	SA: KFSH-RC opens the Kingdom's first public CB bank
	UAE: Cryo-Save Arabia, the largest private CB storage facility in the region, opens in Dubai Healthcare City
2007	EG: National Blood Policy is approved with procedural guidelines for CB collection and storage
2009	QA: Virgin Health Bank moves its headquarters from London to Doha
	EG: CellSafe opens as the country's first private CB bank
2011	QA: Virgin Health Bank is granted the first (and only, to date) license for CB procurement, processing, and storage
	SA: KAIMRC opens the country's second public CB bank and creates the Saudi Donor Registry
	QA: Virgin Health Bank opens storage and processing facility at Qatar Science & Technology Park
	EG: National Stem Cell Committee is created and tasked with establishing regulations for stem cell research and therapy as well as a public CB bank
2012	EG: Stem cell research center opens at Sheikh Zayed Hospital
	QA: Stem cell research policy is enacted into legislation, allowing research using CB stem cells
2013	EG: Center for Stem Cell Research and Regenerative Medicine opens in Zewail City of Science & Technology
2014	JO: New stem cell research law is passed, including regulations for CB banking
2015	JO: Projected opening of the first in-country private CB storage facility by the company, BabyCord Jordan
	EG: Projected opening of the country's first public CB bank, located at Assiut University, in partnership with Zewail City of Science & Technology
2016	JO: Projected opening of the country's first public CB bank, located at KHCC

The potential for cord blood banks as an autologous source for CAR-T cells?

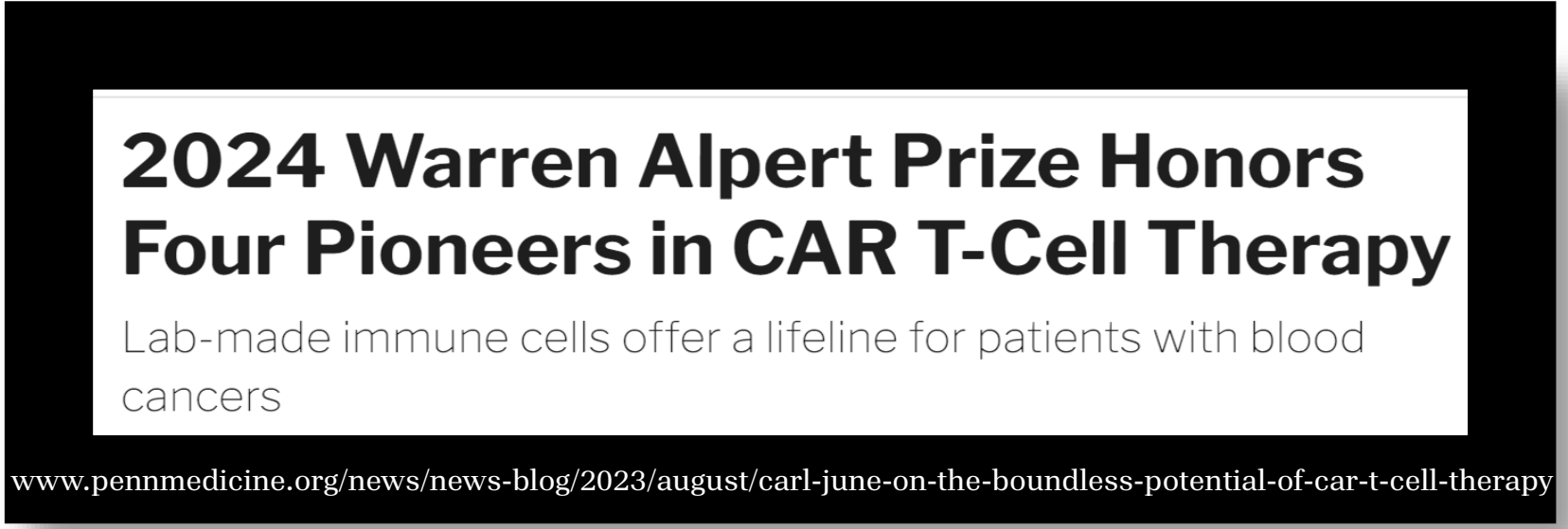
Table 1
Relevant Demographic, Health, and Economic Indicators of 5 Arab Countries Studied: Jordan, Saudi Arabia, UAE, Egypt, and Qatar

Country	Population	Arab	Fert	GNI	Health $	Hosp Beds	Leukemia	Lymphoma
Jordan	7.93M	98%	3.16	$4.95k	8.4%	1.8	6.1	8.2
Saudi Arabia	27.3M	90%	2.17	$26.2k	3.7%	2.2	3.8	7.9
UAE	5.63M	13%‖	2.36	$38.6k	3.3%	1.9	3.7	6.7
Egypt	86.9M	99%	2.87	$3.16k	4.9%	1.7	5.9	9.3
Qatar	2.12M	40%	1.92	$85.5k	1.9%	1.2	4.9	7.7

Table 2
Current CB Banking Options in the Arab World

CB Bank	Type	Storage Location	Collection Office Location(s)
BabyCord	Priv	USA (Boston), Jordan (Amman)*	Jordan
Biovault Family	Priv	UK (Plymouth)	Lebanon, UAE
CellSafe	Priv	Egypt (Cairo)	Egypt
Cells4Life	Priv	UK (Burgess Hill, Essex)	Bahrain, Egypt, Jordan, Kuwait, Lebanon, Qatar, Saudi Arabia, UAE
Center for Stem Cell Research & Regenerative Medicine	Publ	Egypt (Assiut)*	Egypt
Cryo-Save	Priv	UAE (Dubai), Belgium (Niel)	Egypt, Kuwait, Oman, Saudi Arabia, UAE
DCRC†	Hybr	UAE (Dubai)	UAE
Future Health Biobank	Priv	UK (Nottingham), Switzerland (Châtel-St-Denis)	Bahrain, Egypt, Jordan, Kuwait, Lebanon, Morocco, Qatar, Saudi Arabia, Syria, UAE
KAIMRC	Publ	Saudi Arabia (Riyadh)	Saudi Arabia
KFSH-RC†	Publ	Saudi Arabia (Riyadh)	Saudi Arabia
KHCC	Publ	Jordan (Amman)*	Jordan
Precious Cells	Priv	UK (Middlesex)	Jordan, Lebanon, UAE
Smart Cells	Priv	UK (West Drayton)	Egypt, Jordan, Kuwait, Lebanon, Syria, UAE
Sultan Qaboos Univ. Hospital	Publ	Oman (Muscat)	Oman
Virgin Health Bank	Priv, Hybr	Qatar (Doha)	Qatar

Matsumoto MM, Dajani R, Matthews KR. **Cord Blood Banking in the Arab World: Current Status and Future Developments. Biol Blood Marrow Transplant.** 2015 July; 21(7):1188-94. doi: 10.1016/j.bbmt.2015.01.012. Epub 2015 Feb 14. PMID: 25687797.

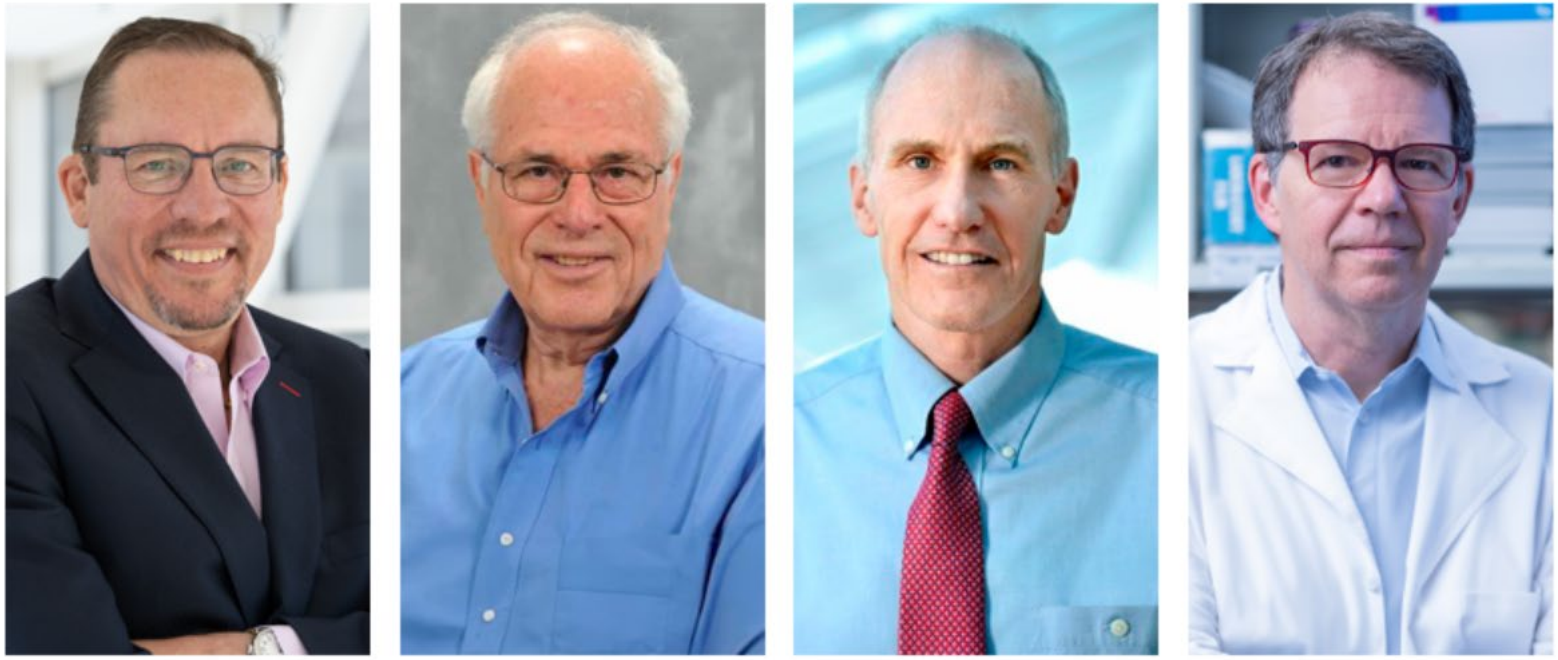


Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A, June CH. **T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia.** Sci Transl Med. 2011 August 10; 3(95):95ra73. doi: 10.1126/scitranslmed.3002842
www.ncbi.nlm.nih.gov/pmc/articles/PMC3393096/pdf/nihms384661.pdf

Porter DL, Levine BL, Kalos M, Bagg A, June CH. **Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia.** N Engl J Med. 2011 Aug 25;365(8):725-33. doi: 10.1056/NEJMoa1103849. Epub 2011 Aug 10. Erratum in: N Engl J Med. 2016 Mar 10;374(10):998. doi: 10.1056/NEJMx160005
www.ncbi.nlm.nih.gov/pmc/articles/PMC3387277/pdf/nihms-320786.pdf

2024 Warren Alpert Prize Honors Four Pioneers in CAR T-Cell Therapy

Lab-made immune cells offer a lifeline for patients with blood cancers



•Renier Brentjens, Katherine Anne Gioia Endowed Chair of Medicine and deputy director of Roswell Park Comprehensive Cancer Center

•Zelig Eshhar, professor emeritus, the Weizmann Institute of Science, chair of Immunology, Division of R&D, Sourasky Medical Center, Israel

•Carl June, Richard W. Vague Professor in Immunotherapy, University of Pennsylvania Perelman School of Medicine

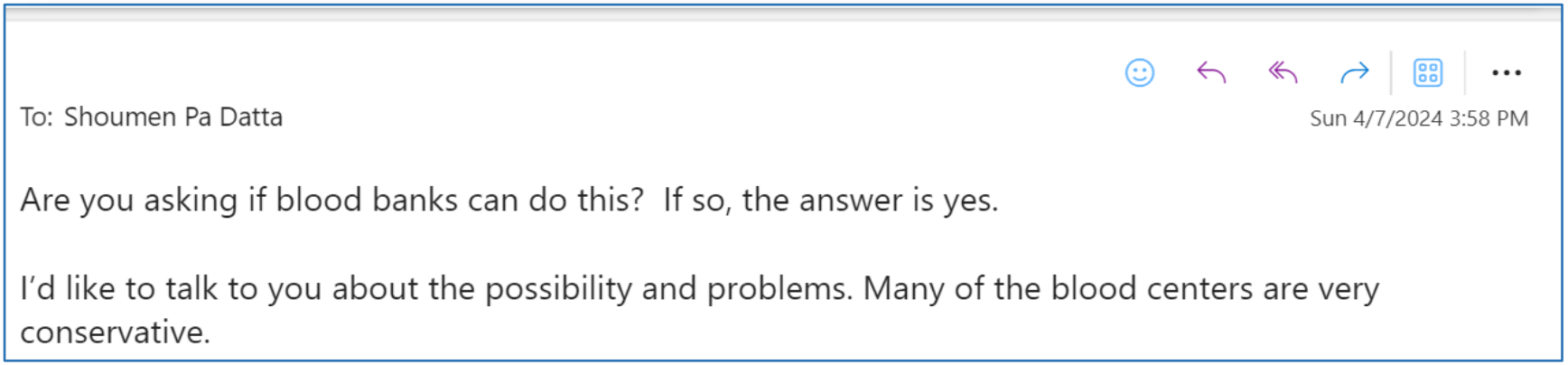
•Michel Sadelain, Stephen and Barbara Friedman Chair, founding director of the Center for Cell Engineering at Memorial Sloan Kettering Cancer Center

https://hms.harvard.edu/news/2024-warren-alpert-prize-honors-four-pioneers-car-t-cell-therapy

Potential for blood banks / cord blood banks in cellular & molecular therapy

FUTURE FORWARD RESEARCH – THINK VERY FAR BEYOND THE HORIZON

- Take any blood and transform HLA gene expression to match recipient (HLA typing) for transfusion medicine
- Apheresis of donor blood to enrich for desired cell types (e.g., CAR-T) and induce HLA gene expression for immune match
- Use CD34+ cord blood cells and induce (iPSC) to make immuno-compatible tissue (any tissue, organoid) for transplantation



To: Shoumen Pa Datta

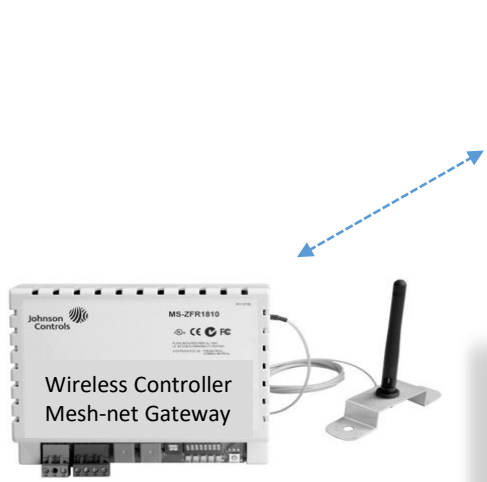
Sun 4/7/2024 3:58 PM

Are you asking if blood banks can do this? If so, the answer is yes.

I'd like to talk to you about the possibility and problems. Many of the blood centers are very conservative.

Former CEO of a Blood Bank

Digital Health Hematology Services (DHHS is far closer at hand)



Local Wireless Sensor Mesh Network

DHHS IN THE NEAR-FUTURE OF BLOOD BANKS ?

Data-Informed Decision Support (DIDS) Systems
Distributed Secure Near Real-time Mobile Digital Health Services

RESEARCH FEATURE

Future of medicine: Lab-on-a-chip devices starting to make an impact

September 27, 2021

Izadifar, Z., Cotton, J., Chen, S. *et al.* Mucus production, host-microbiome interactions, hormone sensitivity, and innate immune responses modeled in human cervix chips. *Nat Commun* **15**, 4578 (2024). https://doi.org/10.1038/s41467-024-48910-0

Article

https://doi.org/10.1038/s41467-024-48910-0

Mucus production, host-microbiome interactions, hormone sensitivity, and innate immune responses modeled in human cervix chips

Received: 22 April 2023

Accepted: 22 March 2024

Published online: 29 May 2024

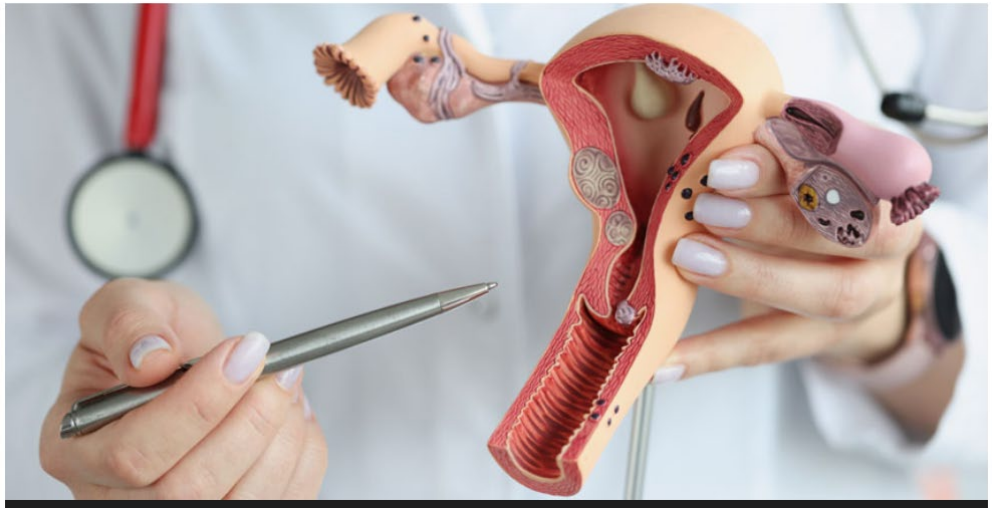
Zohreh Izadifar[1,5], Justin Cotton[1], Siyu Chen[2], Viktor Horvath[1], Anna Stejskalova[1], Aakanksha Gulati[1], Nina T. LoGrande[1], Bogdan Budnik[1], Sanjid Shahriar[1], Erin R. Doherty[1], Yixuan Xie[2], Tania To[1], Sarah E. Gilpin[1], Adama M. Sesay[1], Girija Goyal[1], Carlito B. Lebrilla[2] & Donald E. Ingber[1,3,4]

HARVARD MEDICAL SCHOOL

Cervix-on-a-Chip to Accelerate Research on Women's Health

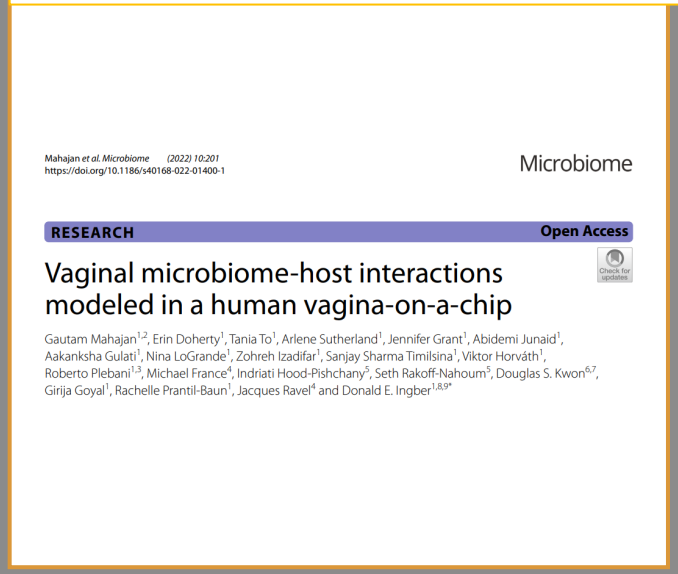
New model could lead to better understanding of, treatments for diseases of female reproductive tract

June 6, 2024 | Research



https://hms.harvard.edu/news/cervix-chip-accelerate-research-womens-health

Mahajan G, Doherty E, To T, Sutherland A, Grant J, Junaid A, Gulati A, LoGrande N, Izadifar Z, Timilsina SS, Horváth V, Plebani R, France M, Hood-Pishchany I, Rakoff-Nahoum S, Kwon DS, Goyal G, Prantil-Baun R, Ravel J, Ingber DE. **Vaginal microbiome-host interactions modeled in a human vagina-on-a-chip.** Microbiome. 2022 Nov 26; 10(1):201. doi: 10.1186/s40168-022-01400-1



Mahajan *et al. Microbiome* (2022) 10:201
https://doi.org/10.1186/s40168-022-01400-1

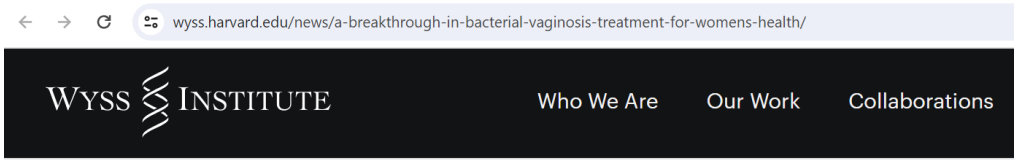
Microbiome

RESEARCH Open Access

Vaginal microbiome-host interactions modeled in a human vagina-on-a-chip

Gautam Mahajan[1,2], Erin Doherty[1], Tania To[1], Arlene Sutherland[1], Jennifer Grant[1], Abidemi Junaid[1], Aakanksha Gulati[1], Nina LoGrande[1], Zohreh Izadifar[1], Sanjay Sharma Timilsina[1], Viktor Horváth[1], Roberto Plebani[1,3], Michael France[4], Indriati Hood-Pishchany[5], Seth Rakoff-Nahoum[5], Douglas S. Kwon[6,7], Girija Goyal[1], Rachelle Prantil-Baun[1], Jacques Ravel[4] and Donald E. Ingber[1,8,9*]

HARVARD
MEDICAL SCHOOL



wyss.harvard.edu/news/a-breakthrough-in-bacterial-vaginosis-treatment-for-womens-health/

WYSS INSTITUTE Who We Are Our Work Collaborations

A breakthrough in bacterial vaginosis treatment for women's health

November 28, 2022

Human Organ Chip allows researchers to study effects of microbiome on vaginal health

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9701078/pdf/40168_2022_Article_1400.pdf
https://wyss.harvard.edu/news/a-breakthrough-in-bacterial-vaginosis-treatment-for-womens-health/

A digital microfluidic analyzer stands behind a disposable lab-on-a-chip cartridge (forefront), where blood samples are collected to screen for the presence of rare diseases.

nhlbi.nih.gov/news/2021/future-medicine-lab-chip-devices-starting-make-impact

Researchers supported by the NHLBI are playing a key role in the development of this technology — and for good reason. The chips not only are capable of quickly diagnosing diseases, but they can also do so at a lower cost, faster speed, and with higher accuracy than their bulkier counterparts, researchers say. Some may be coming to a hospital or medicine cabinet near you.

"Watching discoveries move from the lab to the clinic is incredibly exciting," said Stephanie M. Davis, Ph.D., NHLBI's Small Business Program Coordinator. "The NHLBI Small Business Program is thrilled to see lab-on-a-chip technologies finally move toward the marketplace."

https://www.nhlbi.nih.gov/news/2021/future-medicine-lab-chip-devices-starting-make-impact

Is it in practice? Yes! Massachusetts General Hospital, Harvard Medical School

Published in final edited form as:
Annu Rev Biomed Eng. 2005 ; 7: 77–103. doi:10.1146/annurev.bioeng.7.011205.135108.

BLOOD-ON-A-CHIP

Mehmet Toner and **Daniel Irimia**
BioMEMS Resource Center, Center for Engineering in Medicine and Surgical Services, Massachusetts General Hospital, Shriners Hospital for Children, and Harvard Medical School, Boston, Massachusetts 02114

Mehmet Toner: mtoner@hms.harvard.edu; Daniel Irimia: dirimia@hms.harvard.edu

Abstract

Accurate, fast, and affordable analysis of the cellular component of blood is of prime interest for medicine and research. Yet, most often sample preparation procedures for blood analysis involve handling steps prone to introducing artifacts, whereas analysis methods commonly require skilled technicians and well-equipped, expensive laboratories. Developing more gentle protocols and affordable instruments for specific blood analysis tasks is becoming possible through the recent progress in the area of microfluidics and lab-on-a-chip-type devices. Precise control over the cell microenvironment during separation procedures and the ability to scale down the analysis to very small volumes of blood are among the most attractive capabilities of the new approaches. Here we review some of the emerging principles for manipulating blood cells at microscale and promising high-throughput approaches to blood cell separation using microdevices. Examples of specific single-purpose devices are described together with integration strategies for blood cell separation and analysis modules.

Keywords

lab-on-a-chip; point-of-care diagnostic; cell separation; sample preparation; microfluidic

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3779643/pdf/nihms506695.pdf

https://doi.org/10.1038/s41467-022-28499-y OPEN

Micro-mechanical blood clot testing using smartphones

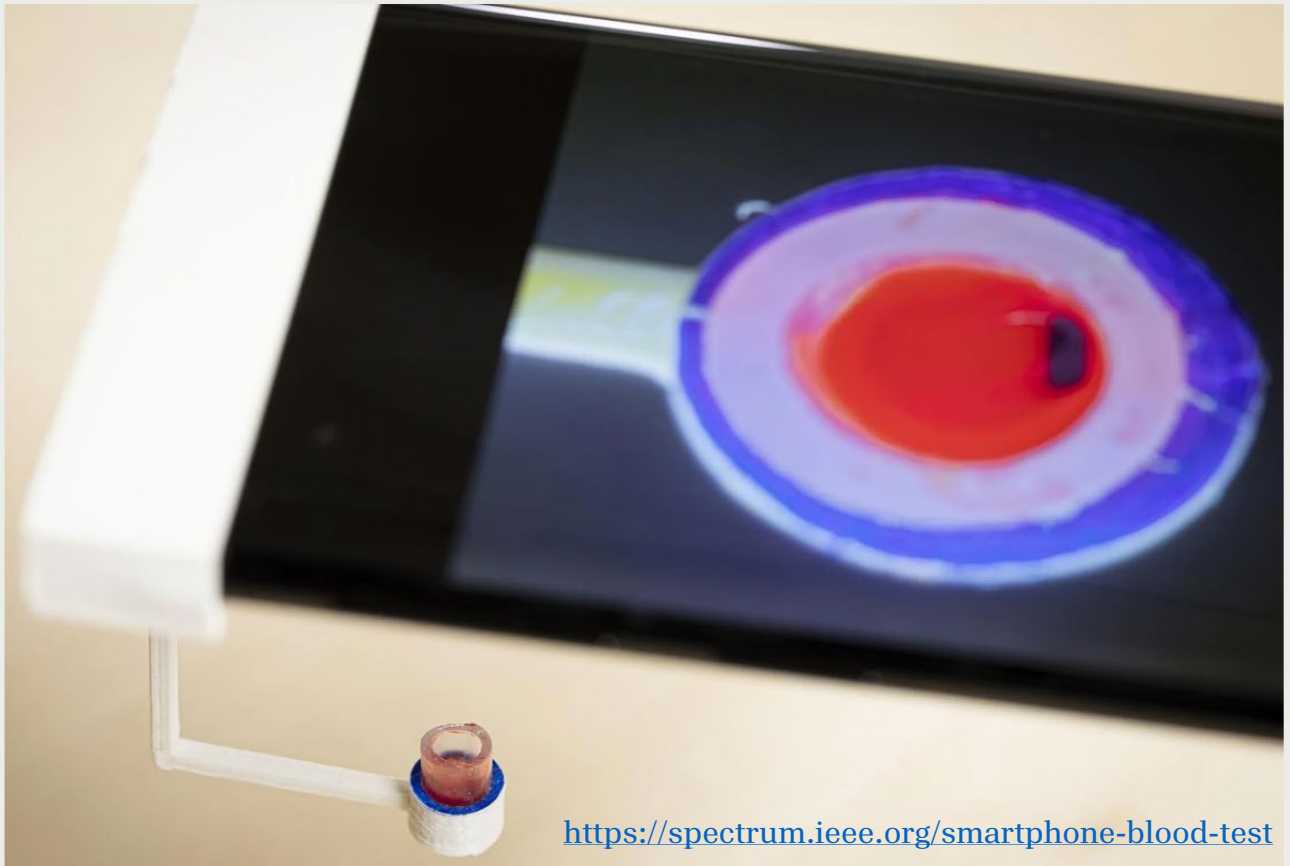
Justin Chan [1✉], Kelly Michaelsen [2✉], Joanne K. Estergreen[3], Daniel E. Sabath [3] & Shyamnath Gollakota [1✉]

University of Washington researchers have developed a new blood-clotting test that uses only a single drop of blood and a smartphone with a plastic attachment that holds a tiny cup [shown here] beneath the phone's camera.

Blood Test Only Needs a Drop and a Smartphone for Results

The tech shows promise, although user-friendly "single drop of blood" platforms are still a few years away

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8837659/pdf/41467_2022_Article_28499.pdf



https://spectrum.ieee.org/smartphone-blood-test

Chan J, Michaelsen K, Estergreen JK, Sabath DE, Gollakota S. ***Micro-mechanical blood clot testing using smartphones.*** Nature Commun. 2022 Feb 11; 13(1):831. doi: 10.1038/s41467-022-28499-y. PMID: 35149711; PMCID: PMC8837659.

DE GRUYTER

Clin Chem Lab Med 2024; aop

Théo Willeman*, Justine Grunwald, Marc Manceau, Frédéric Lapierre, Lila Krebs-Drouot, Coralie Boudin, Virginie Scolan, Hélène Eysseric-Guerin, Françoise Stanke-Labesque and Bruno Revol

Smartphone swabs as an emerging tool for toxicology testing: a proof-of-concept study in a nightclub

https://doi.org/10.1515/cclm-2024-0242
Received February 22, 2024; accepted March 27, 2024;
published online April 5, 2024

From the journal Clinical Chemistry and Laboratory Medicine (CCLM)
https://doi.org/10.1515/cclm-2024-0242

RESEARCH ARTICLE

Resistivity detection of perfluoroalkyl substances with fluorous polyaniline in an electrical lateral flow sensor

Sohyun Park, Collette T. Gordon, and Timothy M. Swager Authors Info & Affiliations

Contributed by Timothy M. Swager; received October 5, 2023; accepted February 6, 2024; reviewed by William R. Dichtel, Howard E. Katz, and John Reynolds

March 12, 2024 | 121 (12) e2317300121 | https://doi.org/10.1073/pnas.2317300121

OPEN

Check for updates

Per- and polyfluoroalkyl substances (PFAS) and thyroid hormone measurements in dried blood spots and neonatal characteristics: a pilot study

Ana K. Rosen Vollmar[1], Elizabeth Z. Lin[1], Sara L. Nason[2], Katerina Santiago[3], Caroline H. Johnson[1], Xiaomei Ma[3], Krystal J. Godri Pollitt[1] and Nicole C. Deziel[1]

Is a PFAS smartphone sensor in the works?

BACKGROUND: Pediatric thyroid diseases have been increasing in recent years. Environmental risk factors such as exposures to chemical contaminants may play a role but are largely unexplored. Archived neonatal dried blood spots (DBS) offer an innovative approach to investigate environmental exposures and effects.

OBJECTIVE: In this pilot study, we applied a new method for quantifying per- and polyfluoroalkyl substances (PFAS) to 18 archived DBS from babies born in California from 1985–2018 and acquired thyroid hormone measurements from newborn screening tests. Leveraging these novel data, we evaluated (1) changes in the concentrations of eight PFAS over time and (2) the relationship between PFAS concentrations, thyroid hormone concentrations, and neonatal characteristics to inform future research.

METHODS: PFAS concentrations in DBS were measured using ultra-high-performance liquid chromatography-mass spectrometry. Summary statistics and non-parametric Wilcoxon rank-sum and Kruskal–Wallis tests were used to evaluate temporal changes in PFAS concentrations and relationships between PFAS concentrations, thyroid hormone concentrations, and neonatal characteristics.

RESULTS: The concentration and detection frequencies of several PFAS (PFOA, PFOS, and PFOSA) declined over the assessment period. We observed that the timing of specimen collection in hours after birth was related to thyroid hormone but not PFAS concentrations, and that thyroid hormones were related to some PFAS concentrations (PFOA and PFOS).

IMPACT STATEMENT: This pilot study examines the relationship between concentrations of eight per- and polyfluoroalkyl substances (PFAS), thyroid hormone levels, and neonatal characteristics in newborn dried blood spots (DBS) collected over a period of 33 years. To our knowledge, 6 of the 22 PFAS we attempted to measure have not been quantified previously in neonatal DBS, and this is the first study to examine both PFAS and thyroid hormone concentrations using DBS. This research demonstrates the feasibility of using newborn DBS for quantifying PFAS exposures in population-based studies, highlights methodological considerations in the use of thyroid hormone data for future studies using newborn DBS, and indicates potential relationships between PFAS concentrations and thyroid hormones for follow-up in future research.

Keywords: PFAS; Per- and polyfluoroalkyl substances; Dried blood spot; Thyroid hormone; Newborn; Environmental exposure

Journal of Exposure Science & Environmental Epidemiology (2023) 33:737–747; https://doi.org/10.1038/s41370-023-00603-4

Rosen Vollmar AK, Lin EZ, Nason SL, Santiago K, Johnson CH, Ma X, Godri Pollitt KJ, Deziel NC. ***Per- and polyfluoroalkyl substances (PFAS) and thyroid hormone measurements in dried blood spots and neonatal characteristics: a pilot study.*** J Expo Sci Environ Epidemiol. 2023 September; 33(5): 737-747. doi: 10.1038/s41370-023-00603-4. Epub 2023 Sep 20. PMID: 37730931; PMCID: PMC10541328. https://www.nature.com/articles/s41370-023-00603-4.pdf

Business strategy of low usage fees lowers the barrier to market entry.

Don't think market of millions. Think about creating markets for the

NEXT BILLION USERS with mobile phones!

◆ Think cable TV

Remember **PAY PER VIEW ?**

◆ Think plain old telephone system (POTS)

Remember **PAY PER CALL ?**

◆ Think purchasing power parity (PPP) of the next billion users

Remember PAPPU (**PAY A PENNY PER USE**)

Victoria Morgan, Lisseth Casso-Hartman, David Bahamon-Pinzon, Kelli McCourt, Robert G. Hjort, Sahar Bahramzadeh, Irene Velez-Torres, Eric McLamore, Carmen Gomes, Evangelyn C. Alocilja, Shoumen Palit Austin Datta and Diana C. Vanegas (2019) ***Sensor-as-a-Service: Convergence of Sensor Analytic Point Solutions (SNAPS) and Pay-A-Penny-Per-Use (PAPPU) Paradigm as a Catalyst for Democratization of Healthcare in Underserved Communities.*** Diagnostics *2020,* 10 *(1), 22* https://doi.org/10.3390/diagnostics10010022 and download from the MIT Library https://dspace.mit.edu/handle/1721.1/123983

PAY PER USE ◦ Analytics-Lab-on-a-Chip-on-a-Flash Drive

BLOOD BANK TEST SENSOR

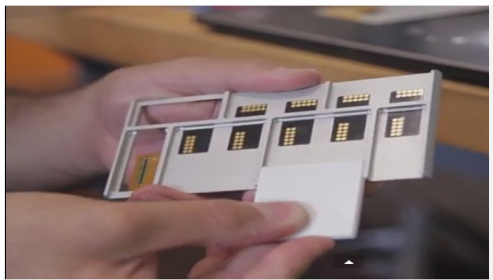
EBV Sensor

Glucose Sensor

Cholesterol Sensor

SARS-CoV-2 Sensor

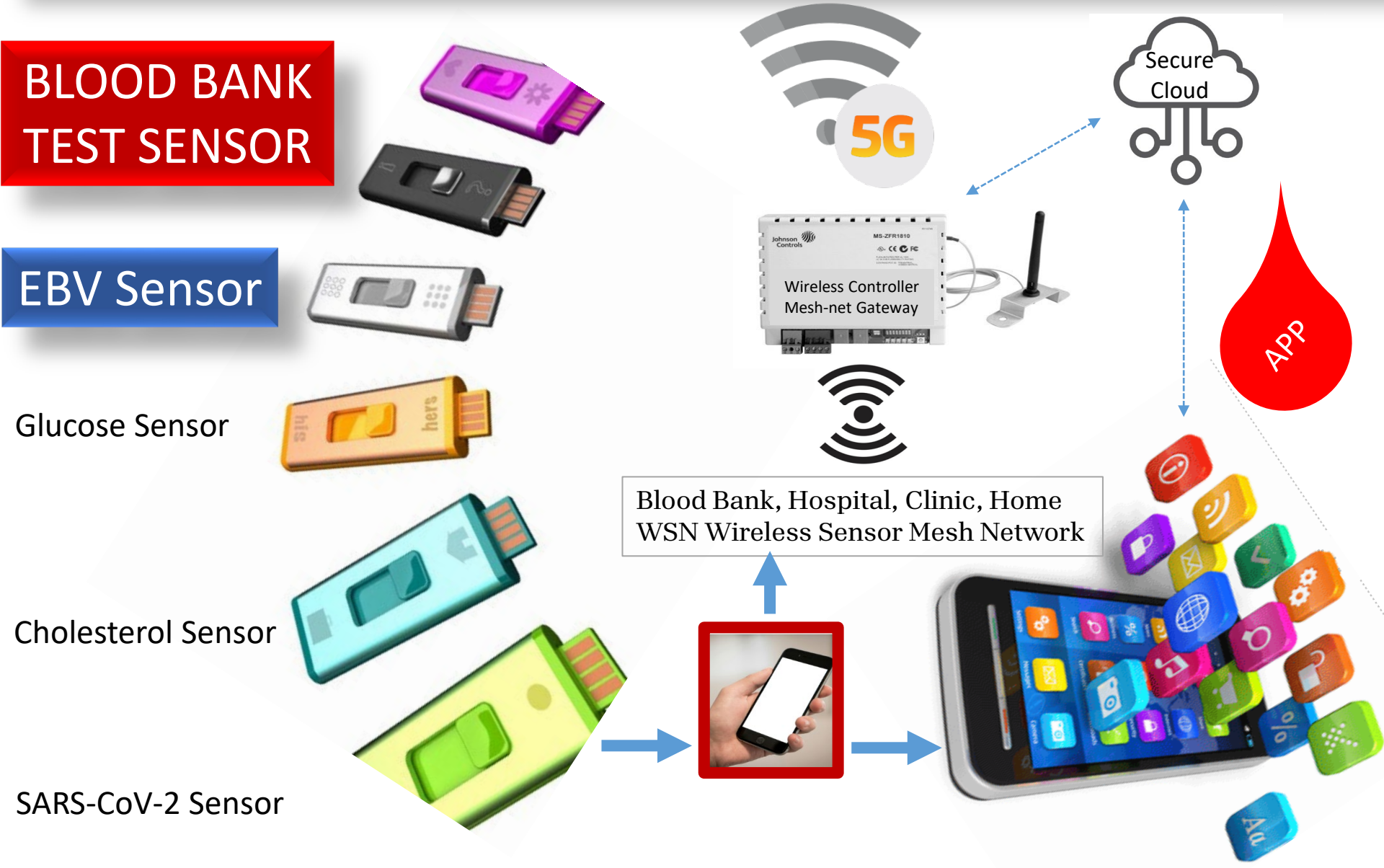
There's an app for that



Hot swappable, modular, smart

NK Labs
ARA Prototype

Digital Health: Analytics-Lab-on-a-Chip-on-a-FlashDrive



Nanotechnology for Hematology, Blood Transfusion, and Artificial Blood

Micro and Nano Technologies

2022, Pages 265-283

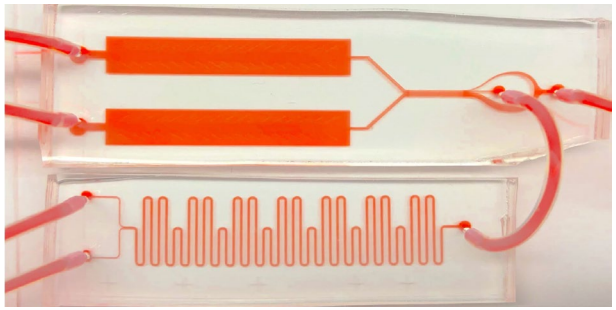
Chapter 12 - Lab-on-a-chip for analysis of blood

Hayder A. Abdulbari

https://doi.org/10.1016/B978-0-12-823971-1.00013-1

Abstract

With the growing popularity of microfluidics devices, medical science is also progressing its way through fast and efficient microfabricated diagnosis devices. Blood testing and analysis are primary and necessary steps in medical diagnosis; hence smart and fast microdiagnostic devices are considered essential. Blood is the most vital fluid, containing all the essential minerals and vitamins, and it can be a carrier for other biological pathogens such as a bacterium, virus, or other microorganism, making it the perfect subject for analysis for an accurate diagnosis. This chapter introduces and discusses microfluidics technology's influence on the diagnosis of blood diseases. The chapter starts with a comprehensive introduction of the rapid development of microfluidics technology and its applications followed by sections that detail the microfluidics science fundamentals, lab-on-chip, and microfabrication techniques. It then explains specifically the influence of microfluidics technology in the development of different blood testing techniques and methods with a more comprehensive focus on its applications in sexually transmitted diseases.



A protoype of the RT-ELISA, essentially an entire lab within a chip with tiny pipes and valves no wider than a human hair | Photo by Caitlin Maikawa

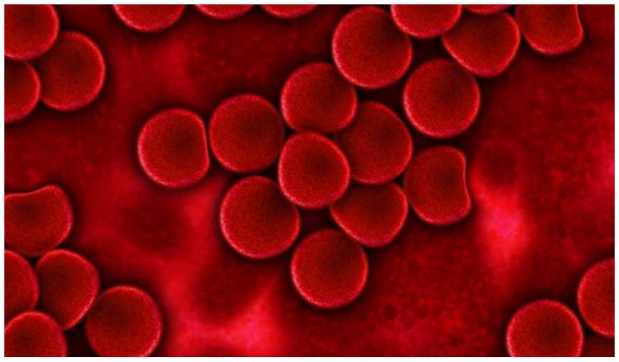
For even the most routine of medical checkups, a blood test is often the first order of business.

https://medicalxpress.com/news/2024-01-biomarker-quality-blood-donations.html

JANUARY 31, 2024 Editors' notes

Researchers identify new biomarker in quality of blood donations

by Kelsea Pieters, CU Anschutz Medical Campus



engineering.stanford.edu/magazine/article/new-lab-chip-turns-blood-test-snapshots-continuous-movies

Stanford University

Stanford | ENGINEERING

Computation & Data, Electronics & Networking, Health

A new lab-on-a-chip turns blood test snapshots into continuous movies

The device can sense levels of virtually any protein or molecule in the blood, and could be transformative for disease detection, patient monitoring and biomedical research.

Poudineh M, Maikawa CL, Ma EY, Pan J, Mamerow D, Hang Y, Baker SW, Beirami A, Yoshikawa A, Eisenstein M, Kim S, Vučković J, Appel EA, Soh HT. (2021) ***A fluorescence sandwich immunoassay for the real-time continuous detection of glucose and insulin in live animals.*** Nat Biomed Eng. 2021 Jan; 5(1):53-63. doi: 10.1038/s41551-020-00661-1. Epub 2020 December 21. PMID: 33349659; PMCID: PMC7856282. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7856282/pdf/nihms-1646031.pdf

To: Shoumen Pa Datta

Sun 4/7/2024 3:58 PM

Are you asking if blood banks can do this? If so, the answer is yes.

I'd like to talk to you about the possibility and problems.

Former CEO of a Blood Bank

Digital Health Hematology Services (DHHS)

Local Wireless Sensor Mesh Network

Wireless Sensors

Blood Bank Digital

Data-Informed Decision Support (DIDS) Systems
Distributed Secure Near Real-time Mobile Digital Health Services

Proof of Concept – Principles & Practice of DIDS

Datta, 2018 / Datta, 2023

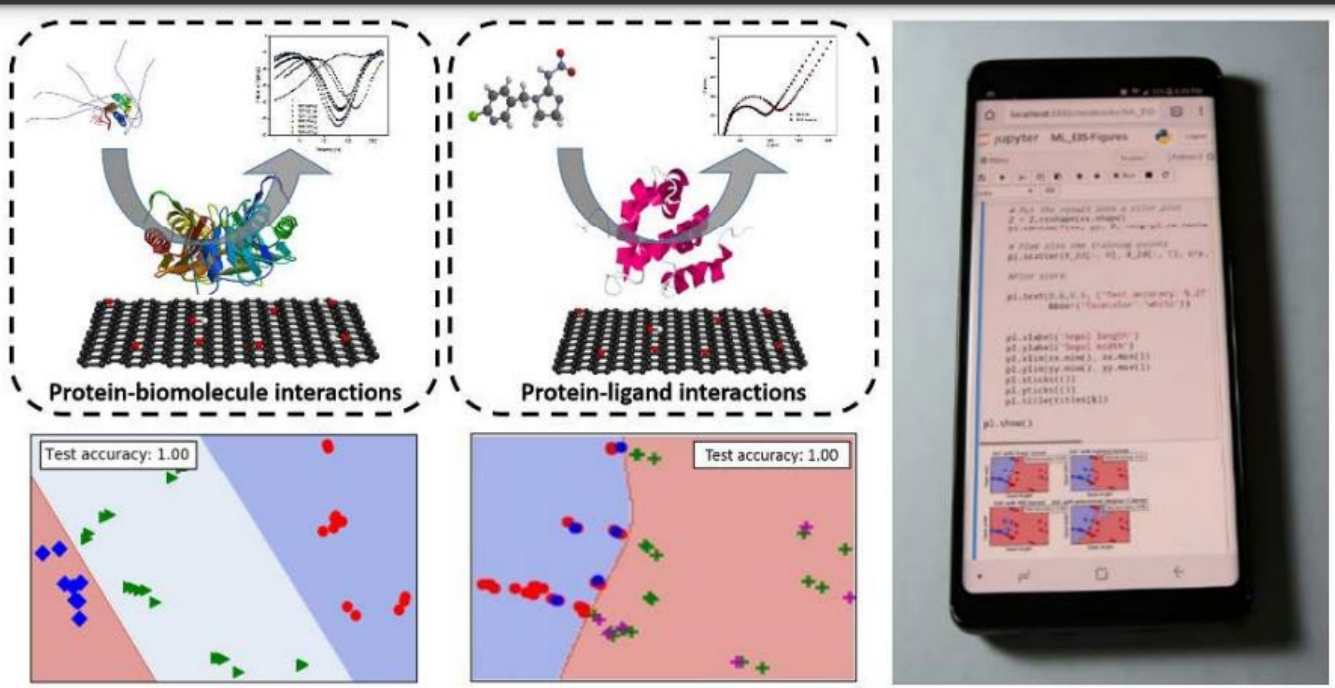
Data-Informed Decision Support (DIDS) Systems

Distributed Near◆ Real-time Mobile Detection Services

Rong Y , Padron AV , Hagerty KJ , Nelson N , Chi S , Keyhani NO , Katz J , **Datta** SPA , Gomes C , McLamore ES (2018) ***Post hoc support vector machine learning for impedimetric biosensors based on weak protein-ligand interactions.*** Analyst. 2018 April 30;143(9):2066-75 doi: 10.1039/c8an00065d

Near◆ Real-time depends on material science (sensor engineering), biochemical & physical chemistry** of molecular interactions (binding kinetics, affinity, equilibrium), timing in software systems (Δt) and network engineering infrastructure with respect to telecommunications (latency, bandwidth and jitter).

** McLamore, Eric S. and **Datta,** Shoumen P.A. (2023) ***A Connected World: System-Level Support through Biosensors*** Annual Review of Analytical Chemistry (Palo Alto, CA) 2023 June 14; 16(1):285-309. doi: 10.1146/annurev-anchem-100322-040914. Epub 2023 April 5. PMID: 37018797.
https://doi.org/10.1146/annurev-anchem-100322-040914
MIT Library https://dspace.mit.edu/handle/1721.1/123983



Proof of Concept: Data-Informed Decision Support (DIDS)

Figure 1. An open source support vector machine learning algorithm was developed for analyzing impedimetric biosensor data. Interactions. We tested the tool for analyzing weak/transient interactions including protein-DNA, protein-protein, and protein-small molecule. The cloud-based tool can be used for point of need applications with a mobile phone or tablet.

Rong Y , Padron AV , Hagerty KJ , Nelson N , Chi S , Keyhani NO , Katz J , Datta SPA , Gomes C , McLamore ES . ***Post hoc support vector machine learning for impedimetric biosensors based on weak protein-ligand interactions.*** Analyst. 2018 Apr 30;143(9):2066-75 doi: 10.1039/c8an00065d PMID: 29629449.

https://pubs.rsc.org/en/content/getauthorversionpdf/c8an00065d

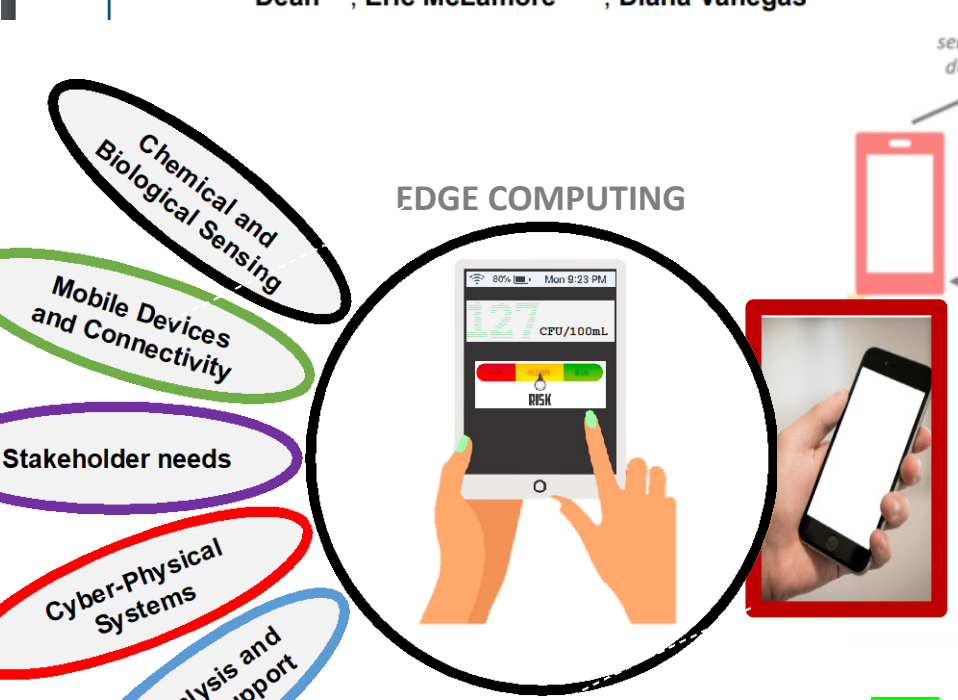
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9386735/pdf/nihms-1827456.pdf

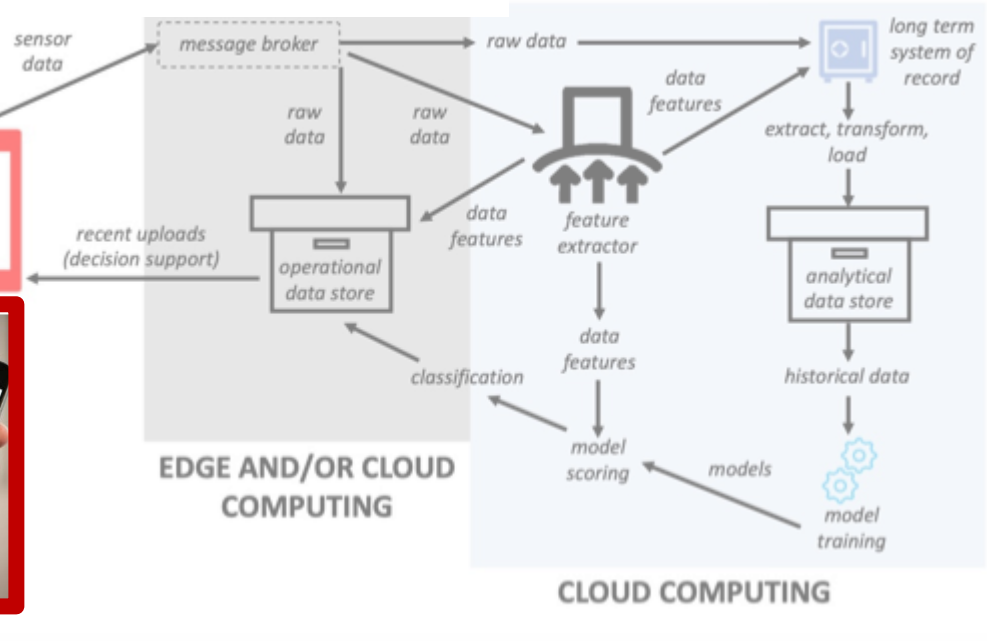
Published in final edited form as:

Front Sens (Lausanne). 2022 ; 3: . doi:10.3389/fsens.2022.917380.

Development of a Biosensor Based on Angiotensin-Converting Enzyme II for Severe Acute Respiratory Syndrome Coronavirus 2 Detection in Human Saliva

Geisianny Moreira[1,2], **Lisseth Casso-Hartmann**[1], **Shoumen Palit Austin Datta**[3,4], **Delphine Dean**[5,6], **Eric McLamore**[1,2,7], **Diana Vanegas**[1,2,*]





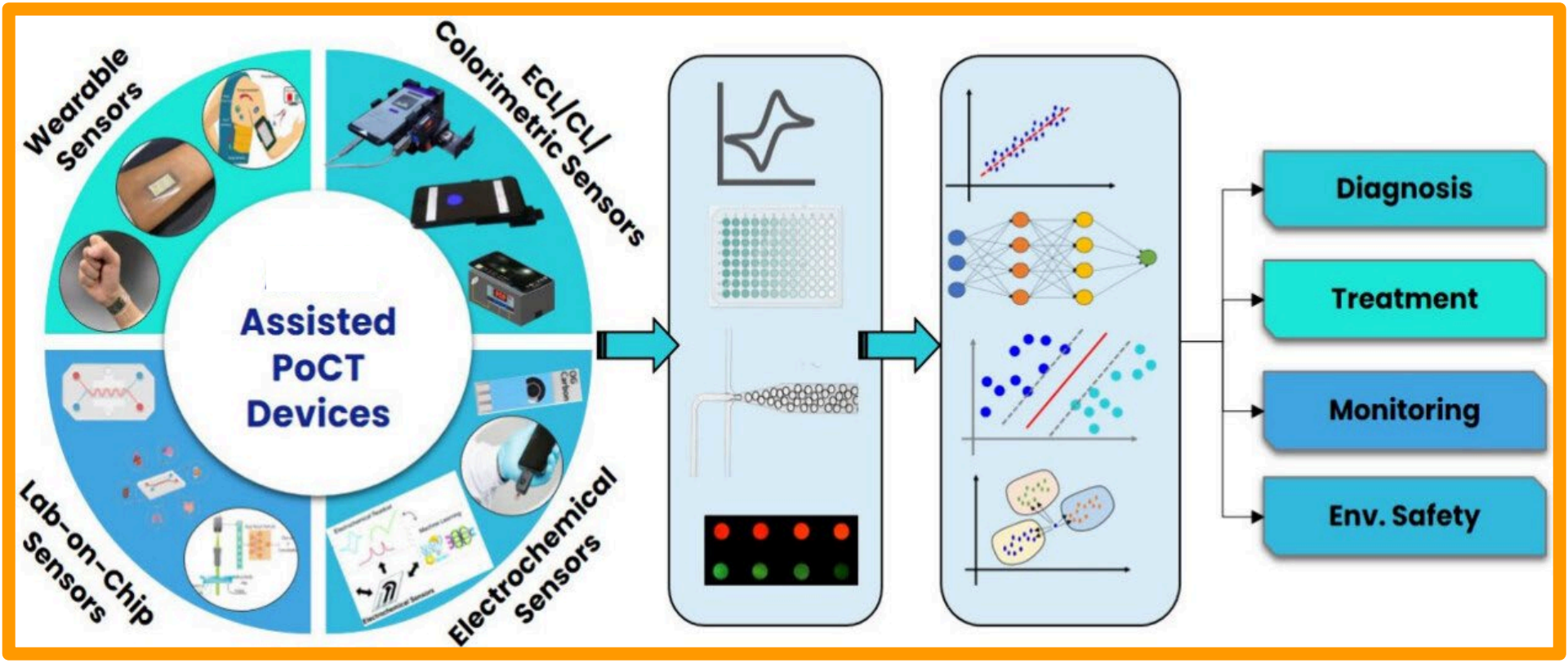
McLamore ES, Palit Austin **Datta** S, Morgan V, Cavallaro N, Kiker G, Jenkins DM, Rong Y, Gomes C, Claussen J, Vanegas D, Alocilja EC. ***SNAPS: Sensor Analytics Point Solutions for Detection & Decision Support Systems***. Sensors (Basel). 2019 November 13; 19(22):4935. doi: 10.3390/s19224935. PMID: 31766116
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6891700/pdf/sensors-19-04935.pdf

Digital Health Hematology Services (DHHS)

not if, but when

Data-Informed Decision Support (DIDS) Systems
Distributed Secure Near Real-time Mobile Digital Health Services

Digital Health and Healthcare Services



Manish Bhaiyya, Debdatta Panigrahi, Prakash Rewatkar, and Hossam Haick (2024) **Role of Machine Learning Assisted Biosensors in Point-of-Care-Testing For Clinical Decisions.** *ACS Sensors* DOI: 10.1021/acssensors.4c01582

https://mdpnp.mgh.harvard.edu/saams-center/

Goldman JM, Weininger S, Jaffe MB. (2020) *Applying Medical Device Informatics to Enable Safe and Secure Interoperable Systems: Medical Device Interface Data Sheets.* Anesthesia and Analgesia 2020 Sep;131(3):969-976. **PMID: 31804406**

Will DHHS (cartoon) evolve to SAMS-HIL (semi-autonomous medical systems with humans in the loop) ?

hematology.org/newsroom/press-releases/2023/studies-highlight-impacts-of-applying-new-technologies-in-everyday-care

Helping hematologists conquer blood diseases worldwide

About ASH ASH Foundation

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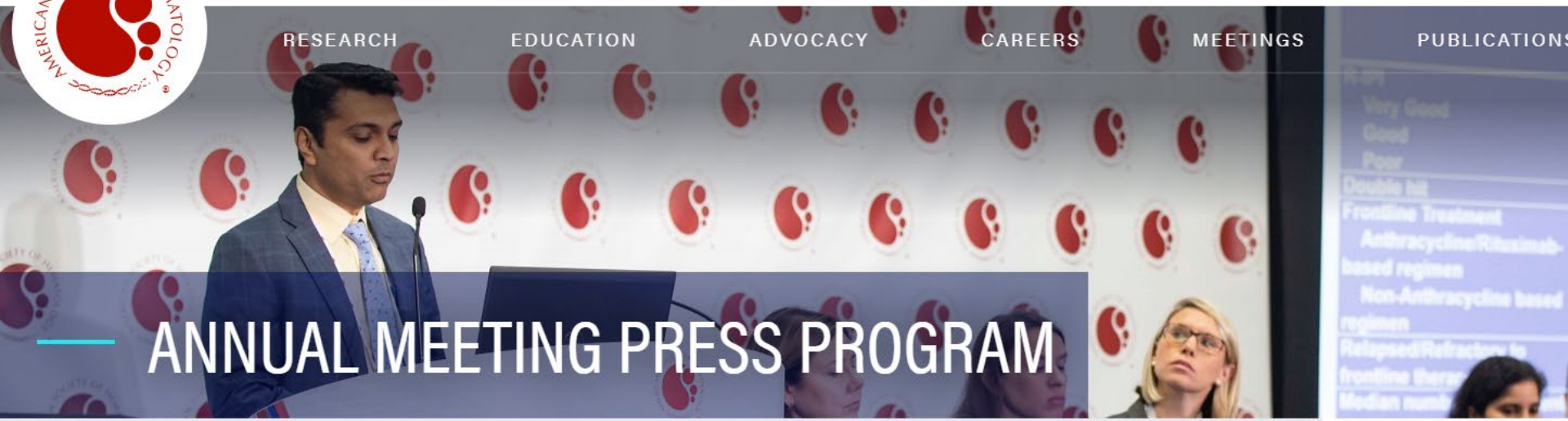


AMERICAN SOCIETY OF HEMATOLOGY / NEWSROOM / PRESS RELEASES / STUDIES HIGHLIGHT IMPACTS OF APPLYING NEW TECHNOLOGIES IN EVERYDAY CARE

Studies Highlight Impacts of Applying New Technologies in Everyday Care

CITATION

PUBLISHED ON:

DEC 09 2023

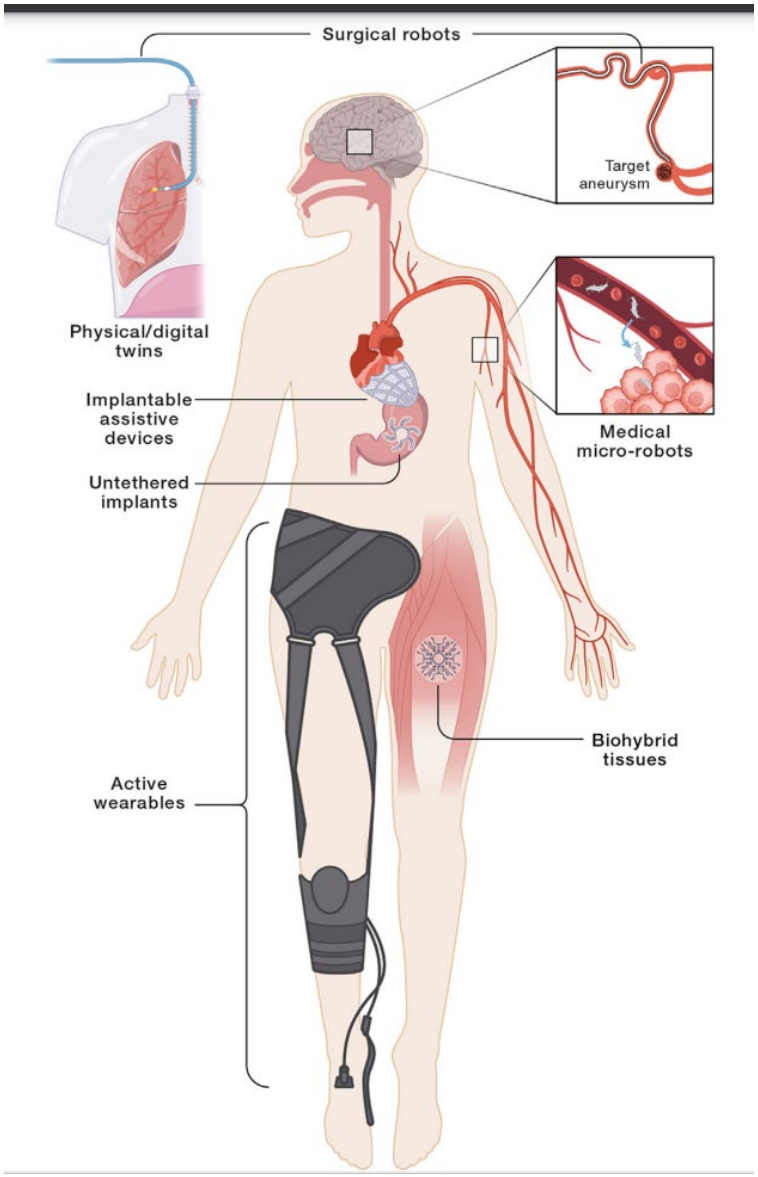
Digital Health : The new BMI ??

Body-Machine Interface (BMI)

not if, but when

Data-Informed Decision Support (DIDS) Systems
Distributed Secure Near Real-time Mobile Digital Health Services

https://meche.mit.edu/people/faculty/ritur%40mit.edu



Therapeutic interventions *in vivo* to provide longitudinal health monitoring & modulation

Soft robotics for human health

Ritu Raman[1,*] and Cecilia Laschi[2,*]

[1]Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA
[2]Department of Mechanical Engineering, National University of Singapore, Singapore, Singapore
*Correspondence: ritur@mit.edu (R.R.), mpeclc@nus.edu.sg (C.L.)

https://doi.org/10.1016/j.device.2024.100432

SOFT

SOFT

meche.mit.edu/people/faculty/etr@mit.edu

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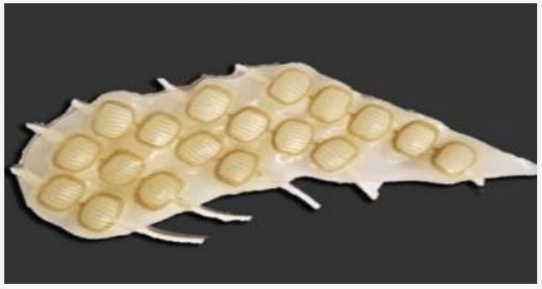
Associate Professor

Ellen Roche

Latham Family Career Development Professor

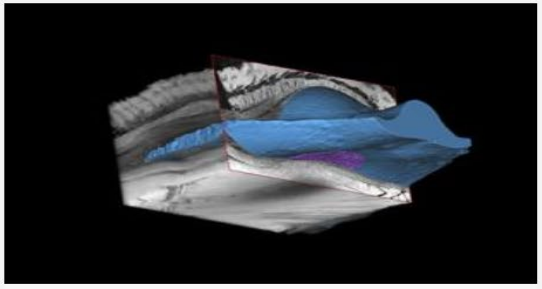
INTERESTS

1. Medical Devices
2. Soft Robotics
3. Therapy Delivery



Engineers design bionic "heart" for testing prosthetic valves, other cardiac devices

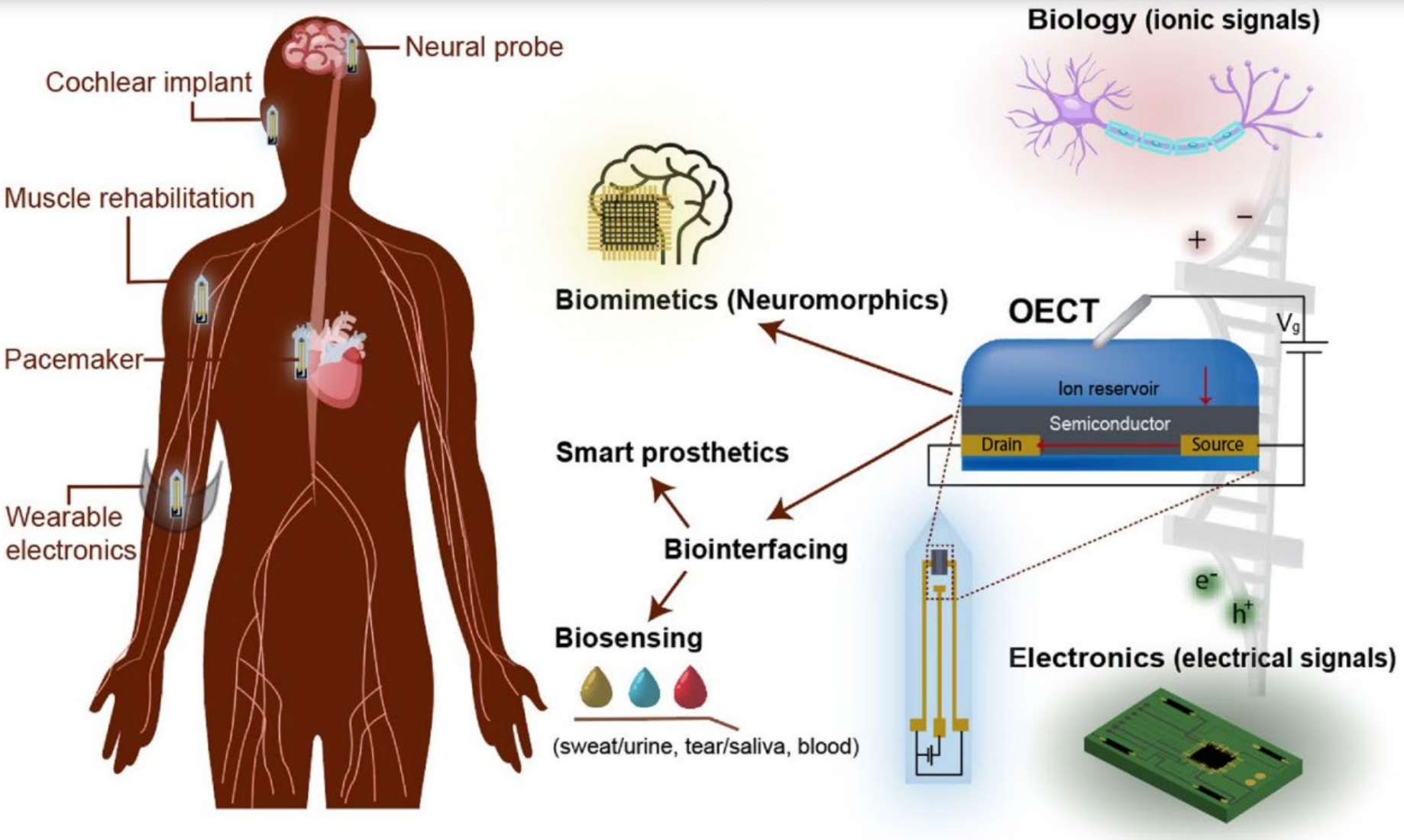
Blending medicine and mechanical engineering



Soft robotics breakthrough manages immune response for implanted devices

Body-Machine Interface (in a material world)

https://dmse.mit.edu/faculty/aristide-gumyusenge



Roh, H., Cunin, C., Samal, S. *et al.* **Towards organic electronics that learn at the body-machine interface: A materials journey.** *MRS Communications* **12**, 565–577 (2022). https://doi.org/10.1557/s43579-022-00269-3

Is this the soul of BMI (body-machine interface) ? Bio-sensing using organic electrochemical transistors

https://dmse.mit.edu/faculty/aristide-gumyusenge ● https://www.aristide.mit.edu

https://docs.google.com/document/d/e/2PACX-1vSJplrGJdAe40FKzeA_pb85Haumn0ZNh-oIKHbb-QRPnUeJMt_fHulub89ZzP-jug/pub

What is the question? Only good questions will unlock the potential of convergence.

CONVERGE ?

Population genetics (local, global)
from metabolomic data acquired
from blood bank (blood donors)
and blood (cord) bank samples

with

BMI (body-machine interface) data

Cellular senescence is a stress response that elicits a permanent cell cycle arrest and triggers phenotypic changes, e.g., production of a bioactive secretome, referred to as the senescence-associated secretory phenotype (**SASP**). Acute senescence induction protects against cancer and limits fibrosis, but lingering senescent cells drive age-related disorders. Targeting senescent cells to delay aging and limit dysfunction, known as “senotherapy,” could be a fool’s errand. Yet, drugs that selectively kill senescent cells, termed “senolytics” are gaining momentum. SASP-centered molecules are targets for senescence-associated diseases. Should we target these molecules, too?

What type of metabolome ?

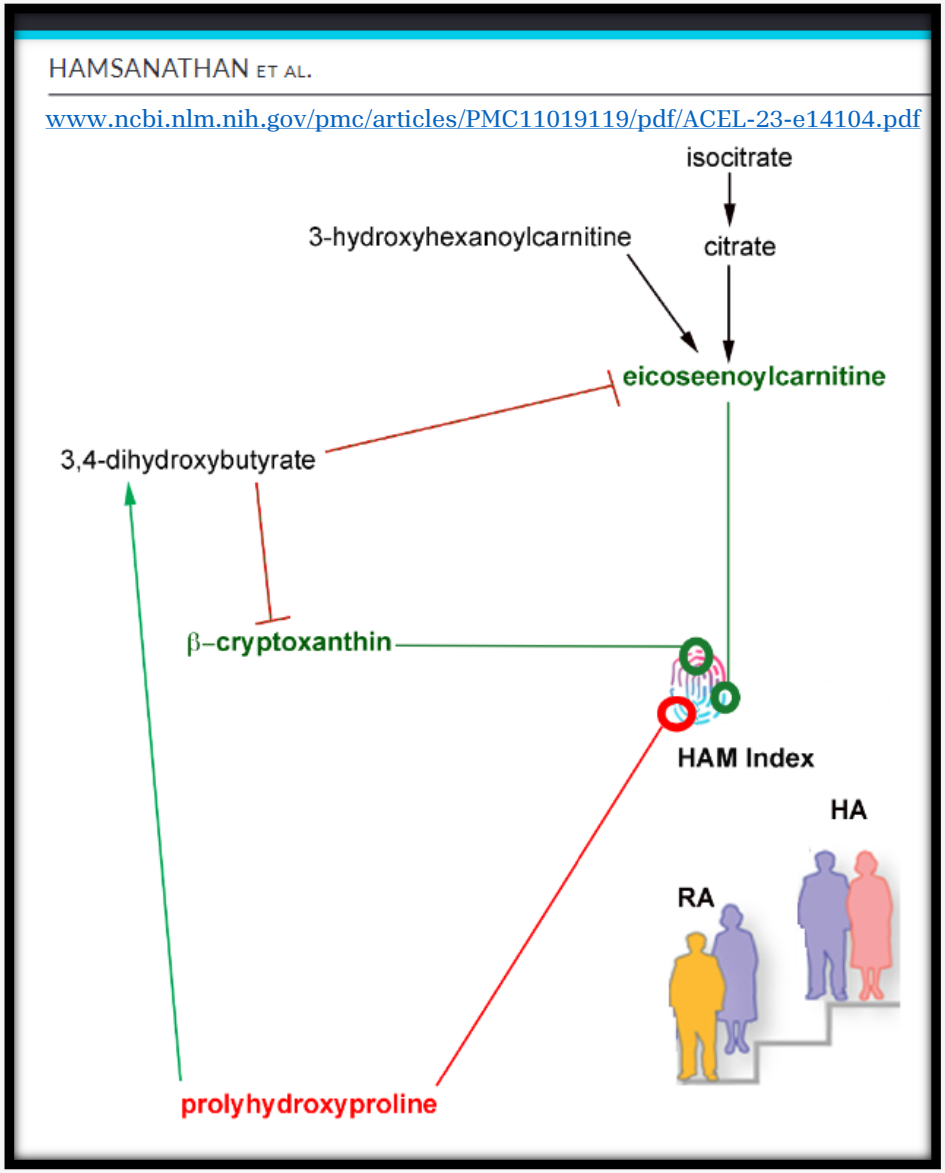
Clues for target molecules ?

Molecular fingerprint from senescence-associated

secretome phenotype (SASP) / inflammation markers

Birch J, Gil J. (2020) **Senescence and the SASP: many therapeutic avenues.** Genes Dev. 2020 Dec 1; 34(23-24):1565-1576. doi: 10.1101/gad.343129.120. PMID: 33262144
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7706700/pdf/1565.pdf

Hamsanathan S, Anthonymuthu T, Prosser D, Lokshin A, Greenspan SL, Resnick NM, Perera S, Okawa S, Narasimhan G, Gurkar AU. **A molecular index for biological age identified from the metabolome and senescence-associated secretome in humans.** Aging Cell. 2024 April; 23(4):e14104. doi: 10.1111/acel.14104. Epub 2024 March 7. PMID: 38454639; PMCID: PMC11019119.



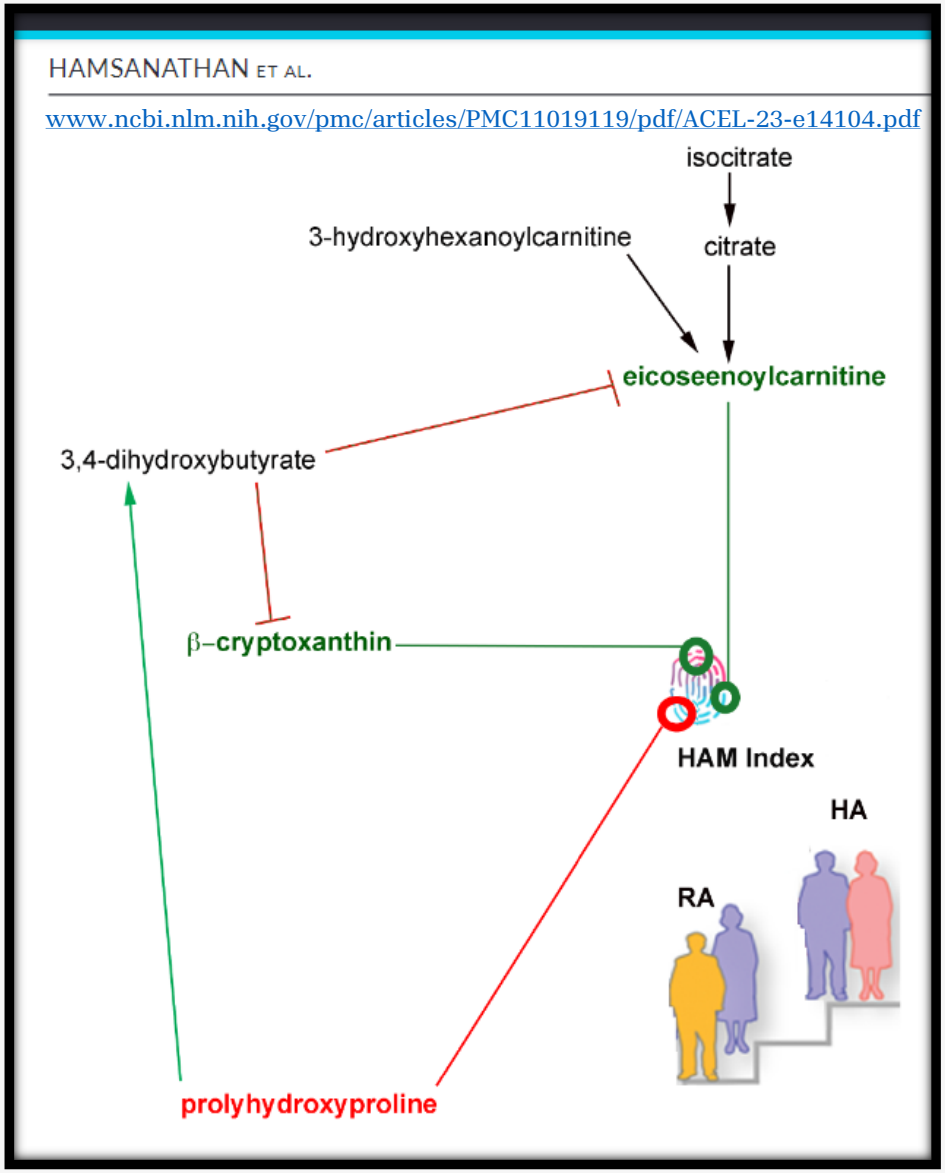
CAUSAL (??) METABOLITES FOR BIOLOGICAL AGING ?

Eicosenoylcarnitine and β-cryptoxanthin were positively causal to the healthy aging metabolic (HAM) index (HAMI) whereas prolyhydroxyproline had a negative impact on HAMI. Other metabolites, for example, 3,4 dihydroxybutyrate were seen to negatively impact β-cryptoxanthin and eicosenoylcarnitine. Prolyhydroxyproline was identified to positively influence 3,4 dihydroxybutyrate, suggesting cross talk between these group of metabolites (implicated in HAM and biological aging).

Could these molecules also serve as targets for testing donor blood samples?

https://onlinelibrary.wiley.com/doi/epdf/10.1111/acel.14104

Hamsanathan S, Anthonymuthu T, Prosser D, Lokshin A, Greenspan SL, Resnick NM, Perera S, Okawa S, Narasimhan G, Gurkar AU. **A molecular index for biological age identified from the metabolome and senescence-associated secretome in humans.** Aging Cell. 2024 April; 23(4):e14104. doi: 10.1111/acel.14104. Epub 2024 March 7. PMID: 38454639; PMCID: PMC11019119.



CAUSAL (??) METABOLITES FOR BIOLOGICAL AGING ?

Could these molecules also serve as targets for testing donor blood samples?

Can we envision a longitudinal epidemiological study where we test for these metabolites in stored blood samples from repeat blood donors in blood banks, locally and globally?

Will such analyses provide time series metabolomic data on the dynamics of these metabolites?

Can such data reveal target molecules for future cellular and molecular therapies?

https://onlinelibrary.wiley.com/doi/epdf/10.1111/acel.14104

MORE MOLECULAR TARGETS

PROTEIN CLOCKS

Blood test uses 'protein clock' to predict risk of Alzheimer's and other diseases

www.nature.com/articles/s41591-024-03164-7
www.nature.com/articles/d41586-024-02576-2
www.nature.com/articles/s41586-023-06802-1

Are your organs ageing well? The blood holds clues

Max Kozlov

Nature | **News** | 06 Dec 2023

Nat Med. 2024 Aug 8. doi: 10.1038/s41591-024-03164-7. Online ahead of print.

Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations

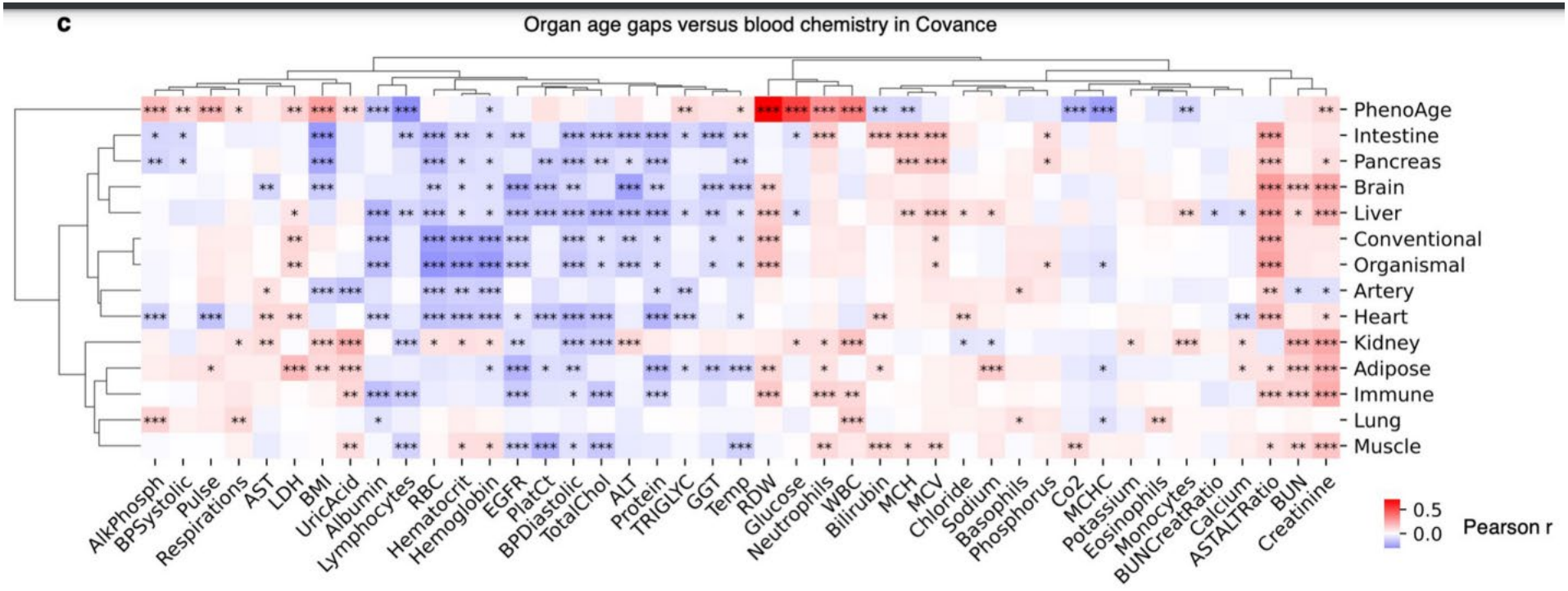
Plasma proteins play key roles in health and may be used to measure biological age, allowing risk prediction for age-related diseases, multimorbidity and mortality. A proteomic age clock in the UK Biobank (n = 45,441) used proteomic platform comprising 2,897 plasma proteins and explored its utility to predict disease morbidity and mortality. **204** proteins that predict chronological age (Pearson r = 0.94) was associated with the incidence of 18 chronic diseases (heart, liver, kidney and lung, diabetes, cancer and neurodegeneration), as well as with multimorbidity.

20 PROTEIN MODEL (2024)
MOLECULAR TARGETS FOR BLOOD ANALYSES?

204 proteins was then reduced to **20** most indicative proteins - it predicted age almost as well as the 204-protein clock did. The 20 proteins included elastin and collagen (support structure between cells), and proteins involved in immune response and hormone regulation.

Argentieri MA, Xiao S, Bennett D, Winchester L, Nevado-Holgado AJ, Ghose U, Albukhari A, Yao P, Mazidi M, Lv J, Millwood I, Fry H, Rodosthenous RS, Partanen J, Zheng Z, Kurki M, Daly MJ, Palotie A, Adams CJ, Li L, Clarke R, Amin N, Chen Z, van Duijn CM. 2024) **Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations.** Nat Med. 2024 August 8. doi: 10.1038/s41591-024-03164-7. Epub ahead of print. PMID: 39117878.

BLOOD CHEMISTRY (2022)
43 clinical markers of health/disease



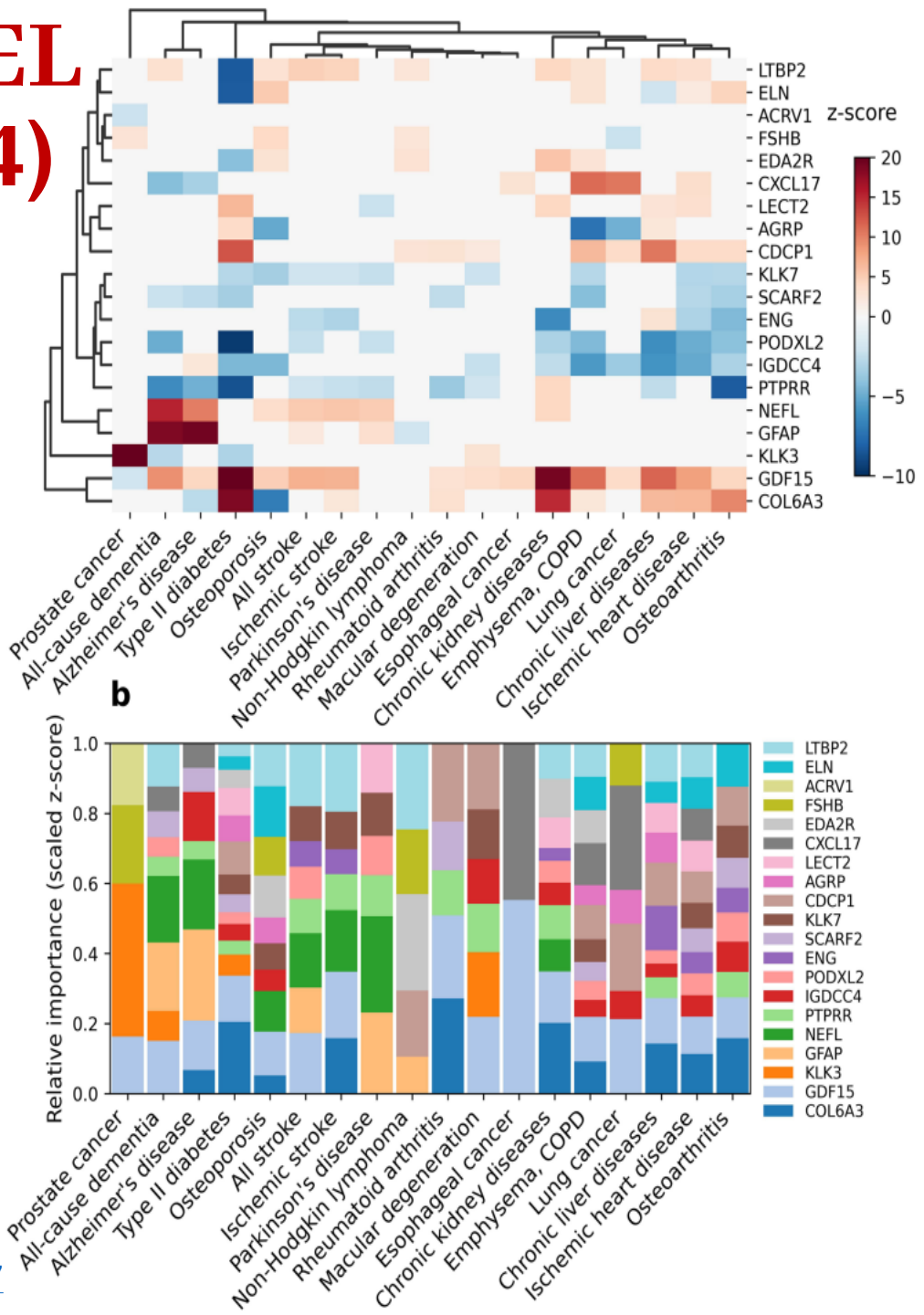
Oh HS, Rutledge J, Nachun D, Pálovics R, Abiose O, Moran-Losada P, Channappa D, Urey DY, Kim K, Sung YJ, Wang L, Timsina J, Western D, Liu M, Kohlfeld P, Budde J, Wilson EN, Guen Y, Maurer TM, Haney M, Yang AC, He Z, Greicius MD, Andreasson KI, Sathyan S, Weiss EF, Milman S, Barzilai N, Cruchaga C, Wagner AD, Mormino E, Lehallier B, Henderson VW, Longo FM, Montgomery SB, Wyss-Coray T. ***Organ aging signatures in the plasma proteome track health and disease.*** Nature. 2023 December; 624(7990):164-172. doi: 10.1038/s41586-023-06802-1. Epub 2023 December 6. PMID: 38057571; PMCID: PMC10700136.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10700136/pdf/41586_2023_Article_6802.pdf

20 PROTEIN MODEL (BLOOD TEST 2024)

Associations between individual protein markers and each disease studied. For each outcome, a Cox proportional hazards model (n = 45,441) was calculated with all 20 proteins from the proteomic age clock 20 proteins model (ProtAgeGap20) score, adjusted for age, sex (except prostate cancer), ethnicity, Townsend deprivation index, recruitment center, IPAQ activity group, smoking status.

TOP - association between each protein and incident disease is colored by z-score.

BOTTOM - importance of each significant protein with a relative contribution.



www.nature.com/articles/s41591-024-03164-7

Hence, it bears to be reiterated …

CONVERGE

Population genetics (local, global) from metabolomic data acquired from blood bank (blood donors) and blood (cord) bank samples

with

BMI (body-machine interface) data, proteomic markers of health and disease predictors, etc.

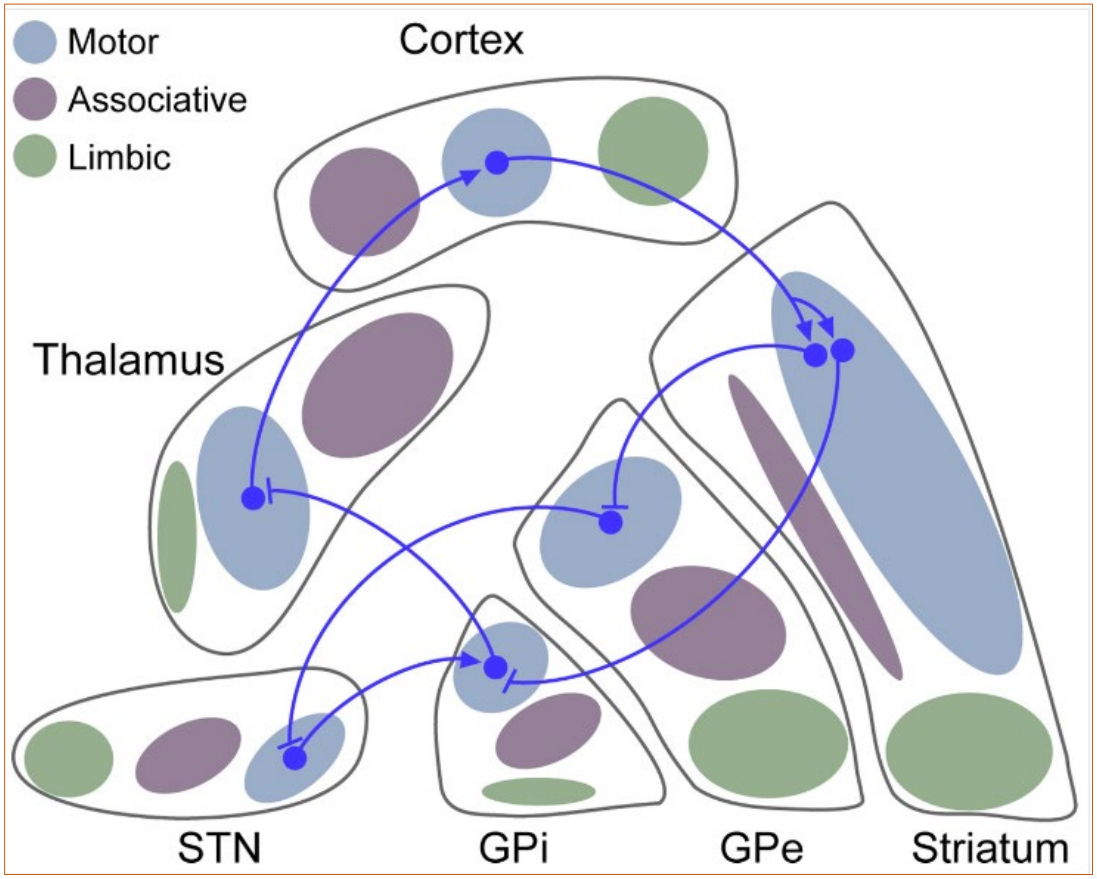
Invention?
Innovation??

*connecting **“spaces unrelated”** to catalyze discovery*

CROSS-POLLINATE ?

CONVERGE ?

- *Connecting* ***“spaces unrelated”*** *to catalyze discovery?*



SENSE OF FUTURE THINKING

SOFT

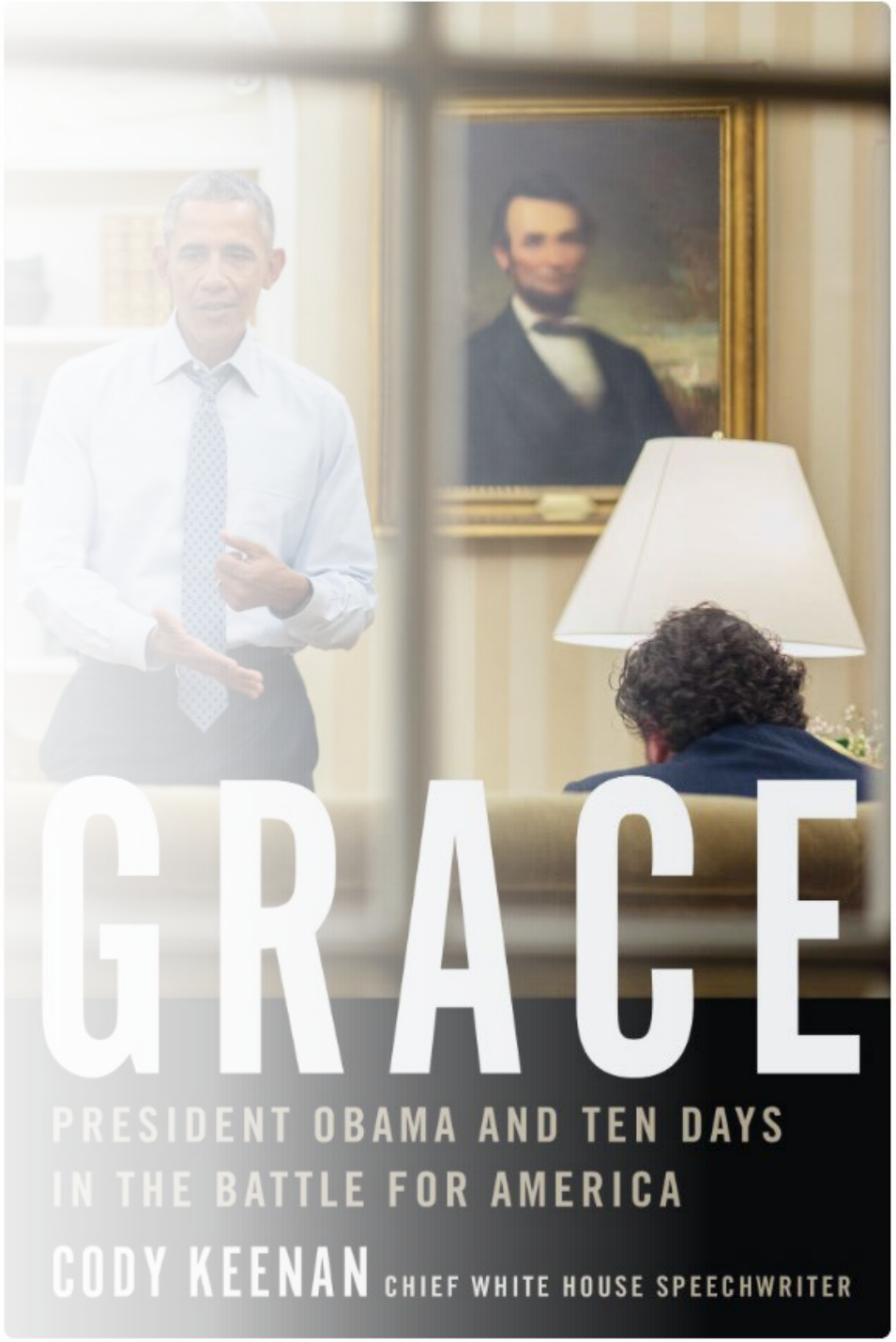
it is

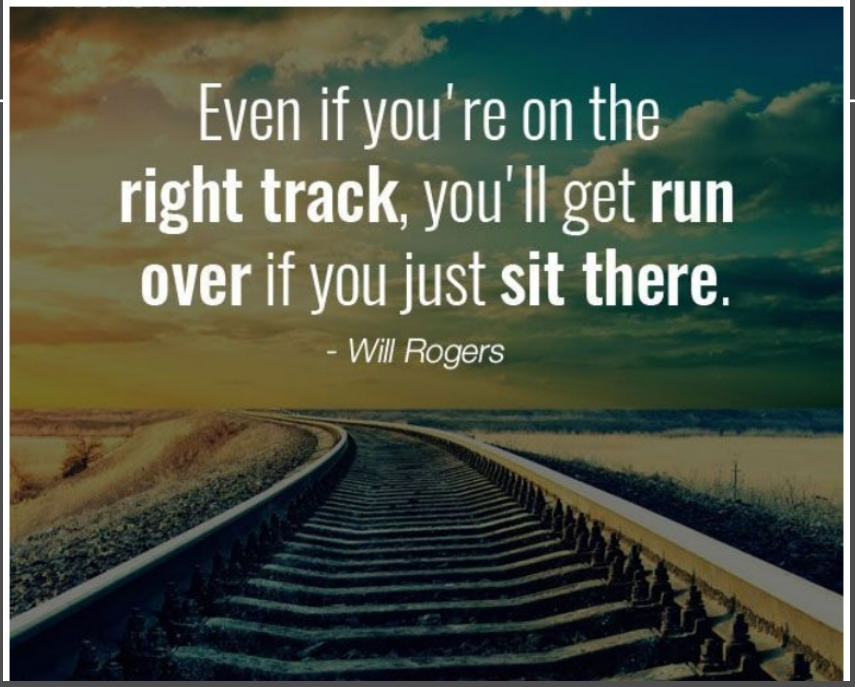
HARD

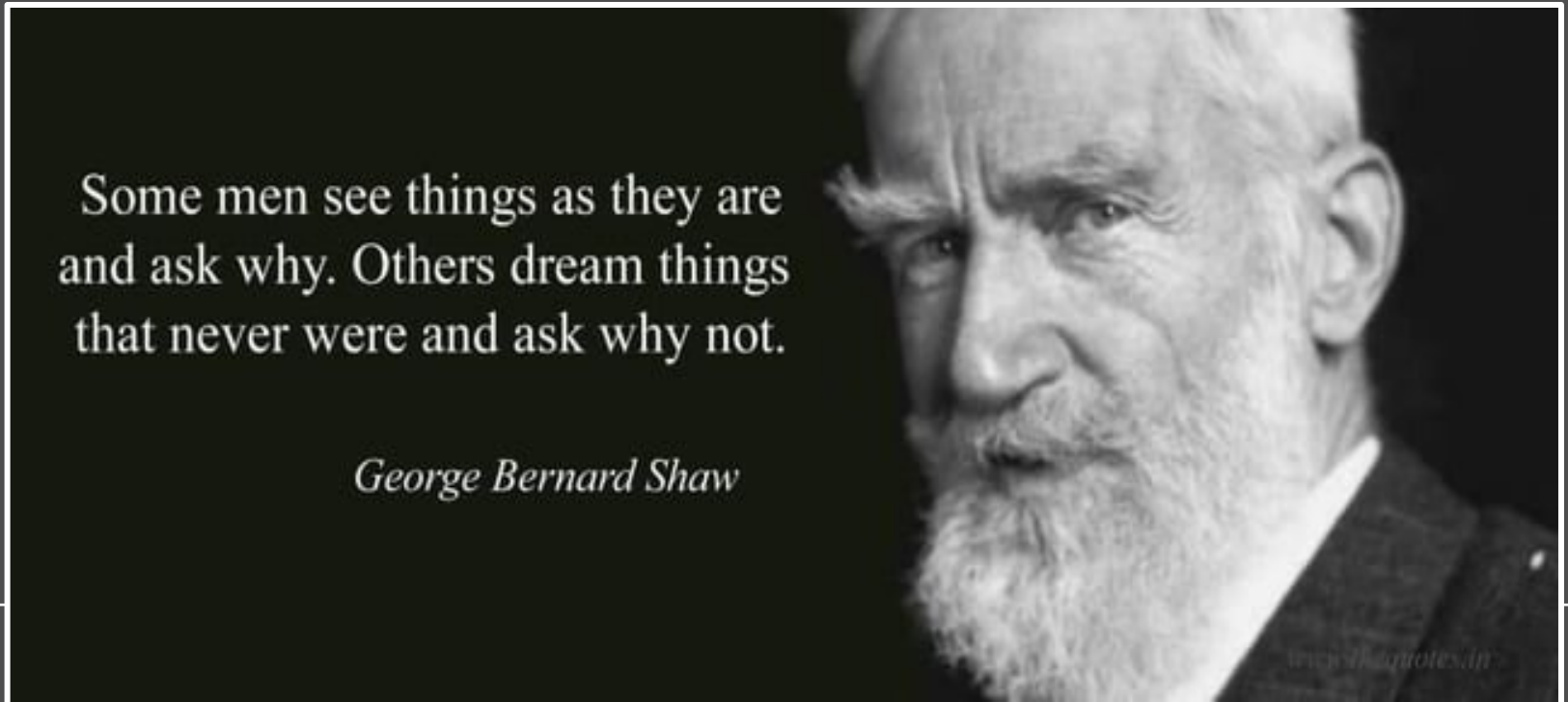
Healthcare-Associated Research & Development

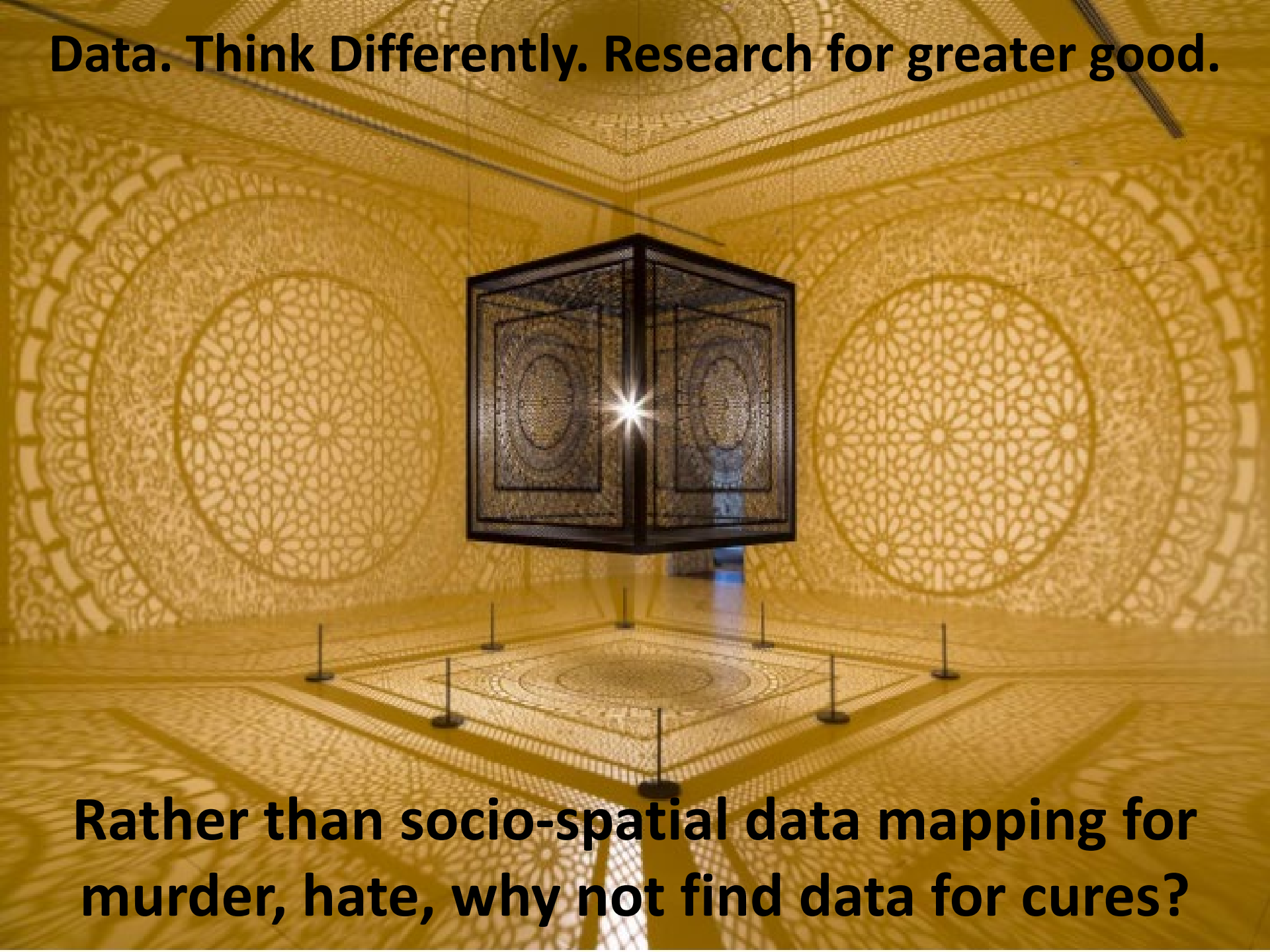
“FOCUS ON PURPOSE, NOT YOUR TITLE.”

“Worry less about what you want to be and think more about what you want to do.” Focus on purpose, for example, helping save lives and you’ll always have an impact, even if it is a drop in the ocean of need.




Even if you're on the
right track, you'll get run
over if you just sit there.
- Will Rogers


Some men see things as they are
and ask why. Others dream things
that never were and ask why not.
George Bernard Shaw


Data. Think Differently. Research for greater good.
Rather than socio-spatial data mapping for murder, hate, why not find data for cures?

DON’T MAKE THIS MISTAKE WITH DATA

PLEASE DON’T LET

AI

CORRUPT AND RUIN YOUR DATA ANALYTICS

https://www.technologyreview.com/2017/10/06/241837/the-seven-deadly-sins-of-ai-predictions/

MIT Technology Review

https://people.csail.mit.edu/brooks

The Seven Deadly Sins of AI Predictions

Mistaken extrapolations, limited imagination, and other common mistakes that distract us from thinking more productively about the future.

By Rodney Brooks

October 6, 2017

Rodney Brooks is the Panasonic Professor of Robotics (emeritus) at MIT. He is a robotics entrepreneur. Dr. Brooks is the former Director (1997 - 2007) of the MIT Artificial Intelligence Laboratory and then the MIT Computer Science & Artificial Intelligence Laboratory (CSAIL). He received a Ph.D. in Computer Science from Stanford University in 1981. He held research positions at Carnegie Mellon University and MIT, and a faculty position at Stanford before joining the faculty of MIT in 1984. From June 2014 until May 2020 he was a member of the Visiting Committee on Advanced Technology, VCAT, at the National Institute of Standards and Technology, NIST. Since June 2015 he has been an external member of GE's Robotics Advisory Council. From January 2016 until mid 2019 he was Deputy Chairman of the Advisory Board of Toyota Research Institute. From February 2019 until January 2021 he was "Luminary" at Bell Labs. Dr. Brooks is a Member of the National Academy of Engineering (NAE), a Founding Fellow of the Association for the Advancement of Artificial Intelligence (AAAI), a Fellow of the American Academy of Arts & Sciences (AAAS), a Fellow of the American Association for the Advancement of Science (the other AAAS), a Fellow of the Association for Computing Machinery (ACM), a Fellow of the Institute of Electrical and Electronics Engineers (IEEE), a Member of the Australian Academy of Science (AAS) and a Fellow of the Australian Academy of Technological Sciences and Engineering (ATSE).

Don’t subject your data to hallucinations

twitter.com/rodneyabrooks/status/1794814225015325154

← **Post**

Rodney Brooks ✓
@rodneyabrooks

The talk about hallucinations in LLMs has gotten it all wrong. The true hallucinations are by company execs who think it is OK to release to general users products that are based on LLMs that confabulate wildly, as all LLMs do. Time will show a high price paid by society.

3:33 PM · May 26, 2024 · **29K** Views

27 85 301 54

Post your reply **Reply**

Gilgamesh Akkadian @WYSnotWYG · 22s
arxiv.org/abs/2402.03927
arxiv.org/pdf/2402.03927

Leak, Cheat, Repeat: Data Contamination and Evaluation Malpractices in Closed-Source LLMs

Simone Balloccu Patrícia Schmidtová Mateusz Lango Ondřej Dušek
Charles University, Faculty of Mathematics and Physics
Institute of Formal and Applied Linguistics
Prague, Czech Republic
{balloccu,schmidtova,lango,odusek}@ufal.mff.cuni.cz

Who is Rodney Brooks? ● https://people.csail.mit.edu/brooks

www.nature.com/articles/d41586-024-02420-7

www.nature.com/articles/s41586-024-07566-y

nature.com/articles/d41586-024-02420-7

nature

AI ... naturally nonsensical

NEWS | 24 July 2024

AI models fed AI-generated data quickly spew nonsense

Researchers gave successive versions of a large language model information produced by previous generations of the AI – and observed rapid collapse.

By Elizabeth Gibney

www.nature.com/articles/d41586-024-02420-7

www.nature.com/articles/s41586-024-07566-y

Article

AI models collapse when trained on recursively generated data

https://doi.org/10.1038/s41586-024-07566-y

Received: 20 October 2023

Accepted: 14 May 2024

Published online: 24 July 2024

Open access

Check for updates

Ilia Shumailov[1,8]✉, Zakhar Shumaylov[2,8]✉, Yiren Zhao[3], Nicolas Papernot[4,5], Ross Anderson[6,7,9] & Yarin Gal[1]✉

Stable diffusion revolutionized image creation from descriptive text. GPT-2 (ref. 1), GPT-3(.5) (ref. 2) and GPT-4 (ref. 3) demonstrated high performance across a variety of language tasks. ChatGPT introduced such language models to the public. It is now clear that generative artificial intelligence (AI) such as large language models (LLMs) is here to stay and will substantially change the ecosystem of online text and images. Here we consider what may happen to GPT-{*n*} once LLMs contribute much of the text found online. We find that indiscriminate use of model-generated content in training causes irreversible defects in the resulting models, in which tails of the original content distribution disappear. We refer to this effect as 'model collapse' and show that it can occur in LLMs as well as in variational autoencoders (VAEs) and Gaussian mixture models (GMMs). We build theoretical intuition behind the phenomenon and portray its ubiquity among all learned generative models. We demonstrate that it must be taken seriously if we are to sustain the benefits of training from large-scale data scraped from the web. Indeed, the value of data collected about genuine human interactions with systems will be increasingly valuable in the presence of LLM-generated content in data crawled from the Internet.

What to do with ideas & uncorrupted data from research outcomes?

Here's one option, perhaps …

techcrunch.com/2024/04/06/when-it-comes-to-building-startups-in-boston-success-begets-success/

When it comes to building startups in Boston, success begets success

And from HubSpot to Klaviyo, it's had its share of successful exits

Ron Miller @ron_miller / 1:07 PM EDT • April 6, 2024

Comment

INNOVATE

https://techcrunch.com/2024/04/06/when-it-comes-to-building-startups-in-boston-success-begets-success

How To Lead Change for Good

Collaborate Globally
Create Partnerships
Foster Key Alliances
Aspire to Inspire
Be Exemplary
Credibility
Dignity
Ethics
Teach
Learn
STEM
R&D

kasanoff.com/blog/2017/3/22/the-incredible-power-of-not-taking-credit

The Incredible Power of Not Taking Credit

February 22, 2019 · Leadership, Career

Image by alex mertzanis/Flickr

Nothing limits your ability to achieve great things more than your desire to take credit for what you have achieved. This paradox is at the center of most problems that companies face.

Happiness is key to success. Success is not the key to happiness.

STEM is a quite smart and fetching (catchy) moniker for marketing due to its global semantic cognitive imprint (aka “buzz”), but in education, it ought to become

STEEMM

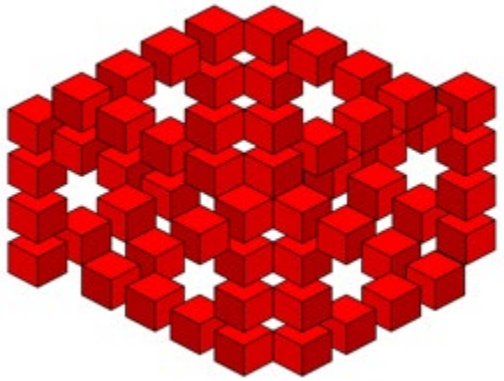
Science ∘ Technology ∘ Engineering ∘ Economics ∘ Medicine ∘ Mathematics

*Utopians will be euphoric with STEEMM**MAHH** with the addition of Music, Arts, Humanities and History, as well.*

DHHS is a sub-section of "The Health of Nations - Part II"

"The Health of Nations" Parts 1, 2, & 3 are in the MIT Library

https://dspace.mit.edu/handle/1721.1/153283



I have created nothing new

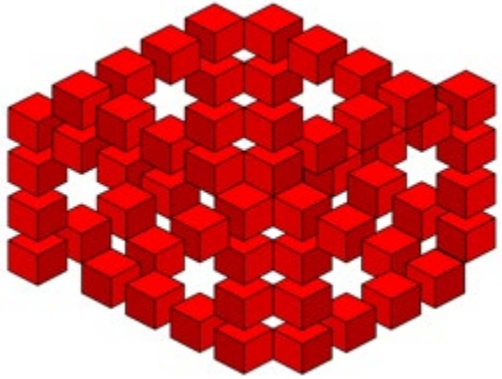
 If you have questions, contact shoumen@mit.edu ▪ sdatta8@mgh.harvard.edu

For information about the author go to https://dspace.mit.edu/handle/1721.1/146158

https://dspace.mit.edu/handle/1721.1/107893

Review "Healthcare" PDF for more cartoons

Forward looking statements and projections in this presentation are neither easy to accomplish nor instantaneous but are possible and credible.



Dr Shoumen Palit Austin Datta

MIT Auto-ID Labs, Senior Member, Affiliate, Department of Mechanical Engineering, Massachusetts Institute of Technology ▪ shoumen@mit.edu

Senior Scientist, MDPnP Lab Medical Device Interoperability, Massachusetts General Hospital, Harvard Medical School ▪ sdatta8@mgh.harvard.edu

NEW BLOOD

www.science.org/content/article/ultimate-blood-substitute-us-military-betting-46-million

THERE WILL BE BLOOD

Is mimicking the cells that carry hemoglobin the key to a blood substitute?

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WILL THERE BE SUFFICIENT BLOOD ?

40% of the global blood supply is collected in high-income countries with < 20% of the world's population.

Ensuring a Safe and Sufficient Global Blood Supply

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A safe and sustainable blood supply remains elusive for many low- and middle-income countries (LMICs). The World Health Organization (WHO) considers blood and blood components to be essential medicines, which underscores their importance to health systems. Essential medicines are products that are deemed to be necessary to meet the health care needs of the majority of the population and therefore must be in adequate supply, accessible, and affordable, with their quality assured. Yet nearly two thirds of countries — including countries in central, eastern, and western sub-Saharan Africa, Oceania, and South Asia — lack sufficient blood to meet clinical demand.[1]

There are substantial disparities in the availability and safety of blood between high-income countries and LMICs. Forty percent of the global blood supply is collected in high-income countries, despite these countries having less than 20% of the world's population.[1] The WHO recommends collecting a minimum of 10 units of blood per 1000 population; as of 2018, the donation rate in high-income countries was 31.5 units per 1000 people, as compared with 6.6 units and 5.0 units per 1000 people in lower-middle-income countries and low-income countries, respectively. Evidence supporting both the WHO's minimum target and the application of a single global target is weak, however. Limited availability of blood in LMICs has meant that transfusion practices differ between high-income countries and LMICs. For example, hemoglobin thresholds for administering transfusions to children are lower in LMICs (4 to 5 g per deciliter) than in high-income countries, although recent trials indicate that this cutoff may be appropriate for some children.[2]

The global blood deficit has wide-ranging adverse effects, given that many clinical disciplines (e.g., obstetrics, pediatrics, hematology, oncology, emergency medicine, and surgery) depend on blood transfusion. There are notable effects on maternal and child health. For example, one quarter of maternal in-hospital deaths caused by peripartum hemorrhage in sub-Saharan Africa have previously been attributed to blood shortages.[3] The Fluid Expansion as Supportive Therapy (FEAST) trial, conducted in Uganda, Kenya, and Tanzania, found that more than half of children who presented with febrile illness and severe anemia (i.e., a hemoglobin level below 5 g per deciliter) died when

Better than nature?

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Decades of efforts have failed to develop a good substitute for oxygen-carrying red blood cells. A new candidate, ErythroMer, is still in preclinical testing but could be more durable and versatile than the real thing.

	Red blood cells	ErythroMer
SHELF LIFE	42 days	2 years
SIZE	7–8 μm	~0.2 μm
COMPATIBILITY	By blood type	Universal

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For now, no human blood substitute is commercially available in the U.S. "There's a real gap here where we don't have access to blood for people bleeding to death outside of the hospital," says Doctor, who co-founded and is chief science officer of KaloCyte, a company hoping to develop ErythroMer into a commercial product.

Universal Medium of Health, Healing, Humanity

~ 5 million Americans will need a blood transfusion each year. Someone needs blood every 2 seconds. 1 in 7 people entering a hospital need blood. ~ 22,000 liters of donated blood used each day, i.e., almost ~ 1,000 liters of blood transfused every hour, every day, every year, to save lives.

www.aha.org/news/headline/2024-01-29-groups-release-updated-statistics-us-blood-donation-use ◆ www.bloodbankofalaska.org/blood-facts

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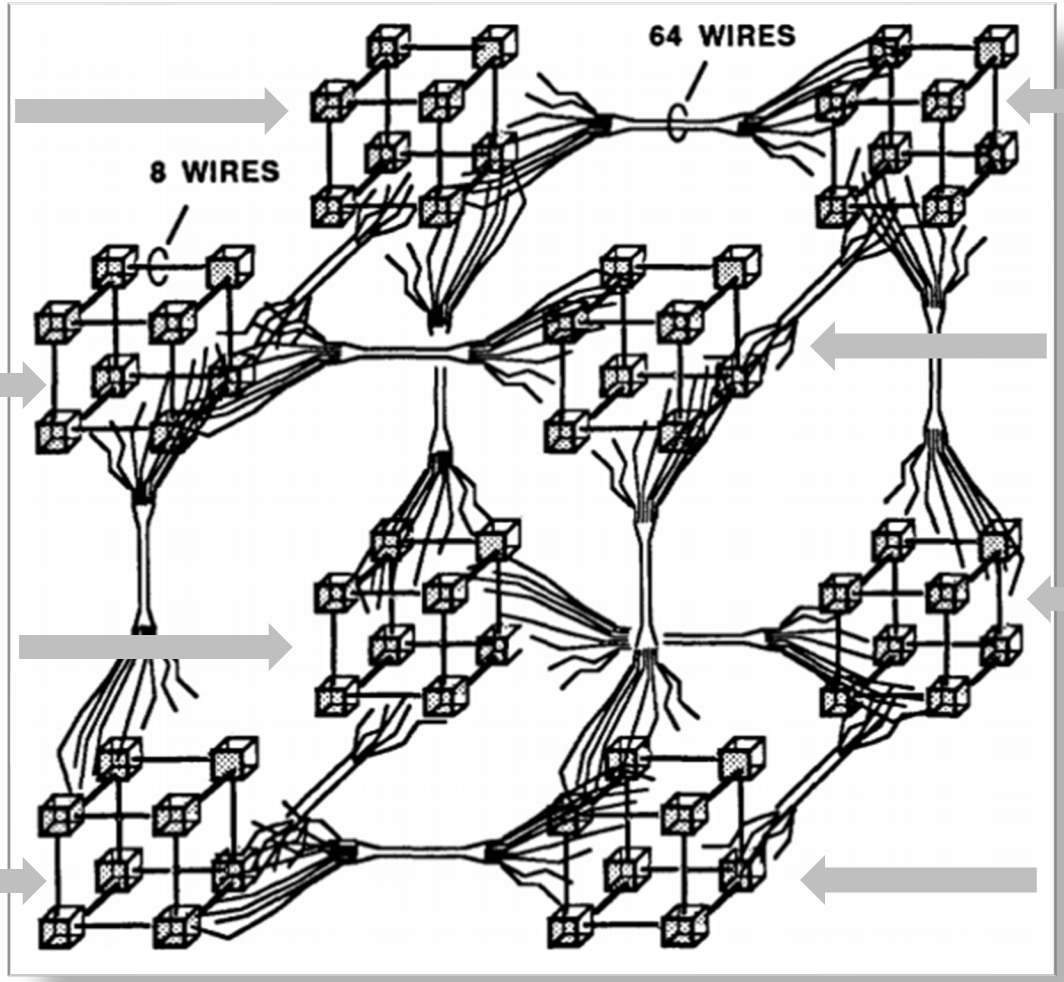

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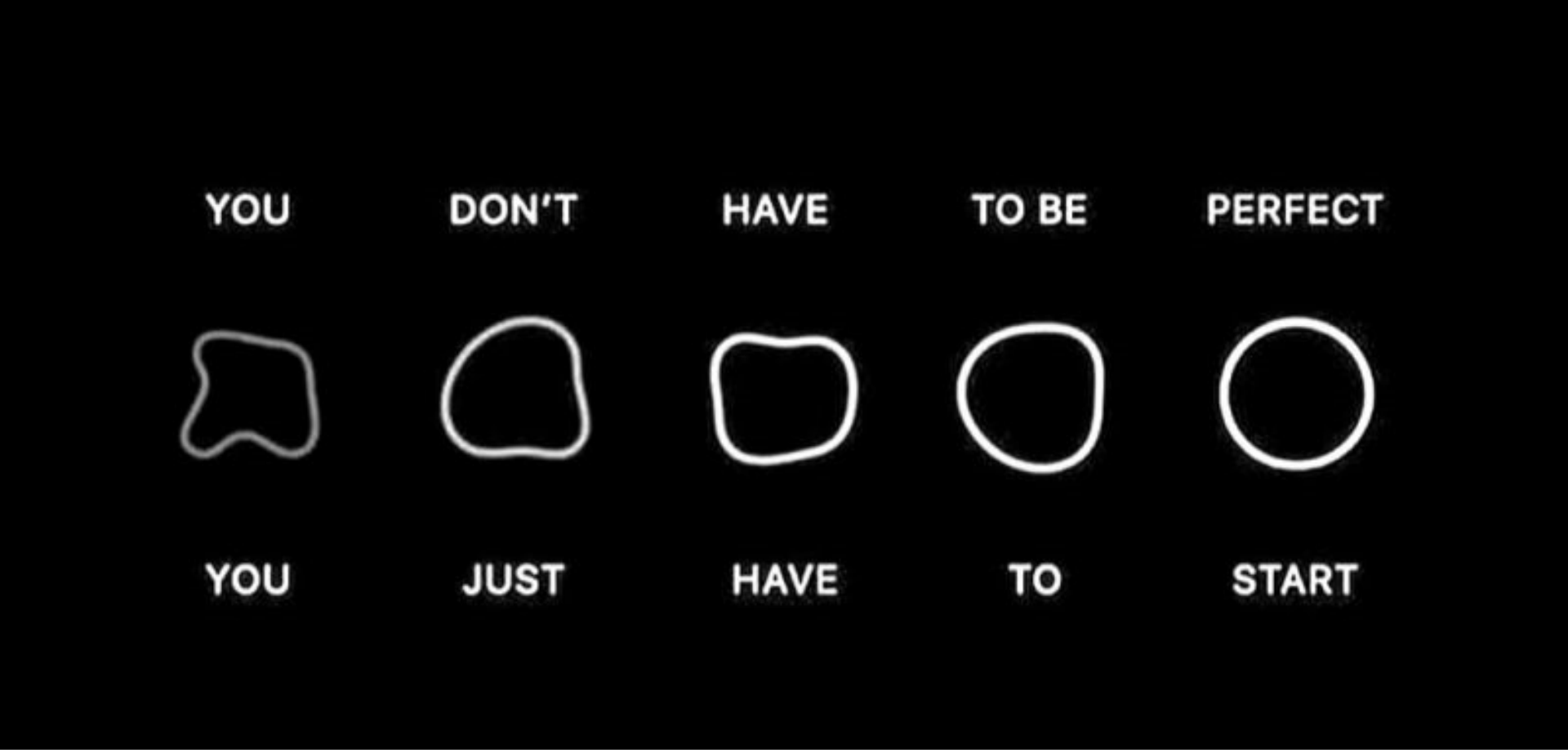

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