City of Hope

2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Investigating the Link Between Metabolic Health, Obesity, and Cancer Risk in Diverse Los Angeles Women

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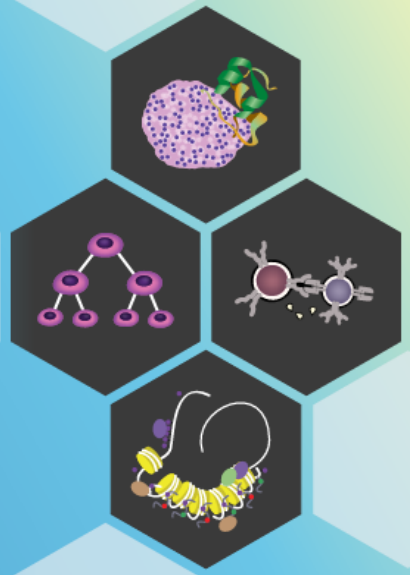
Postdoctoral Research Fellow
T32 Cancer Metabolism Fellow
Dr. Victoria L. Seewaldt Lab
Department of Population Sciences
City of Hope



Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

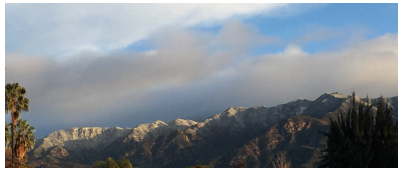
The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

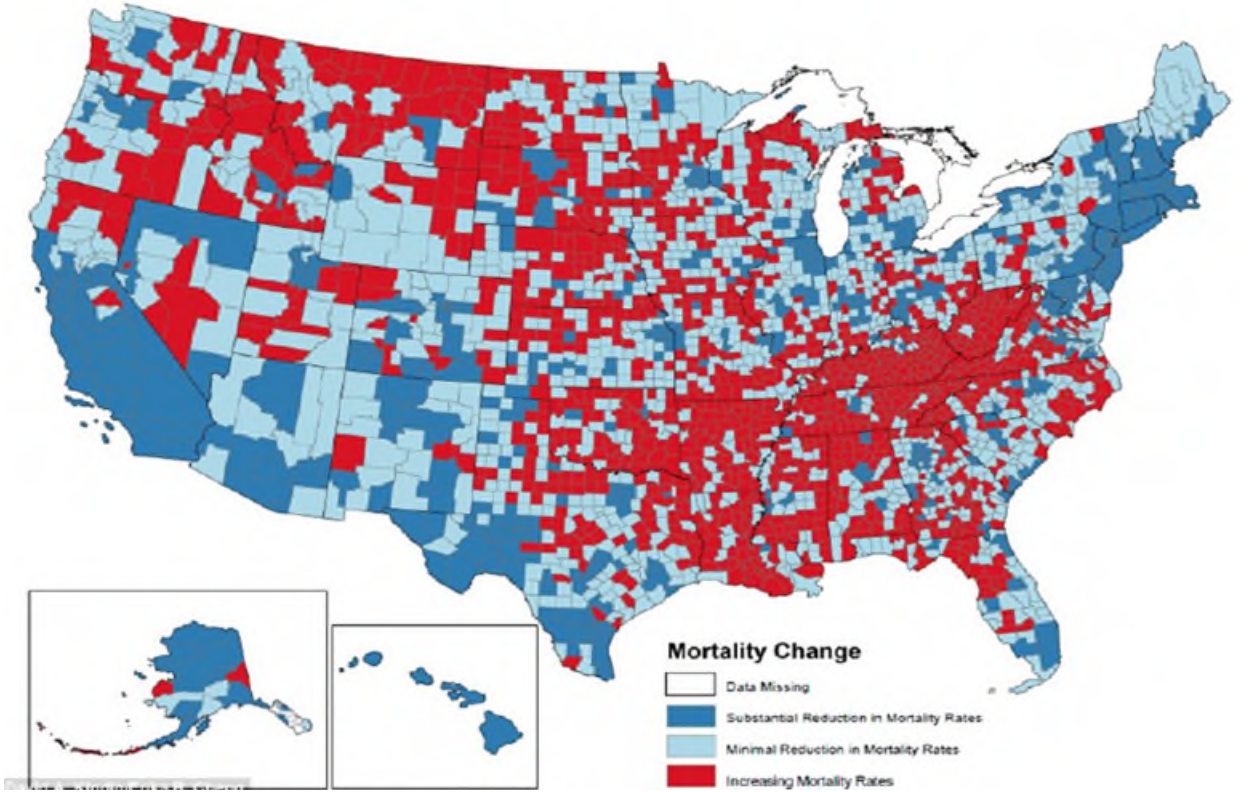
Thank you to our Collaborators


Loretta Erhunmwunsee MD	City of Hope	Environmental Epi - Disparities
Veronica Jones MD	City of Hope	Luminal B Breast Cancer
Lily Lai MD	City of Hope	Clinical trials
Tijana Talisman, PhD	City of Hope	Super-Resolution Microscopy
Michael Press, MD PhD	USC	Biomarkers
Mark LaBarge, PhD	City of Hope	Microenvironment signaling
Dustin Schones, PhD	City of Hope	Epigenetics
Rama Natarajan, PhD	City of Hope	Epigenetics
Rob Winn, MD	VCU	Disparities, lung cancer
Terry Hyslop, PhD	Sidney Kimmel	Multi-Scale Modeling, Disparities
Grace Yao, PhD	Sidney Kimmel	Disparities, biology, and cancer
Lucio Miele MD	LSU	Luminal B breast cancer
Shankar Subramaniam, PhD	UCSD	Systems Biology
Augusto Ochoa MD	LSU	Immunology, Disparities
Ruth O'Regan, MD	U. Rochester	Clinical – Phase I clinical trials
Jean Abrams, MD	Cambridge	Omics, microenvironment
Sheeba Irshad, MD	Kings	Omics, microenvironment
Anita Grigoriadis, PhD	Kings	Microenvironment

Early death in women > 50% US Counties 2006

- David Kindig and Erika Cheng, University of Wisconsin
- Chris Murray, University of Washington

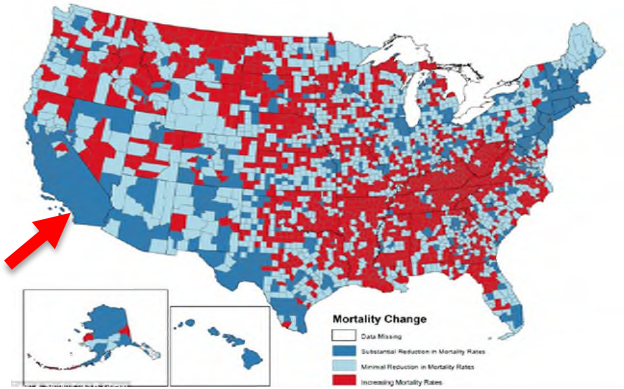


Early death, inactivity, type-2 diabetes

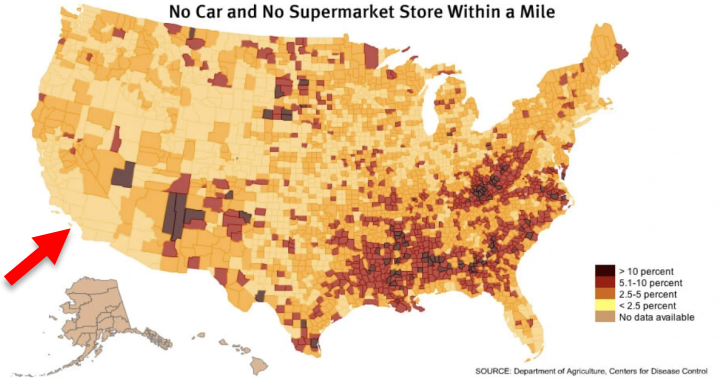
David Kindig and Erika Cheng, University of Wisconsin
Chris Murray, University of Washington

County data does not tell the full story

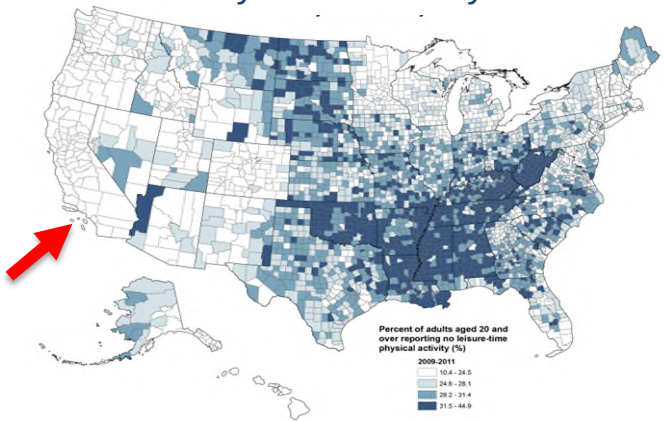
Earlier Age Death Women



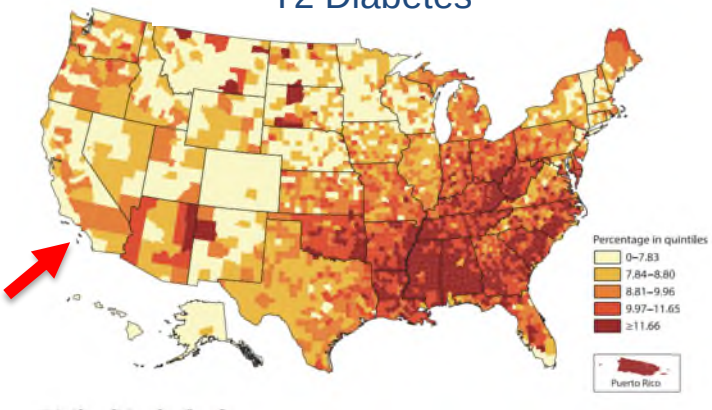
Lack of access to healthy food



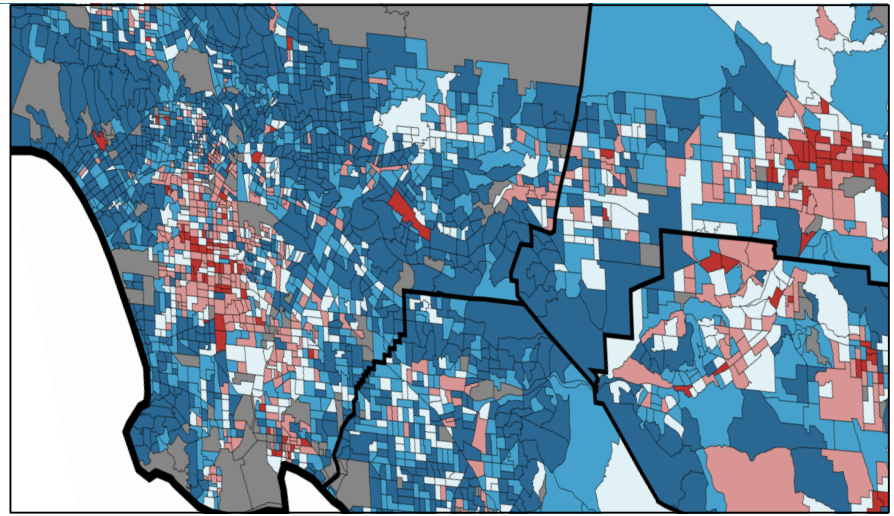
Physical Inactivity

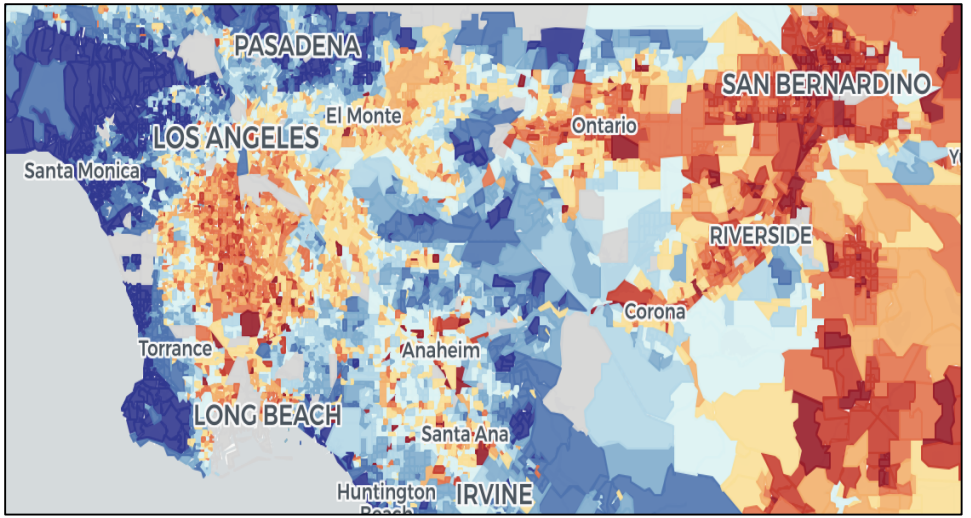


T2 Diabetes

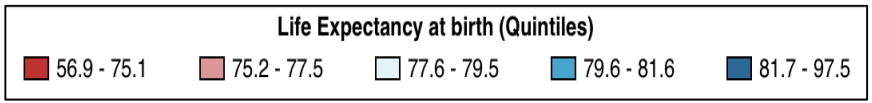


Los Angeles – unequal distribution of life and wealth

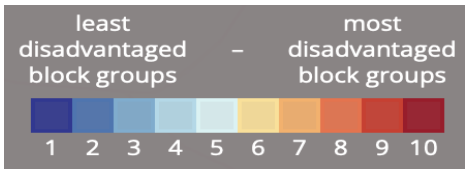




CDC Life Expectancy 2023



Disadvantage Index

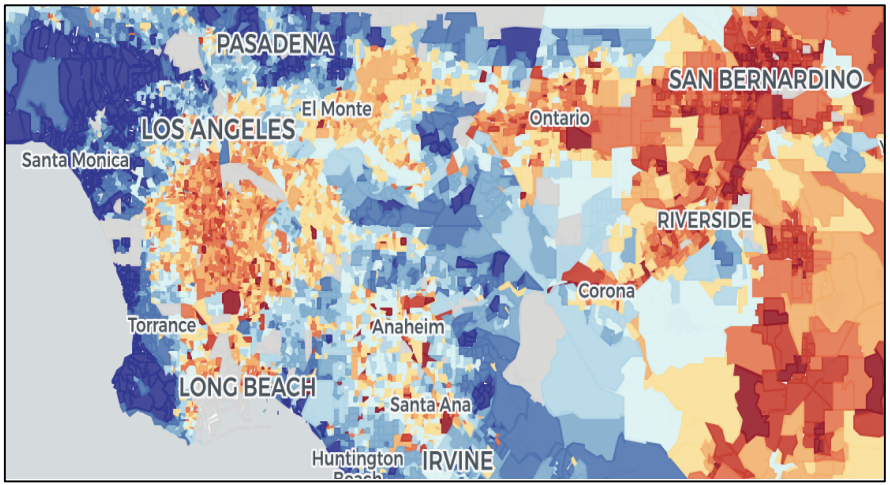


https://www.cdc.gov/nchs/data-visualization/life-expectancy/index.html

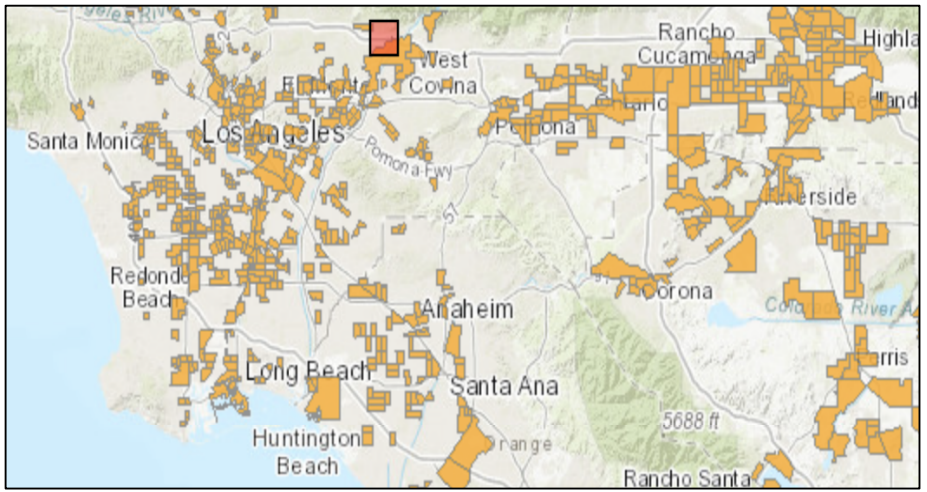
A. Kind and W. Buckingham, NEJM, 2018

Where there is Disadvantage there are Food Deserts

Disadvantage Index



Food Deserts



Defined no source of health food within 1 mile urban and 10 miles rural

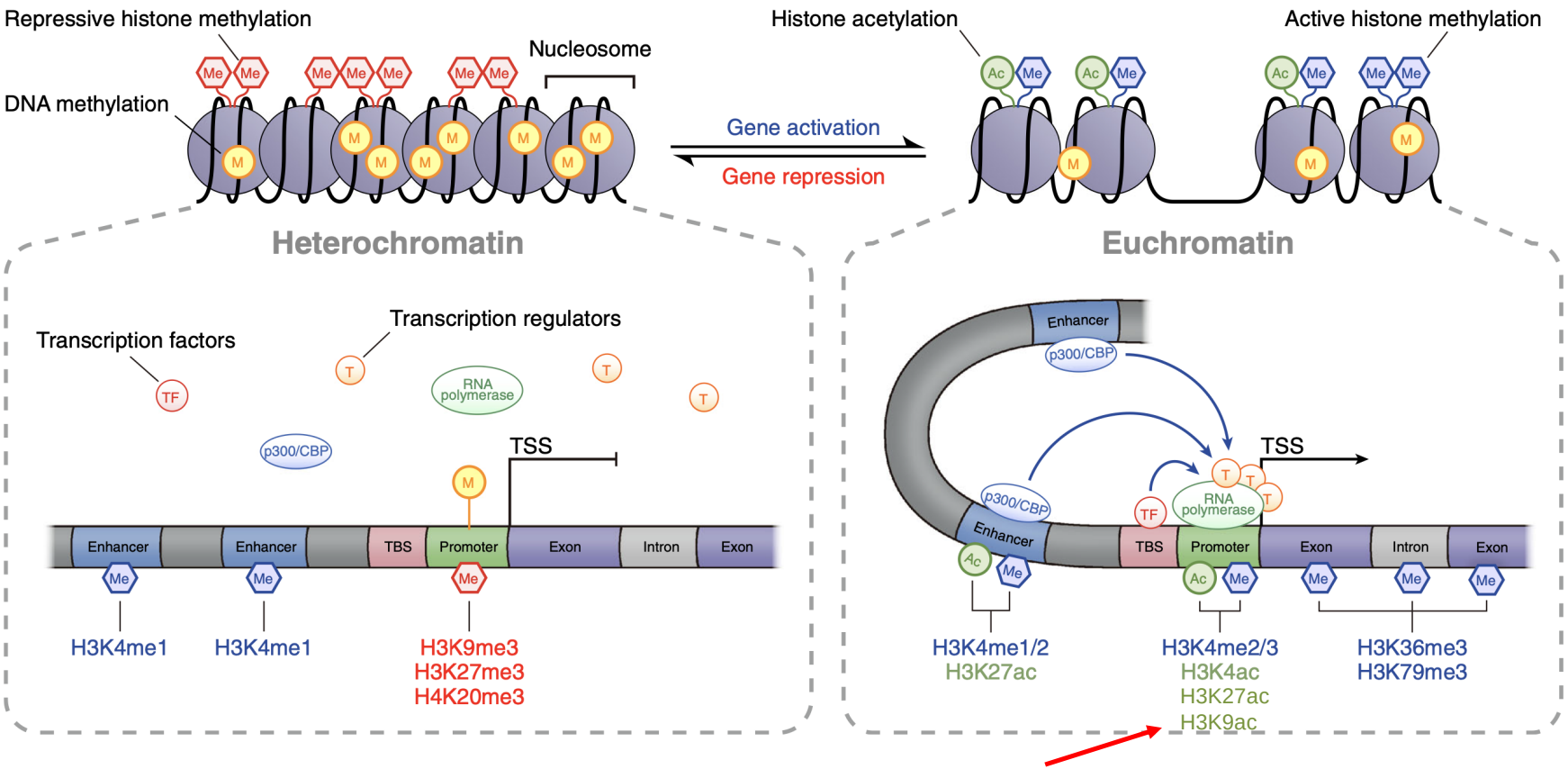
- Poverty, liquor stores, fast food, crime, and heavy metal pollution

Increased incidence of

- Type 2 Diabetes, heart disease, and obesity – ***cancer link weak***

https://www.epa.gov/ejscreen http://www.ers.usda.gov/data-products/food-access-research-atlas/go-to-the-atlas.aspx

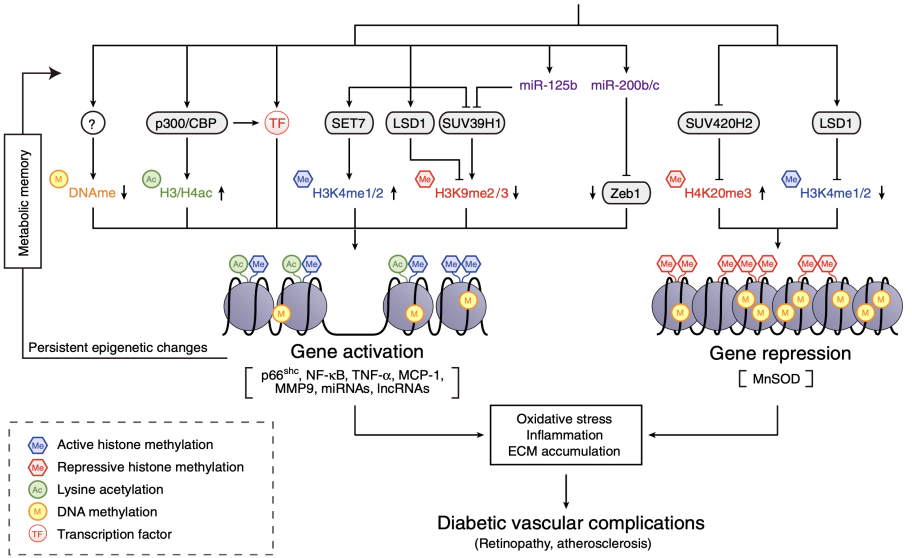
Gene Activation/Repression – histone methylation/acetylation



Reddy *et al.* Epigenetic mechanisms in diabetic complications and metabolic memory *Diabet.* 58: 443–455 (2015)

Metabolic memory – Rama Natarajan

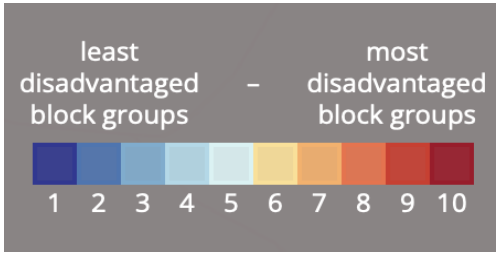
Type 1 DM – Epigenetic changes irreversible
Are epigenetic changes in insulin-resistance reversible?
Is there a threshold “of no return” – what is the mechanism?



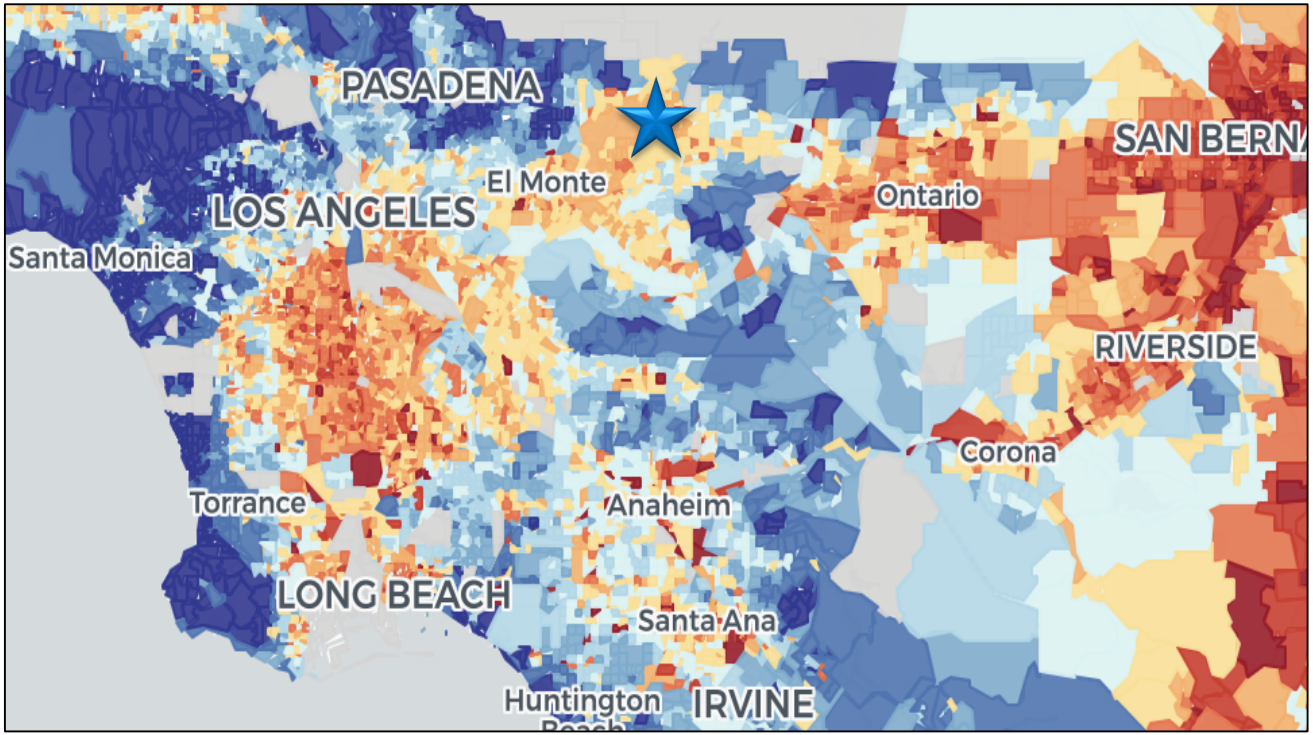
Reddy *et al.* Epigenetic mechanisms in diabetic complications and metabolic memory *Diabetologia* **58:** 443–455 (2015)

CoHCCC Catchment Area – 981 women enrolled

Exclusion: women w/ Type 2 Diabetes and Smokers



Disadvantage Index

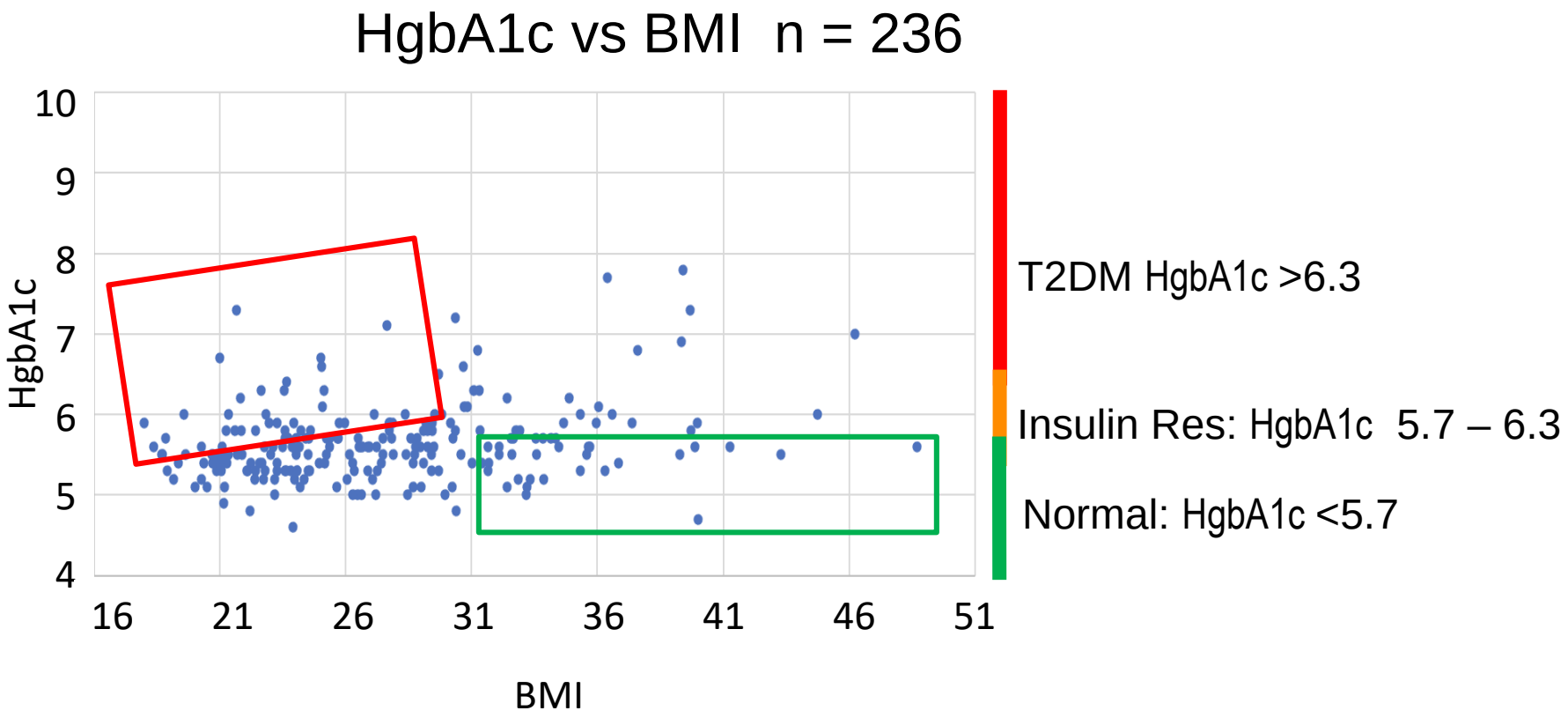


Catchment Area Study – 981 women enrolled

Redcap survey – demographics, zip code, education, employment, nutritional survey, food shopping and access

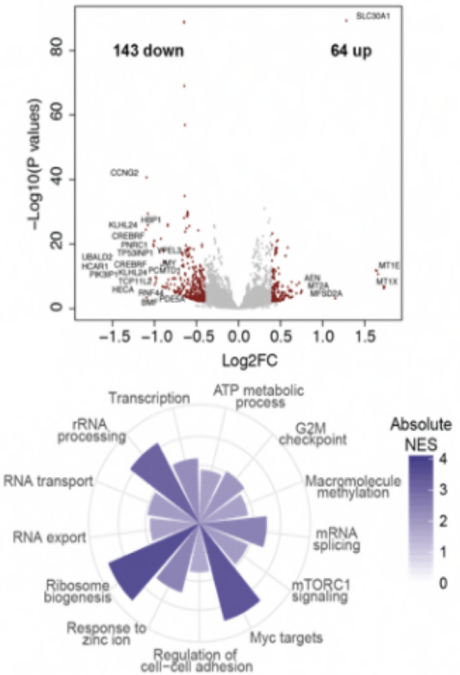
Age	31-61 (mean 43)				
Race/Ethnicity	**NHW**	**HW**	**Black**	**Asian**	**NA**
	288 (35%)	378 (46%)	41 (5%)	116 (14%)	4 (<1%)
Neighborhood Disparity Index	**1-3 (adv)** 312 (38%)	**4-6** 426 (52%)	**7-10** 89 (11%)		
HgbA1C	**≤ 5.6**	**5.7-5.9**	**≥ 6.0**		
236 analyzed	138 (58%)	59 (25%)	39 (17%)		

Catchment Area – exclusion known Type-2 DM
Metabolically unhealthy low BMI

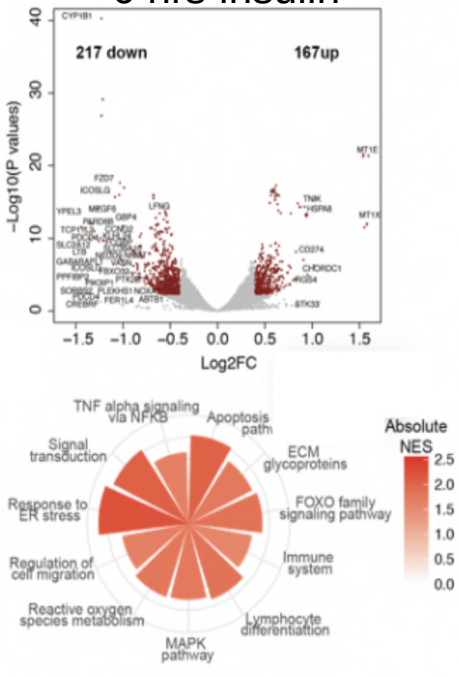


In vitro and *in vivo*: Insulin - acetylation –opens chromatin - increases transcription - top hit H3K9Ac

3 hrs insulin



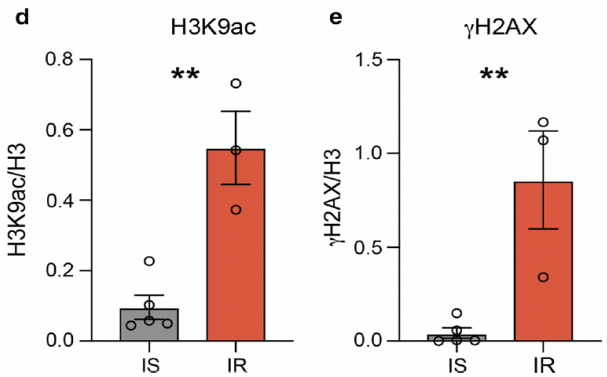
6 hrs insulin



Up-regulated transcripts

- AKT/mTOR
- Metabolism, ROS
- TNFalpha/IL6

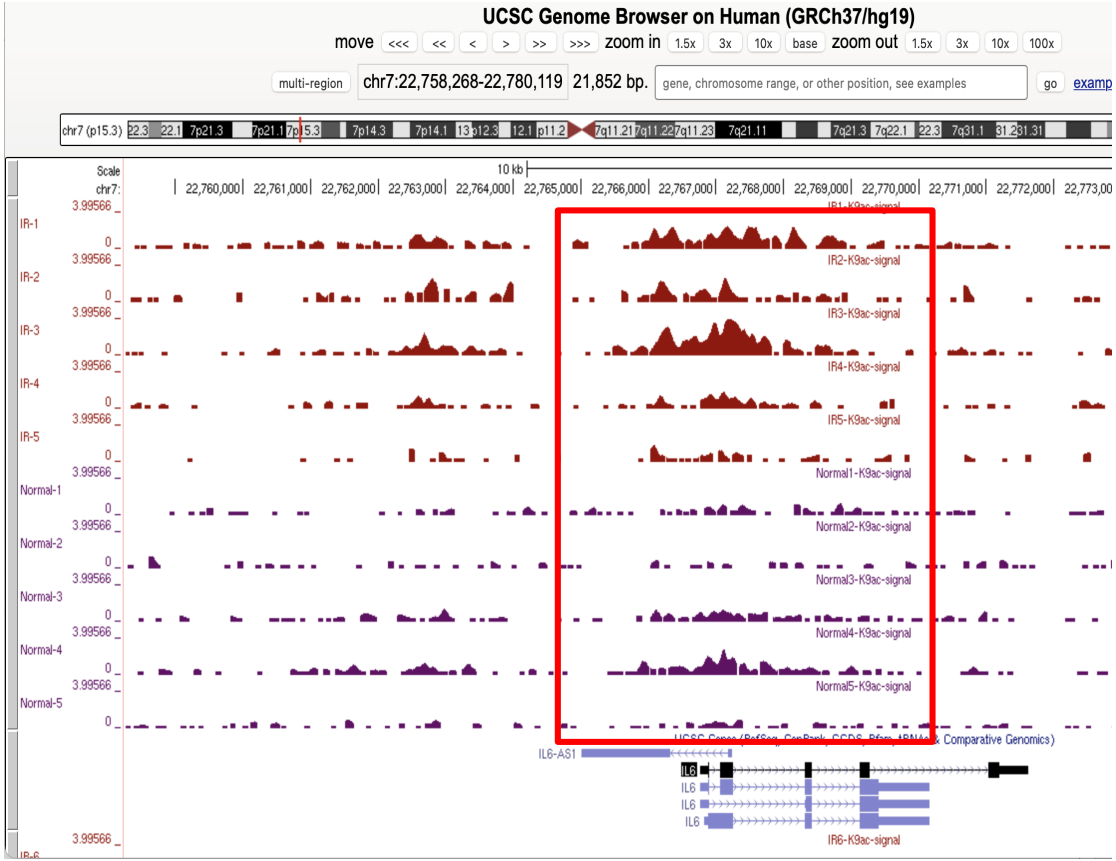
Increased - gammaH2AX



Senpati *et al*. *Epigenetics Chromatin* 2019 - *in vitro* modeling MCF7 and HMECs, *in vivo* xenograft

ChIP-seq - H3K9Ac

n=28: 15 HgbA1c < 5.7 and 13 HgbA1c 5.7-6.3



Normal Insulin Resistant

Dustin Schones PhD

Parajat Senapati PhD

Top Hits:

- TNFα
- IL6

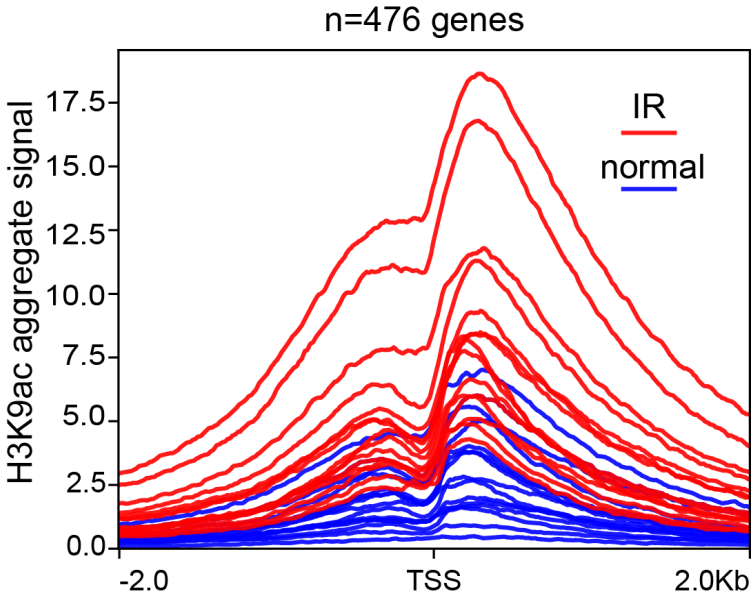
Pathway Analysis: Genes w/increase in H3K9ac promoter signal in insulin-resistant women vs. normal controls (age matched)

Christina Vidal PhD

Parajat Senapati PhD

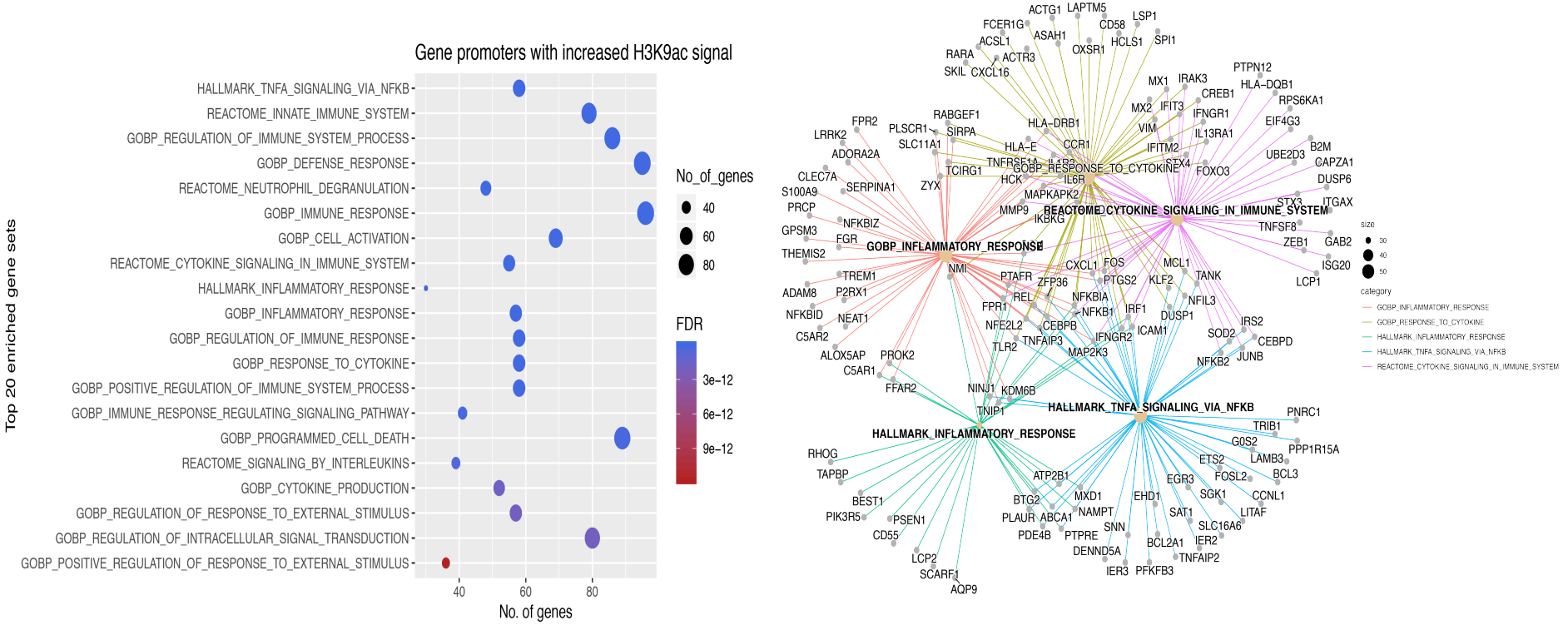
Genes with highest increase in H3K9ac signal in insulin-resistant women were identified by DESeq2

log2FC > 1 and FDR < 10^{-8}



Genome browser trackhub: https://parijat.s3.amazonaws.com/ChIP-seq/PBMC-K9ac/hub.txt

Gene promoters w/ increased H3K9Ac Signal



Top Pathways: NFκB/TNFα-signaling, inflammation, cytokine signaling, innate immunity

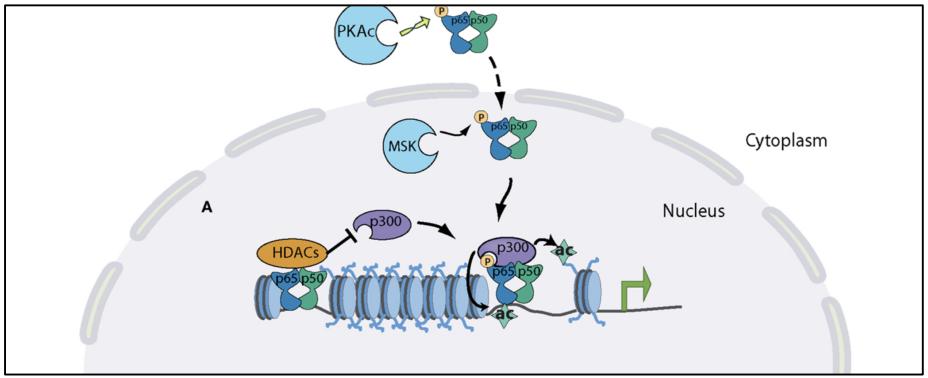
Transcription factor motifs enriched at promoters w/ increased H3K9ac signal in insulin-resistant women

Parajat Senapati PhD

	p-value
SP1	10^{-38}
SPIB	10^{-38}
RUNX1	10^{-38}
ETS1	10^{-38}
GABPA	10^{-38}
FOSL2	10^{-38}
CRE	10^{-38}
IRF1	10^{-38}
ELF4	10^{-38}
PU.1/SPI1	10^{-38}
KLF9	10^{-38}
NRF1	10^{-38}
EGR2	10^{-38}
NF-kB p50	10^{-38}

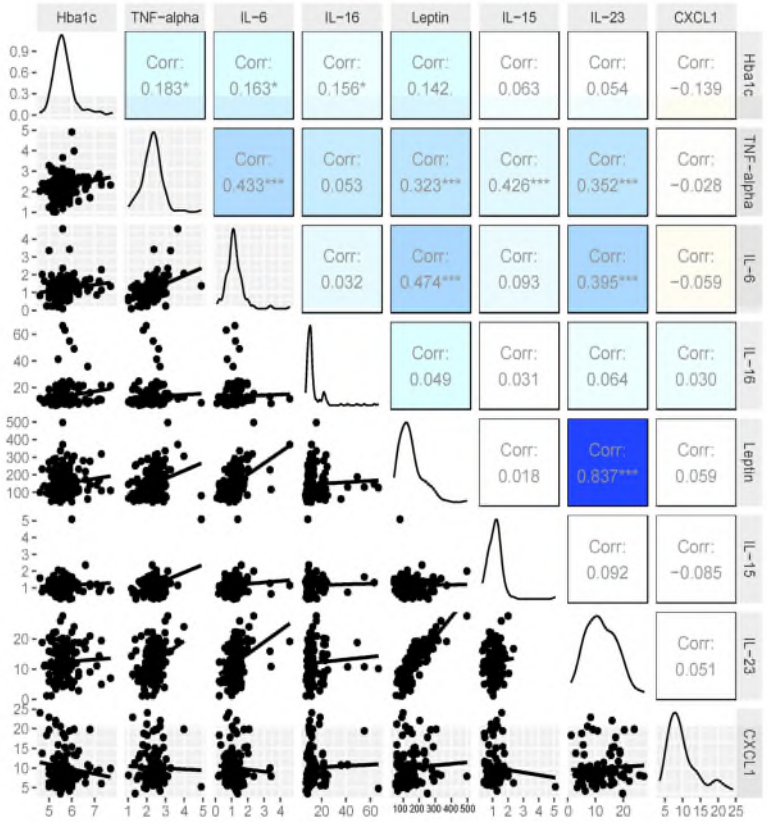
NF-kB/IRF1 - INF-beta signaling

- recruitment of IRF1 and ATF-2/c-Jun
- platform for PCAF chromatin modification complex and p300/CBP acetyltransferase



Cytokine array – positive correlation HbA1c and TNFα & IL6

Consistent with ChIP-seq chromatin analysis



n= 245

TNFα and IL6 were significantly positively associated with Hba1c

Significant correlation of TNFalpha to - IL6, Leptin, IL15, IL23

Strong positive association of Leptin and IL23

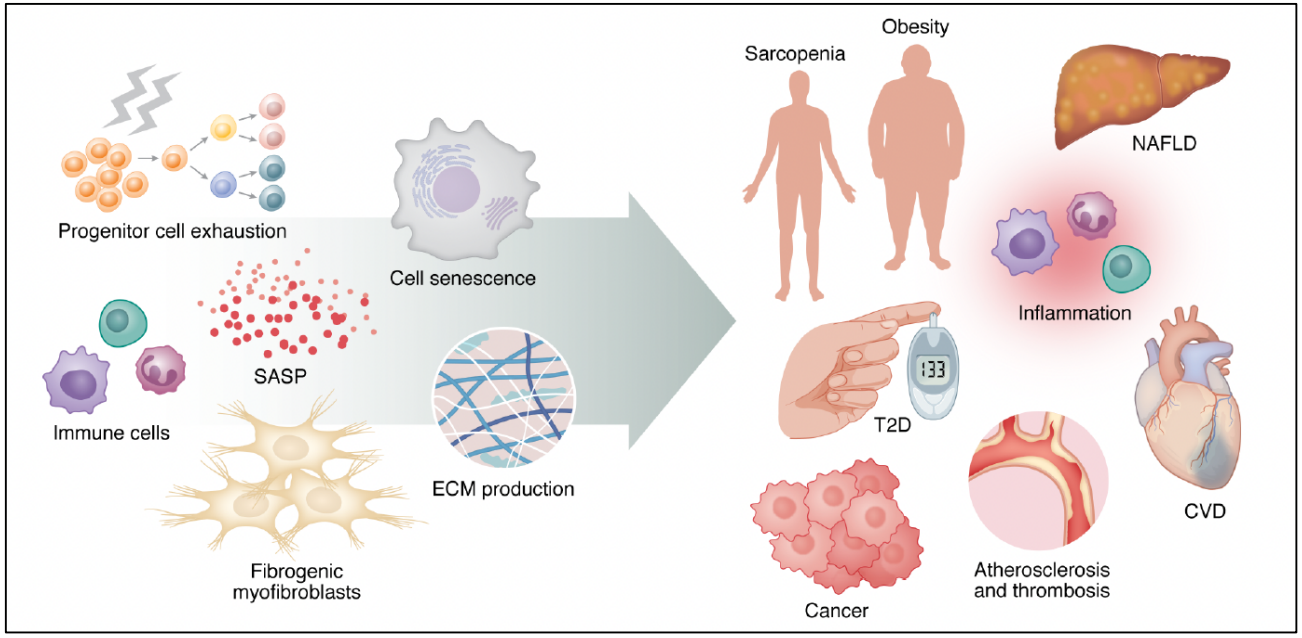
Type 2 Diabetes – disease of senescence and accelerated aging

JCI The Journal of Clinical Investigation

Increased cell senescence in human metabolic disorders

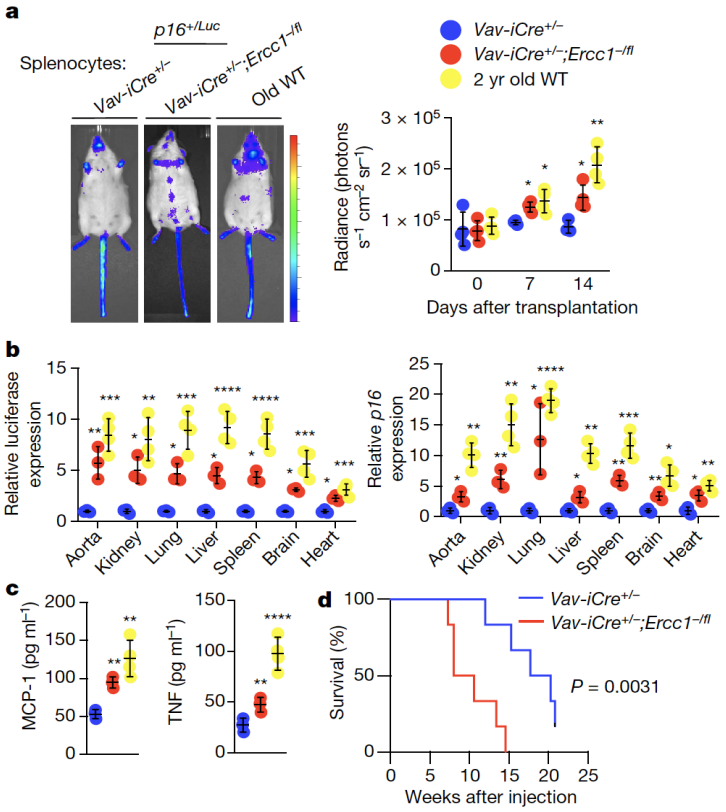
Rosa Spinelli, … , Annika Nerstedt, Ulf Smith

J Clin Invest. 2023;133(12):e169922. https://doi.org/10.1172/JCI169922.



Senescence of heart, pancreas, brain, lung can be driven by immune system. Can be transplanted.

Adoptive transfer of splenocytes from 10 mos old Ercc1 – deficient mice – aging of recipient mice



Article

An aged immune system drives senescence and ageing of solid organs

https://doi.org/10.1038/s41586-021-03547-7

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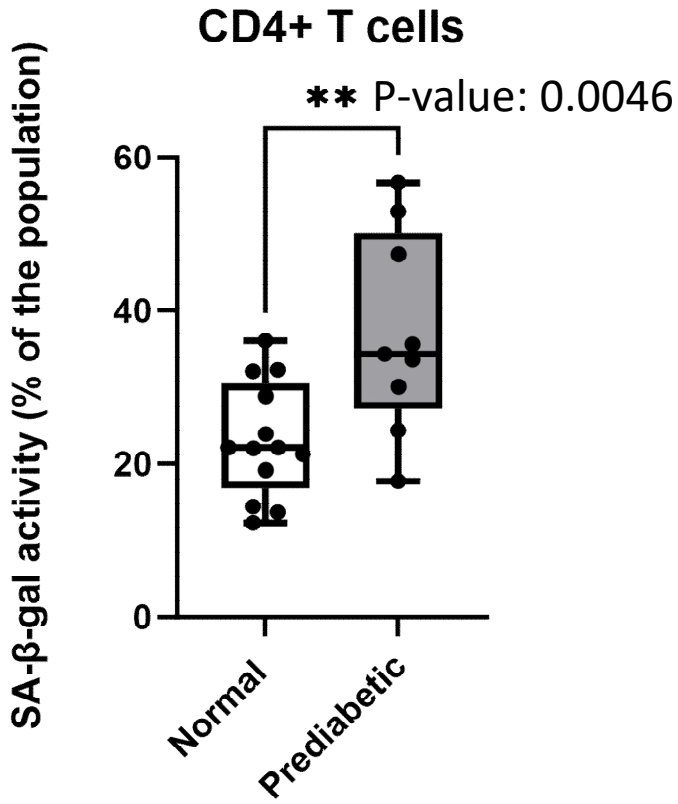
Check for updates

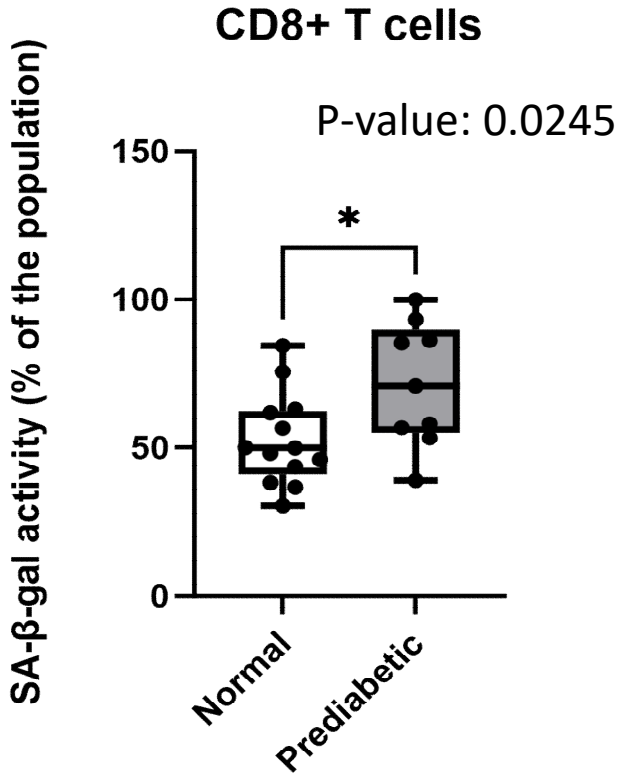
Matthew J. Yousefzadeh[1,2,14], Rafael R. Flores[1,2,14], Yi Zhu[3], Zoe C. Schmiechen[4], Robert W. Brooks[5], Christy E. Trussoni[6], Yuxiang Cui[7], Luise Angelini[1,2], Kyoo-A Lee[1,2], Sara J. McGowan[1,2], Adam L. Burrack[4], Dong Wang[8], Qing Dong[8], Aiping Lu[9], Tokio Sano[5], Ryan D. O'Kelly[1,2], Collin A. McGuckian[1,2], Jonathan I. Kato[5], Michael P. Bank[5], Erin A. Wade[5], Smitha P. S. Pillai[10], Jenna Klug[11], Warren C. Ladiges[11], Christin E. Burd[12], Sara E. Lewis[13], Nicholas F. LaRusso[6], Nam V. Vo[8], Yinsheng Wang[7], Eric E. Kelley[13], Johnny Huard[9], Ingunn M. Stromnes[4], Paul D. Robbins[1,2]✉ & Laura J. Niedernhofer[1,2]✉

Nature Vol 594 3 June 2021 - Niedernhofer

Senescence: β-gal FACS analysis

n=15 normal, 10 insulin-resistant women



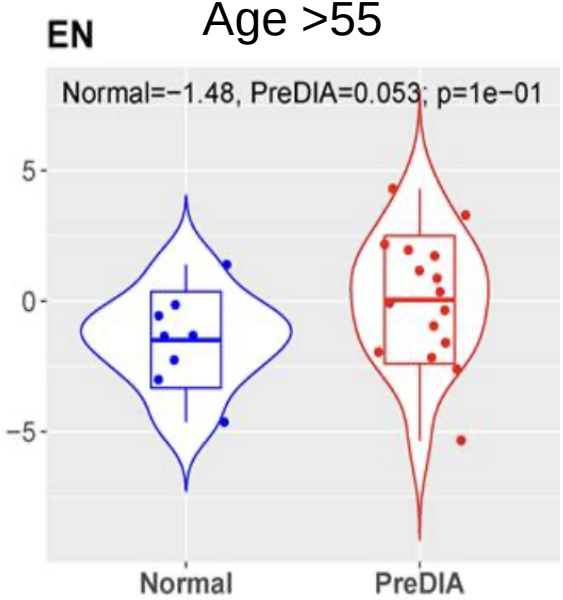


Accelerated aging: Epigenetic Clocks

In the subjects with age > 50, Pre-diabetes showed higher age acceleration estimated by DNA methylation comparing to normal group (mean 0.053 vs. -1.48) at marginal p=0.10 (two-sided t test).

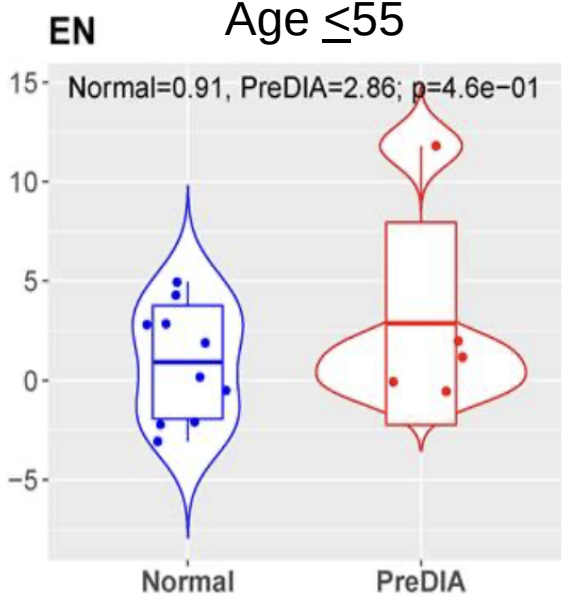
Rama Natarajan, PhD

Age >55



- 8 in Normal Group (HbA1c < 5.7)
- 16 in pre-Diabetes group (HbA1c ≥ 5.7)

Age ≤55



- 18 in Normal Group (HbA1c < 5.7)
- 12 in pre-Diabetes group (HbA1c ≥ 5.7)

Matched for BMI, age

Conclusions:

Insulin resistance is associated with the acetylation of H3K9 in peripheral blood mononuclear cells (PBMCs) of women with insulin resistance.

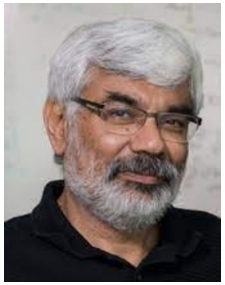
- Promotes cytokine production/inflammation (interleukin-6, IL6; tumor necrosis factor-alpha, TNFα; and cytokine signaling)
- Cellular senescence (NFκB-signaling and innate immunity)
- Insulin resistance is potentially associated with accelerated aging in postmenopausal women.
  - In process – epigenetic clock – methylation analysis
  - Age 40-60 n=50 insulin resistant vs. metabolically healthy

Future Directions

- If IR normalized – can epigenetic changes/inflammation be reversed?
- Racial and ethnic differences in senescent cells

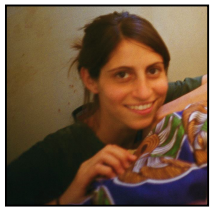
Angie Sanchez, Nancy Sanchez, Myriam Robles, Allen Nunez, Angela Wong, Tanya Chavez, Christina Tsai, Omi Idassi, Kendal Kennedy

leap



Shankar Subrmaniam
UCSD

Faye Burt



Terry Hyslop PhD
Duke

Christina Vidal PhD

Parajat Senapati PhD





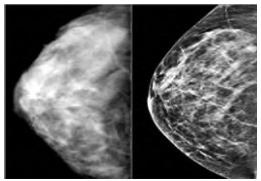








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