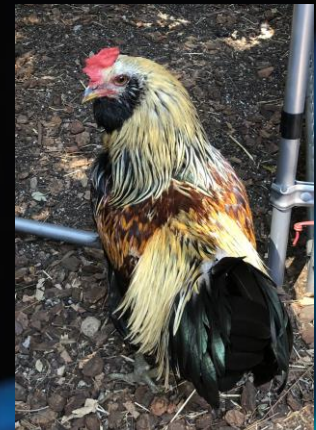


Why Breast Cancer Oncologists Should Care About Insulin

Victoria Seewaldt, MD

Ruth Ziegler Professor and Chair
Department of Population Sciences
Beckman Research Institute
City of Hope

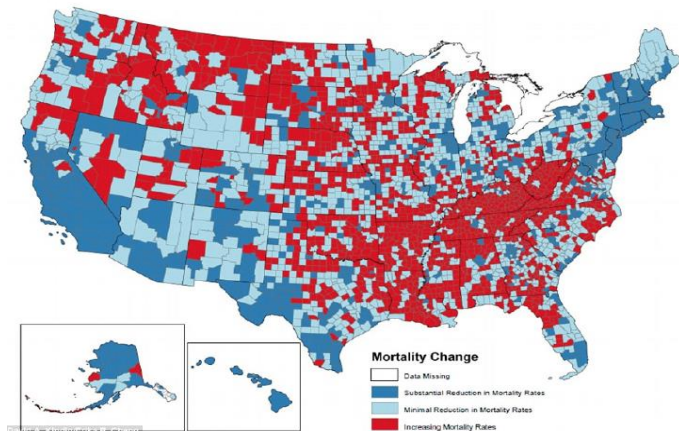
No conflict of interest. Nothing to disclose. No off-label use of drugs.



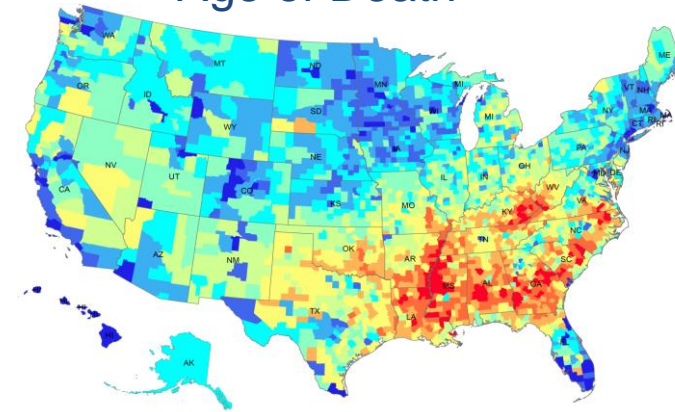
Epidemic of type 2 diabetes, breast cancer, lack of activity, lack of access to healthy food, early death

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

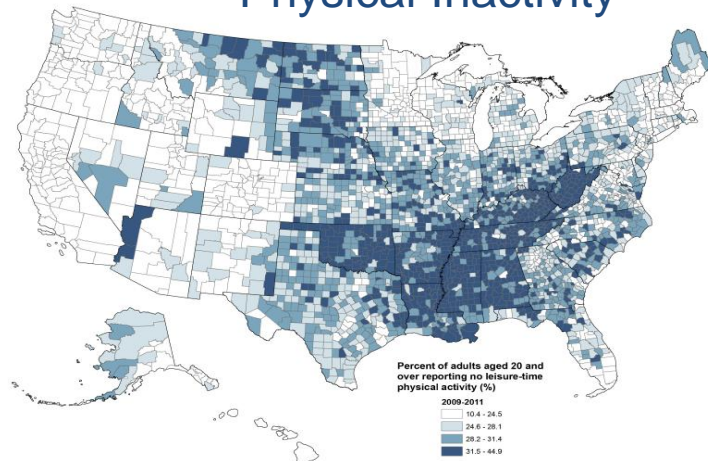
Earlier Age Death Women



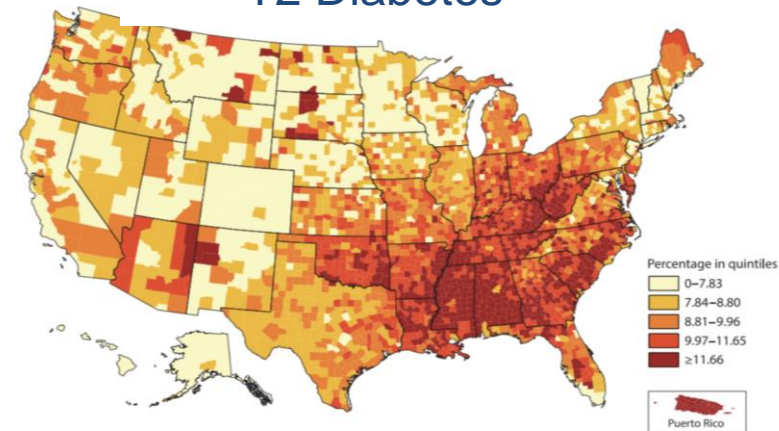
Age of Death



Physical Inactivity



T2 Diabetes



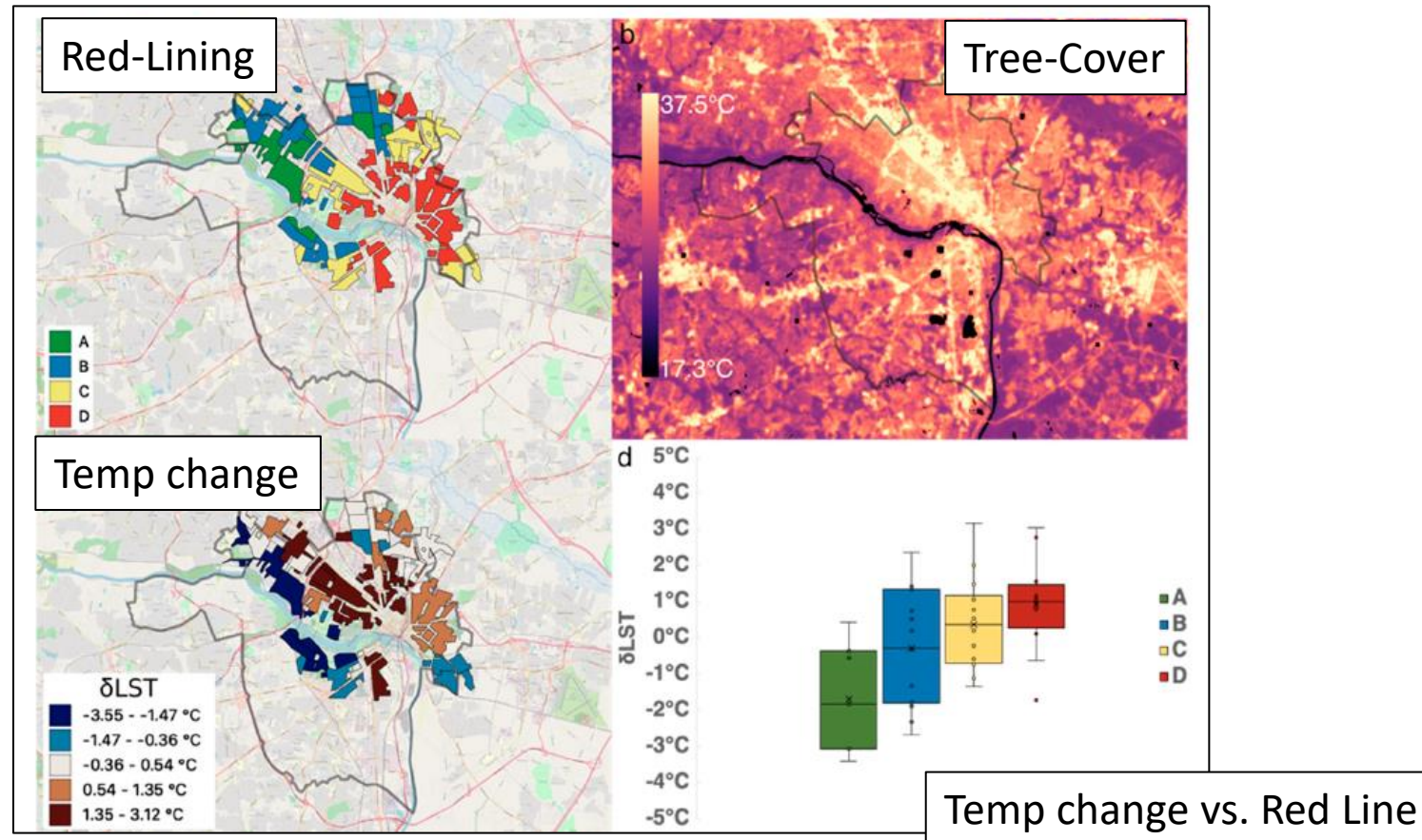
Neighborhood redlining

Denial of loans, insurance, health care, and supermarkets.

Systematic denial of services to residents of specific neighborhoods or communities - frequently racially targeted – highly discriminatory

Increase in temperature

Richmond, VA



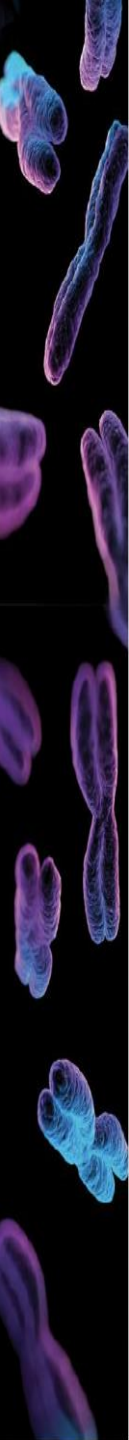
Jeremy Hoffman et al. Climate , 2020




Insulin resistance, insulin, breast cancer

Evidence for insulin-driven aggressive biology

Systems biology and prevention



Obesity does not consistently increase risk of premenopausal TNBC in Black/AA women

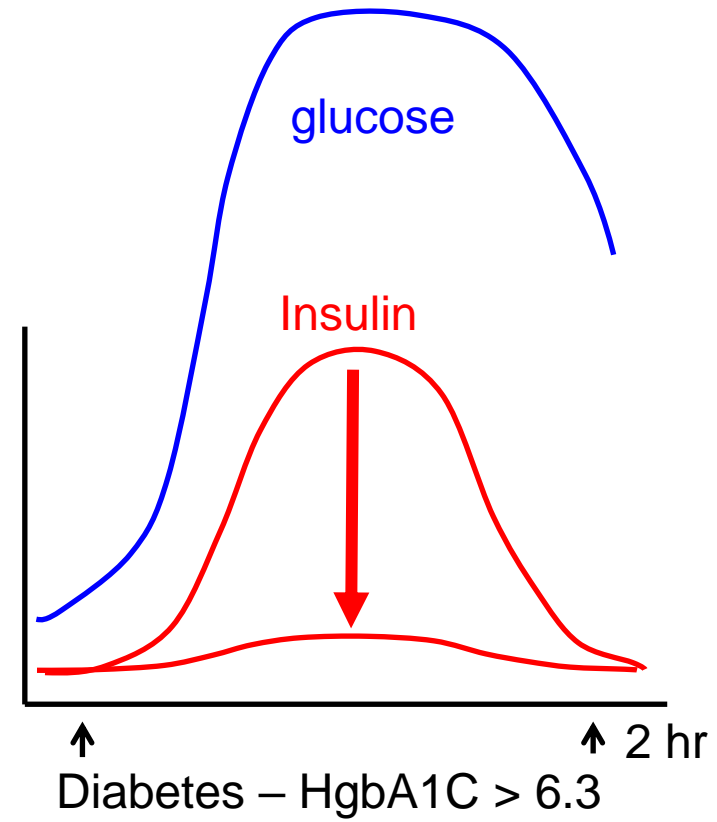
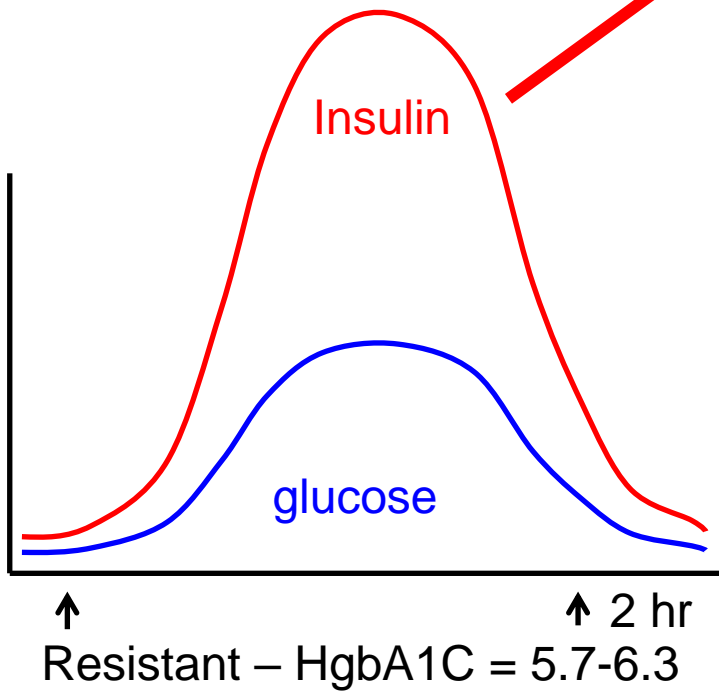
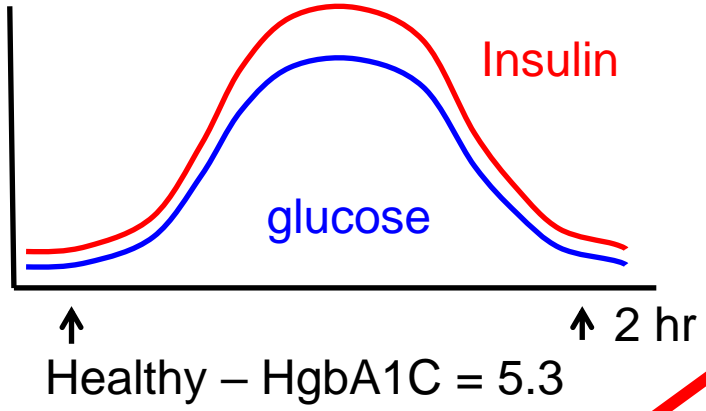
-  Carolina Breast – Basal type TNBC increased in obese premenopausal Black/African American women (WHR).
- Women's Contraceptive and Reproductive Experience (CARE) (BMI ≥ 30) – No association
 - Black Women's study (BMI) – ***Adams-Campbell*** - inverse association BMI and premenopausal cancer
 - AMBER Association – consortium Carolina Breast, Multi-ethnic cohort, Black Women's study ***Adams-Campbell***, Women's Circle of Health - NO association (BMI, WHR)

Biphasic variable e.g. BMI ≥ 30 YES or NO

Insulin resistance and Type II Diabetes

- Increased Black/African American women
- Younger age of onset

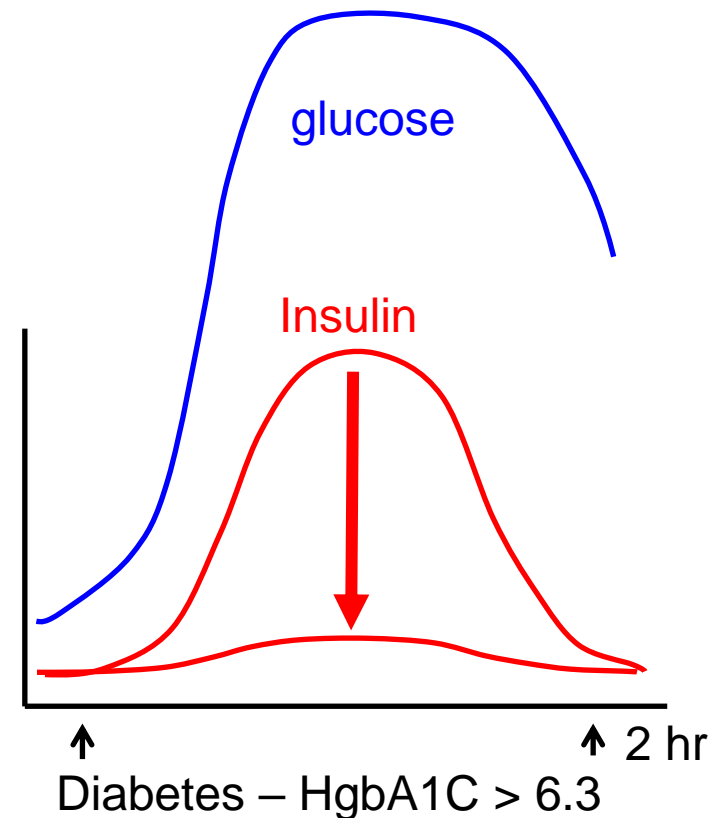
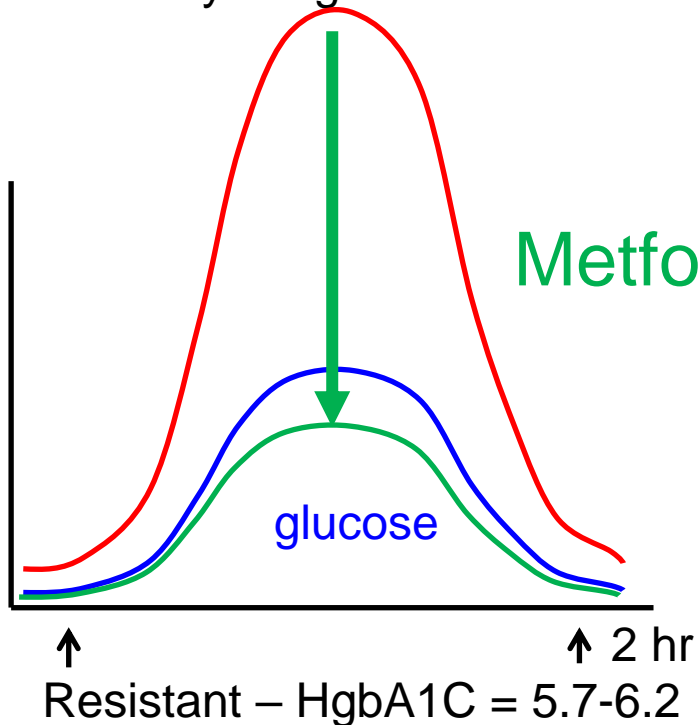
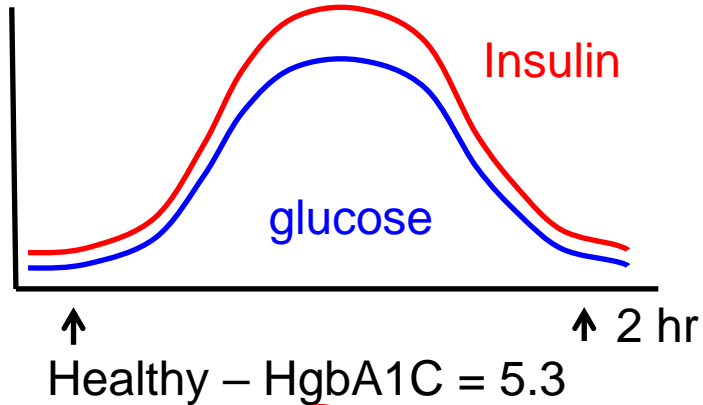
- stimulates hunger
- promotes carbohydrate to fat
- prevents fat access (breast feeding)



Metformin mobilizes fat, decreases hunger

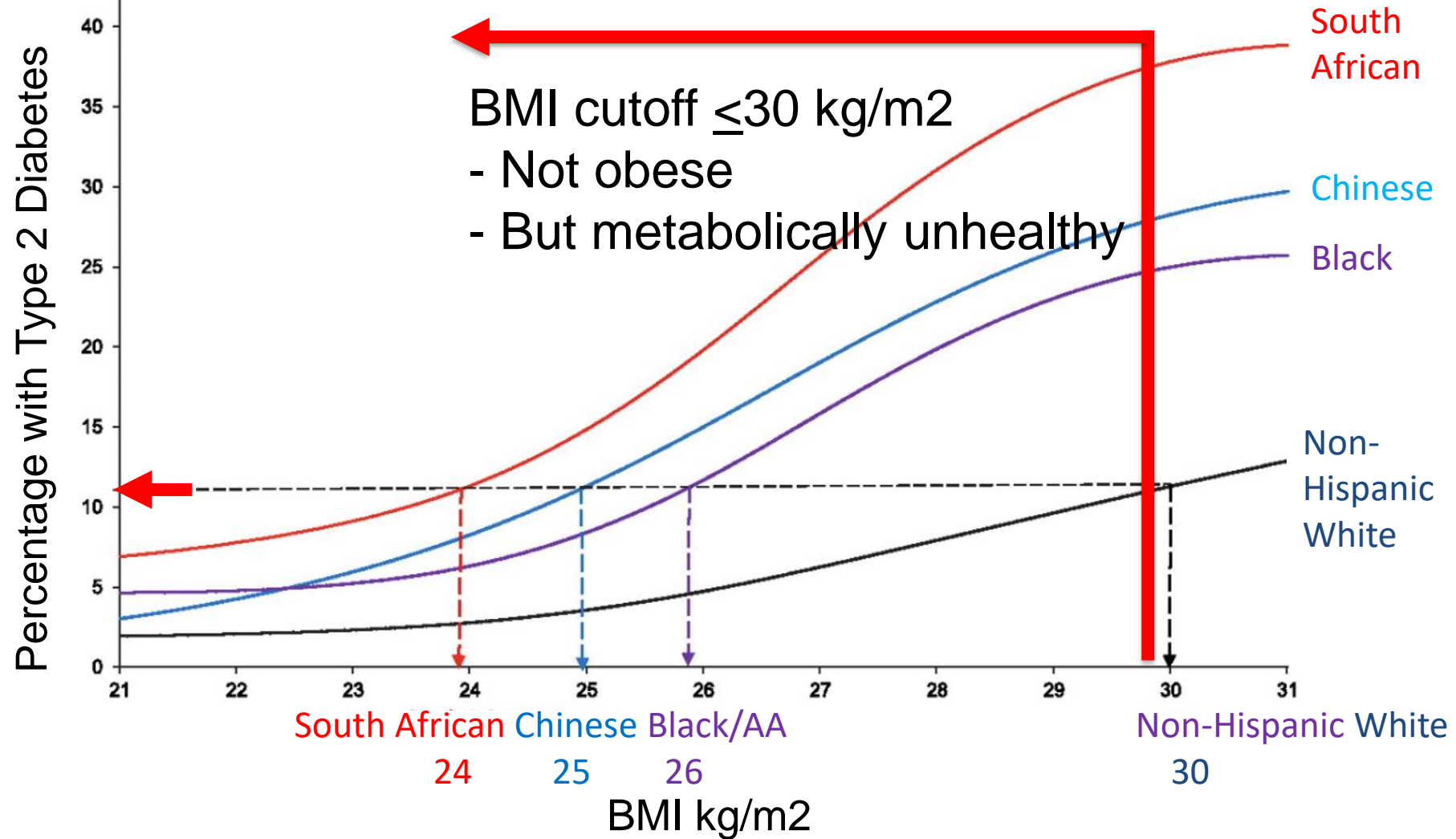
Metformin - decreases serum insulin

- decreases hunger
- increases fat breakdown
- prevents >60% T2D



BMI does not always equal metabolic potential

- importance of race/ethnicity
- threshold for insulin-resistance



Metabolic changes after Cytotoxic Chemotherapy in women with Early-Stage breast cancer

963 women, 53% premenopausal, 47% postmenopausal

Mean age 48.2

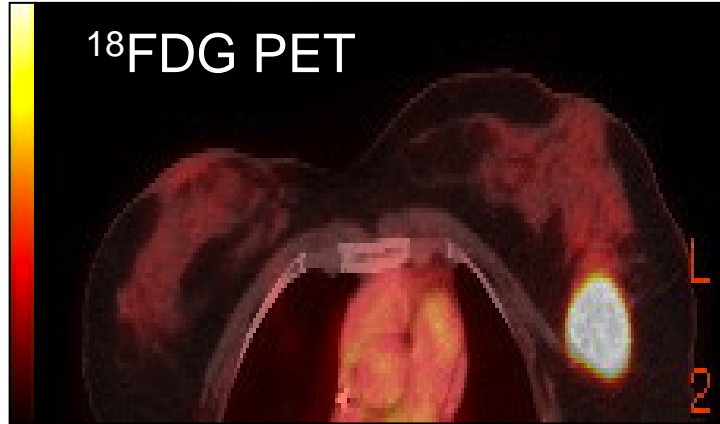
White Non-Hispanic (54%); White Hispanic (33%); Asian (7%); Black (8%)

		PRE	POST	% Change	P
Waist	Circumference	86.7(12.9)	91.7(11.2)	5.7	<0.01
BP	Diastolic	80(13)	90(18)	6.1	<0.01
Lipids					
	Total Cholesterol	185.5 (48.3)	201.9 (45.5)	8.8	<0.001
	LDL-C	100.5 (34.4)	111.1 (43.7)	10.5	<0.001
Glucose					
	Fasting insulin	18.9 (21.8)	32.6 (17.3)	73.1	0.05
	HgbA1c	5.4 (0.36)	5.9 (0.6)	8.6	<0.001

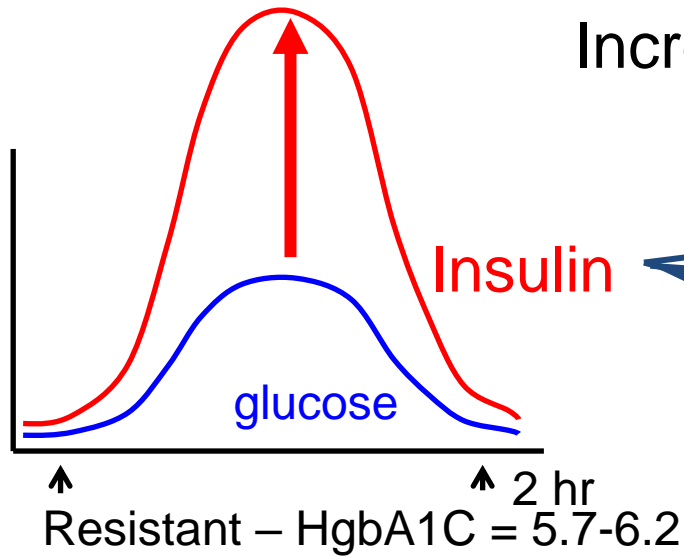
Dieli-Conwright CM, **Bernstein, L., Mortimer JE** et al. An Observational Study to Examine Changes in Metabolic Syndrome Components in Patients With Breast Cancer Receiving Neoadjuvant or Adjuvant Chemotherapy. *Cancer* 2016

Woman: Insulin Resistant

Insulin resistance, produces high insulin



At risk breast tissue
Increased insulin sensitivity



AKT/mTOR/glycolysis

Wnt/beta-catenin

EZH2/Notch/cMyc

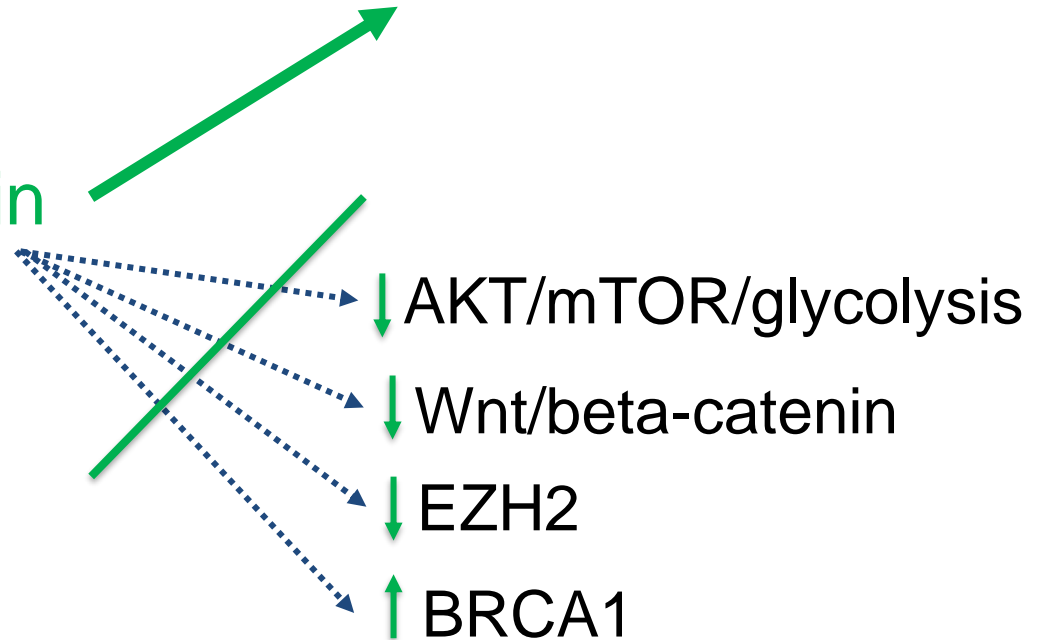
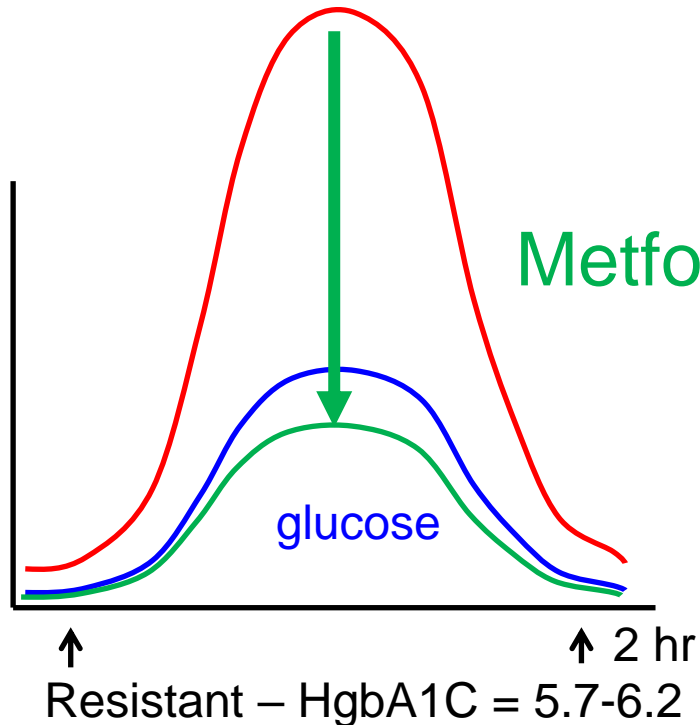
Stat3

Metformin mobilizes fat, decreases hunger

45% T2DM prevented
diet/exercise/metformin
Diabetes Prevention
Study – *Aroda et al.*
Diabetologia (2017)

Insulin - stimulates hunger
- promotes carbohydrate to fat
- prevents fat access

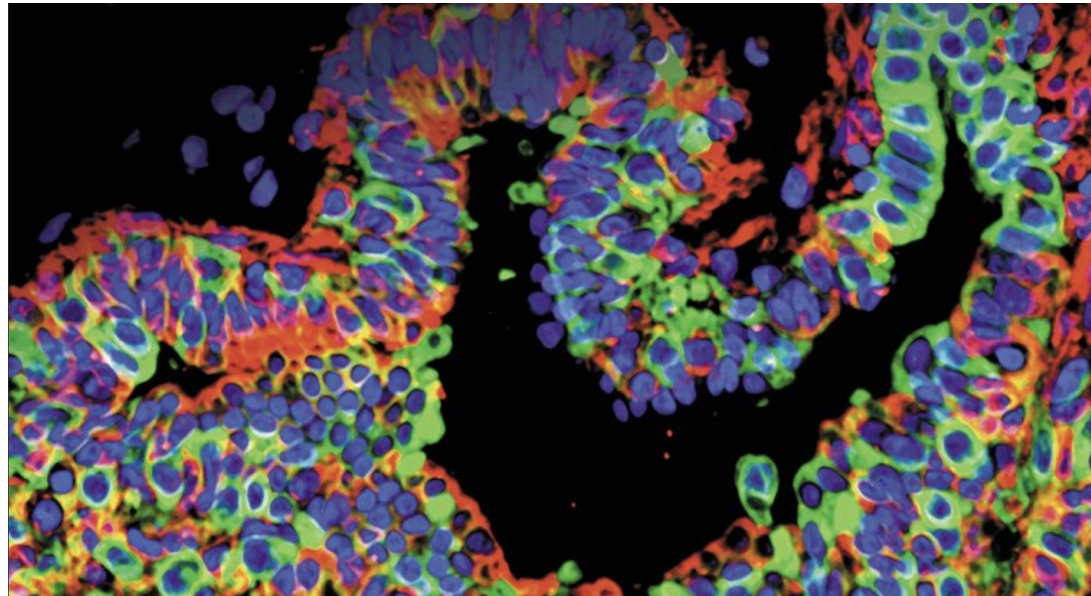
Metformin - decreases serum insulin
- decreases hunger
- increases fat breakdown



Insulin resistance, insulin, breast cancer

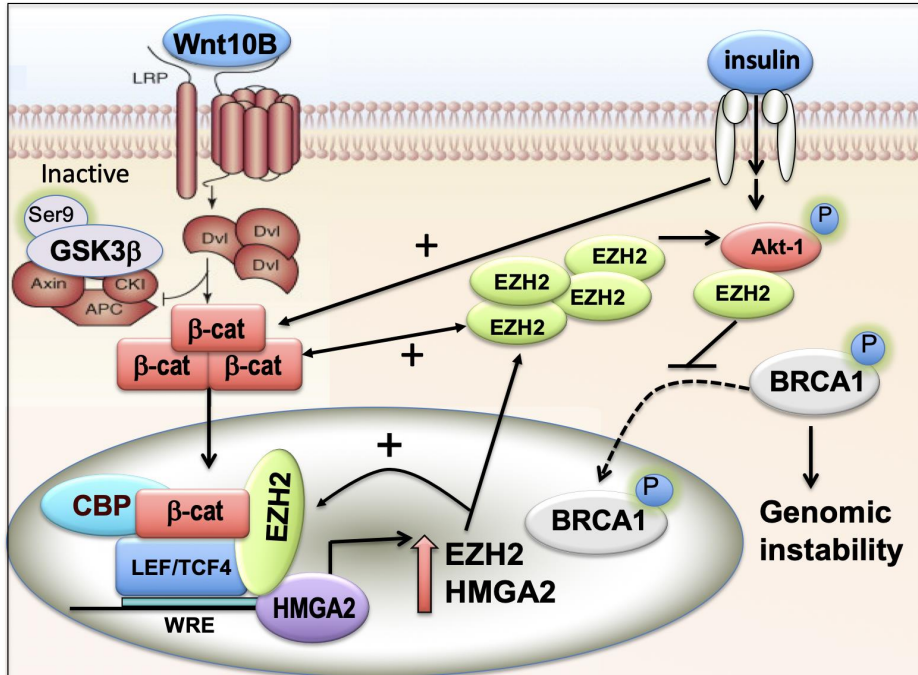
➔ Evidence for insulin-driven aggressive biology

Systems biology, early detection, risk-reduction



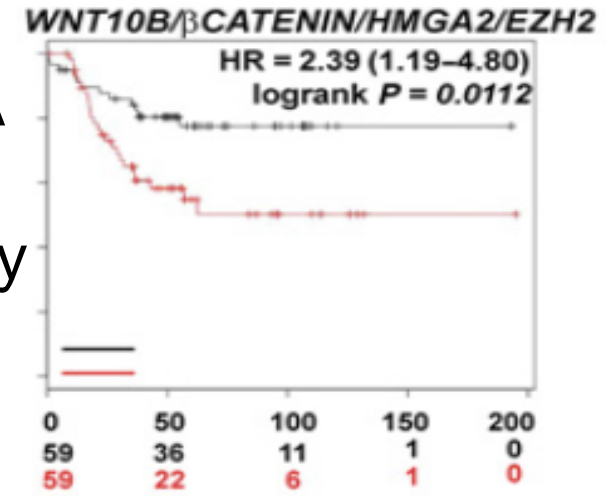
TNBC: Wnt/beta-catenin/EZH2/Akt/mTOR

- Activated in Basal-Like and Mesenchymal TNBC
- WNT10B/EZH2 predicts poor survival – human TNBC
- Metastasis in MMTV transgenic mouse model

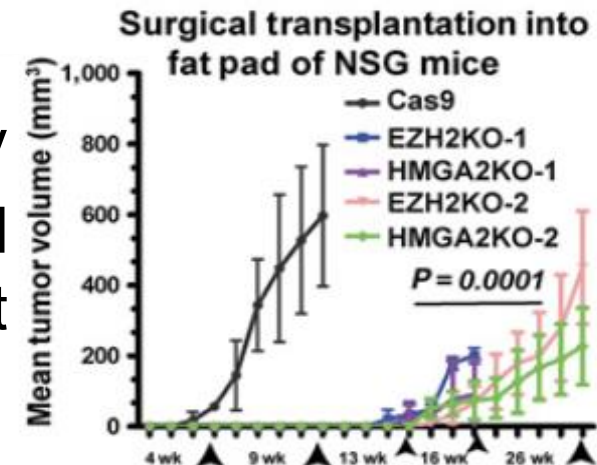


Wend et al. EMBO, 2012
 Ayachi et al. Cancer Res. 2019
 Fatima et al. Cancers, 2020

TCGA
 Risk-
 Stratify
 TNBC



MMTV
 Fat-pad
 Transplant



ALLIANCE **A211102** Metformin vs. placebo

- Precision Prevention 13 institutions – L. Yee MD



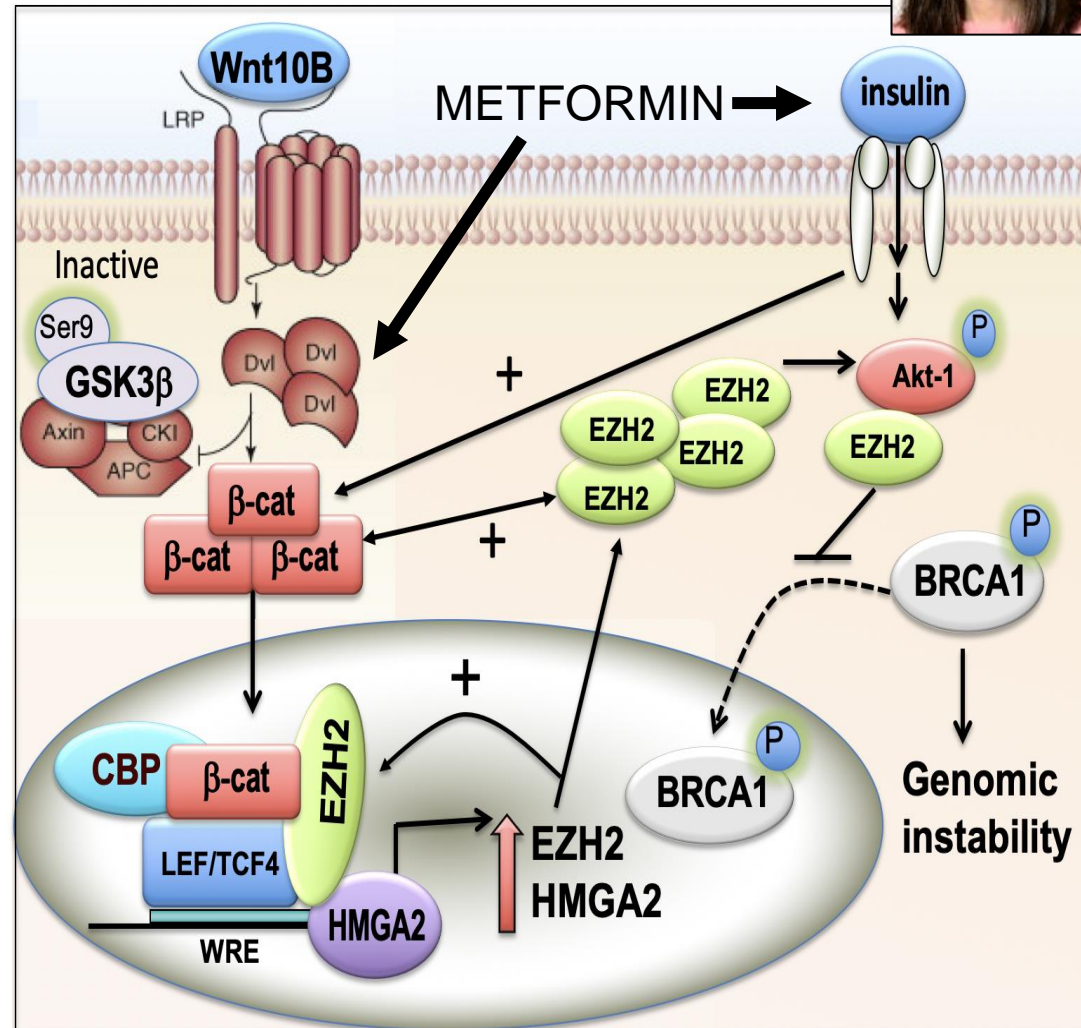
Premenopausal women with mammary atypia



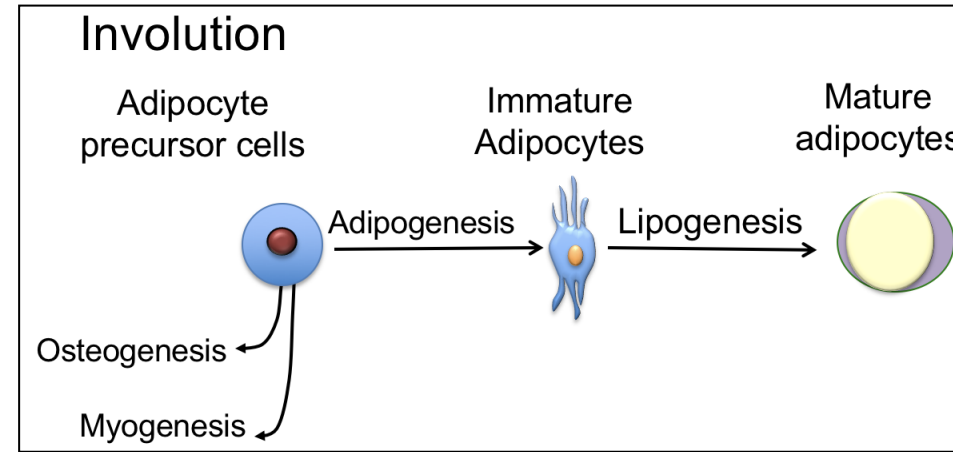
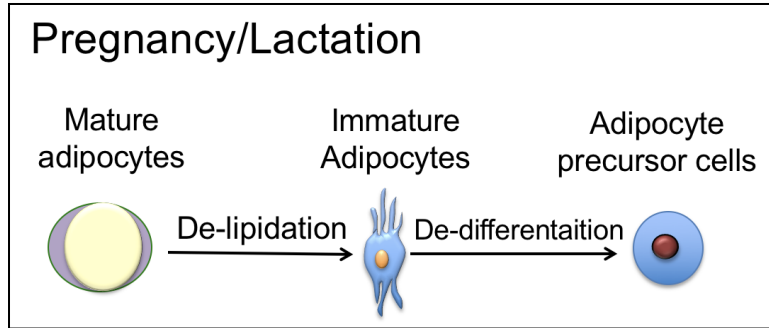
Metformin 850 bid vs. placebo 12 months



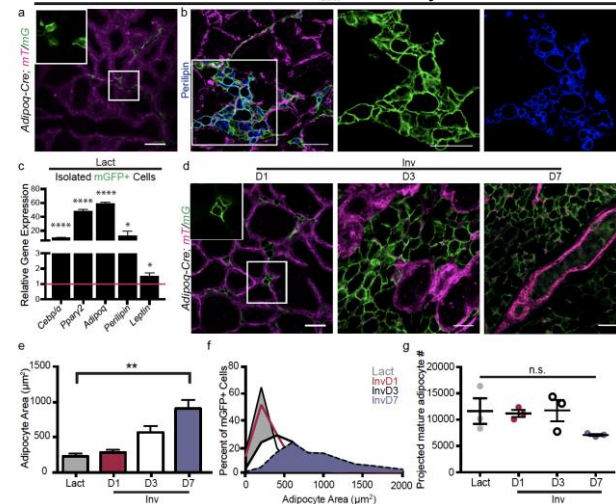
RPFNA, RPPM,
- 12 mos
- 24 mos



Pregnancy - Adipocytes - de-lipidation, de-differentiation Involution – Wnt blocks adipocyte re-differentiation



Adipocyte hypertrophy and lipid dynamics underlie mammary gland remodeling after lactation"
R. Zwick, V Seewaldt, V_{Lact} Horsely. Nature Comm. 2019

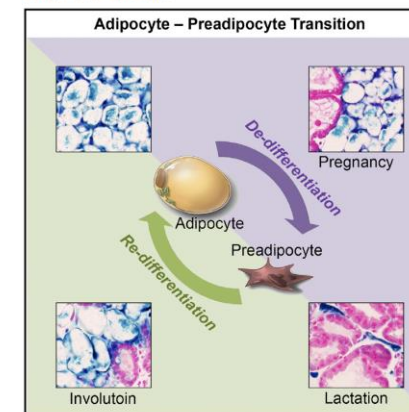


Cell Metabolism

Short Article

Reversible De-differentiation of Mature White Adipocytes into Preadipocyte-like Precursors during Lactation

Graphical Abstract



Authors

Qiong A. Wang, Anying Song, Wanze Chen, ..., Rana K. Gupta, Bart Deplancke, Philipp E. Scherer

Correspondence

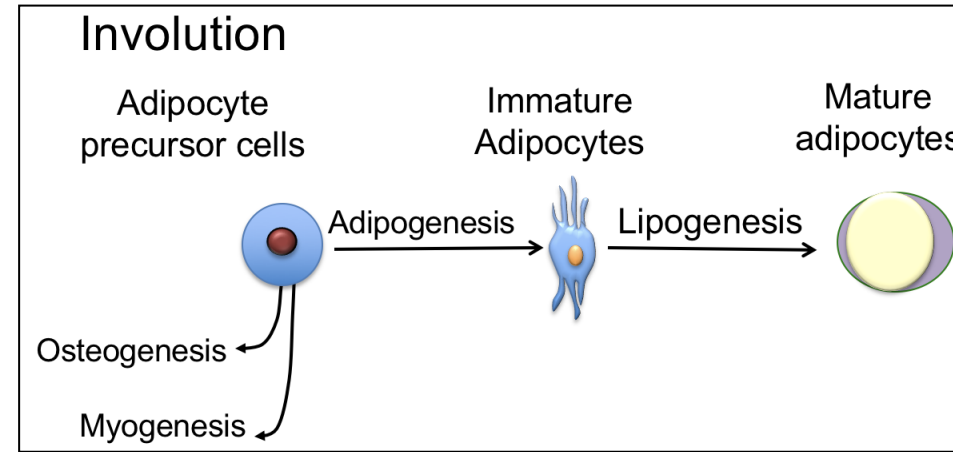
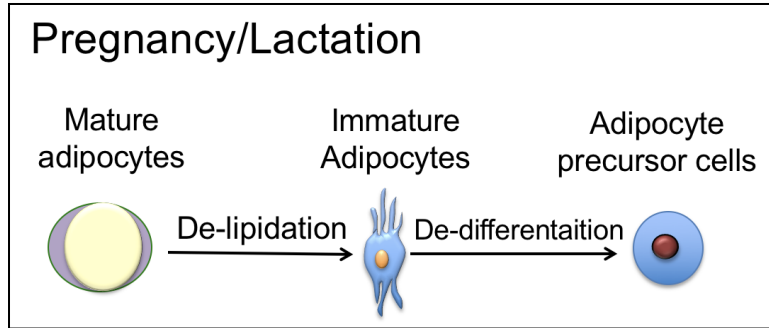
qwang@coh.org (Q.A.W.), philipp.scherer@utsouthwestern.edu (P.E.S.)

In Brief

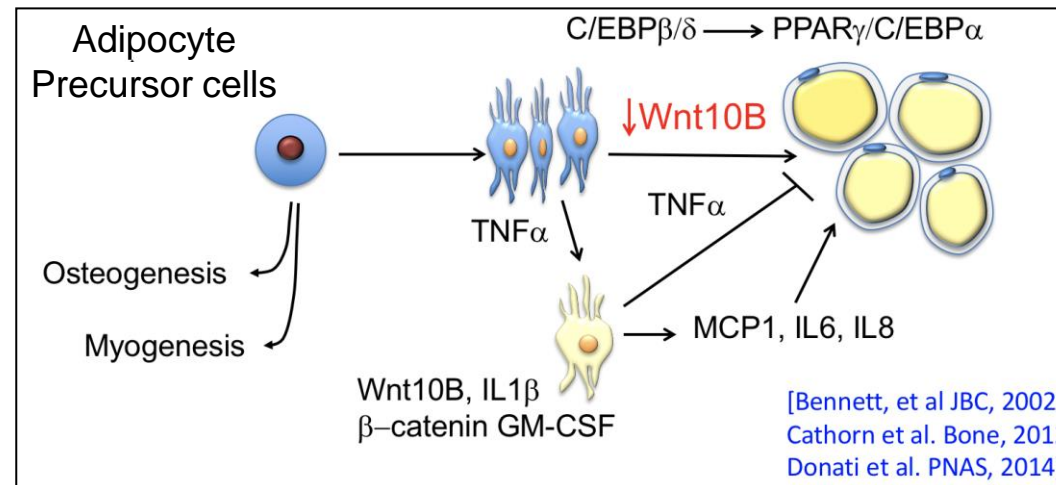
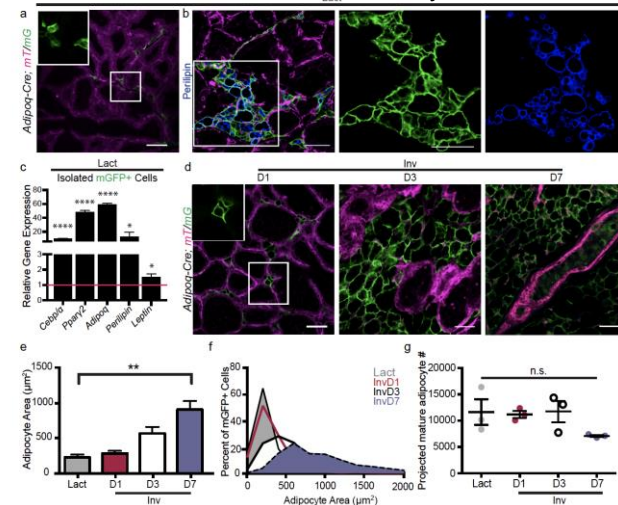
Adipocytes in the mammary gland disappear during lactation. Wang et al. show that these mammary adipocytes fully de-differentiate into preadipocytes during lactation and readily re-differentiate during involution. The same adipocytes are therefore "recycled" over multiple rounds of pregnancies. De-differentiation constitutes a new possible fate for terminally differentiated adipocytes.

Anabelle (Qiong) Wang, PhD

Pregnancy - Adipocytes - de-lipidation, de-differentiation Involution – Wnt blocks adipocyte re-differentiation



Adipocyte hypertrophy and lipid dynamics underlie mammary gland remodeling after lactation"
R. Zwick, V Seewaldt, V_{Lact} Horsely. Nature Comm. 2019



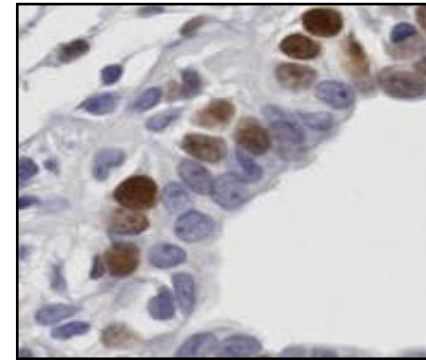
[Bennett, et al JBC, 2002
Cathorn et al. Bone, 2012
Donati et al. PNAS, 2014]

Insulin resistance, insulin, TNBC

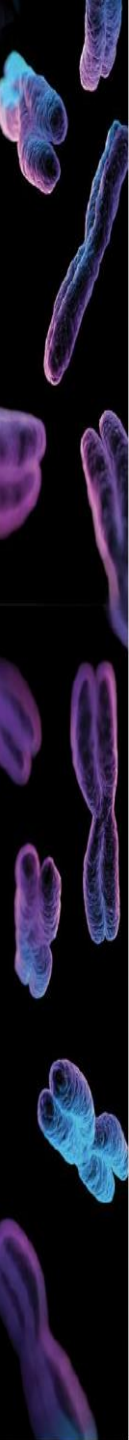
Evidence for insulin-driven aggressive biology

Systems biology

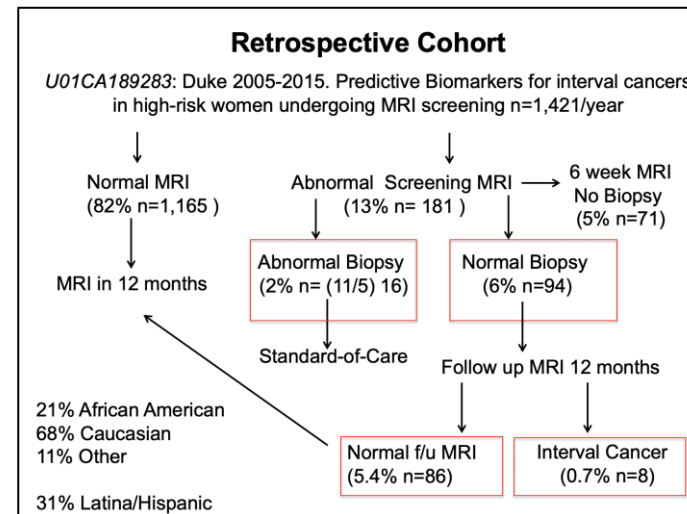
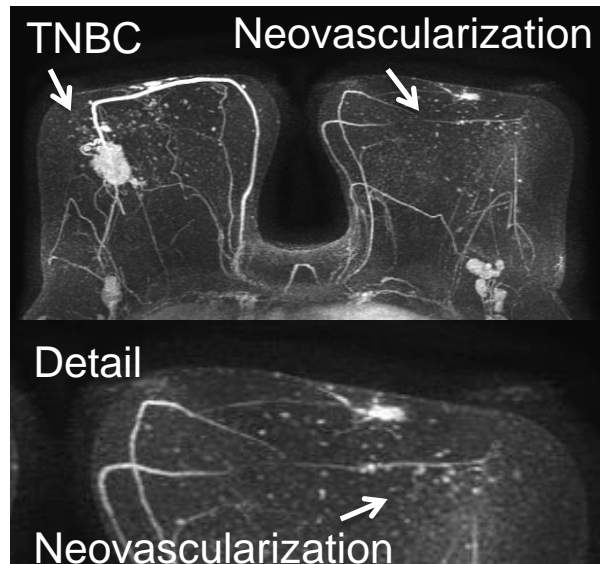
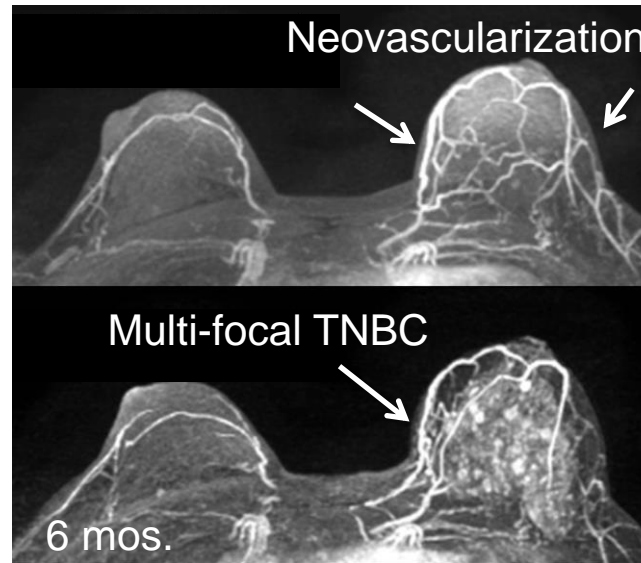
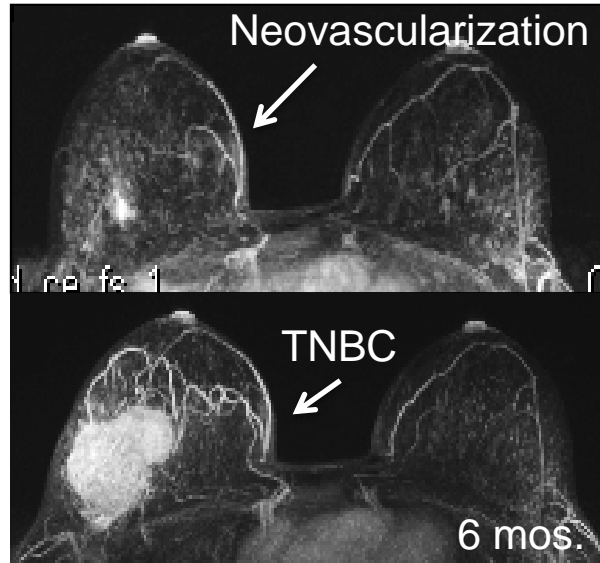
➔ early detection and risk reduction



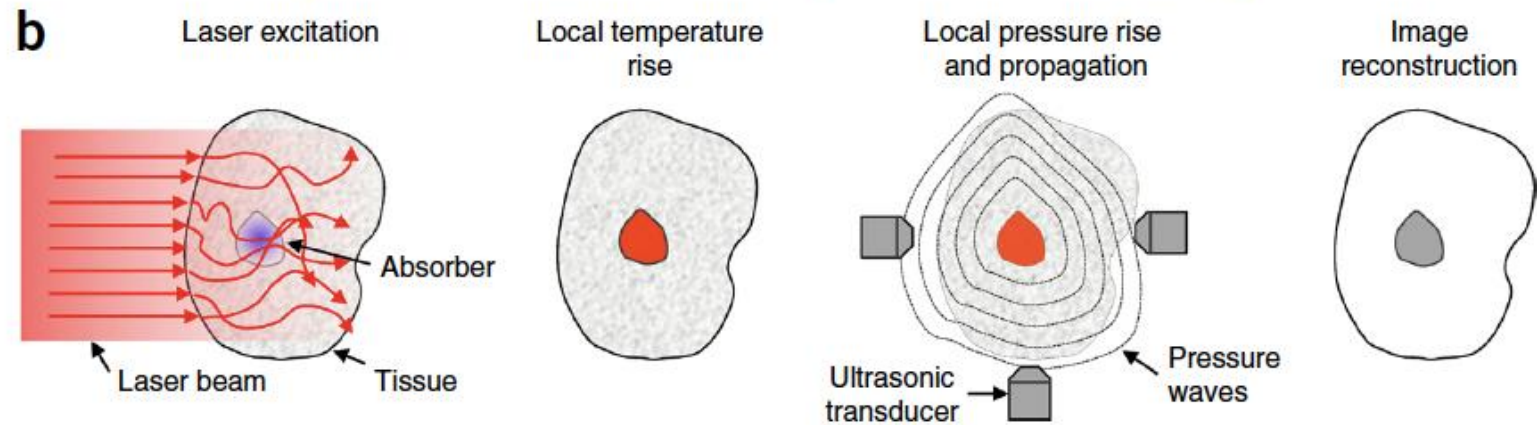
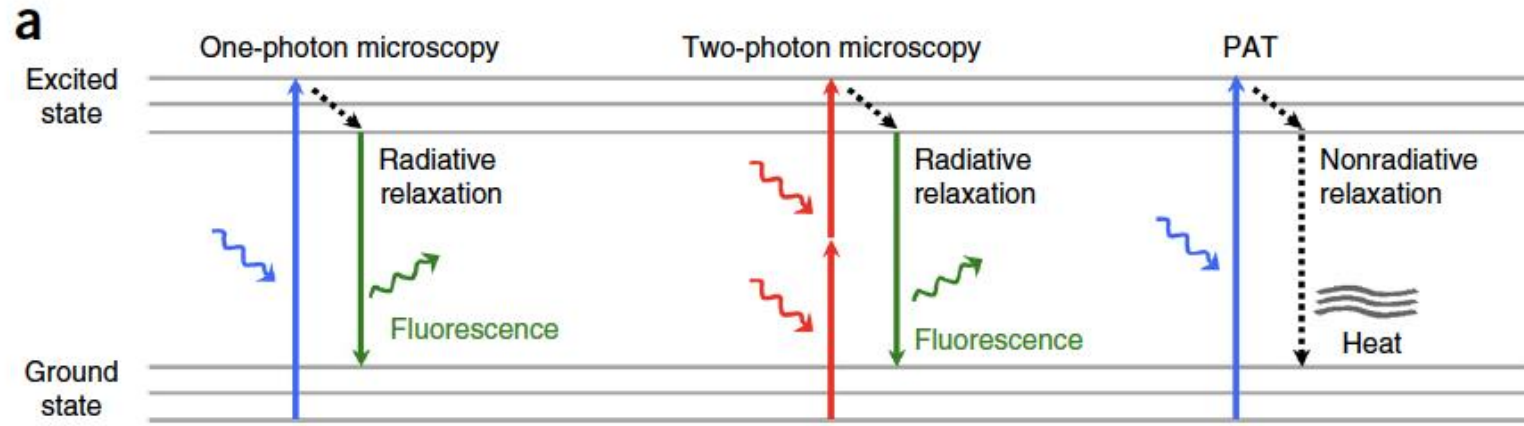
Lihong Wang. Long Cai



Neovascularization and progression



Vascular/Metabolic Imaging - Photoacoustic Tomography (PACT) - Caltech - Lihong Wang, PhD



Short laser pulse

Photons propagate

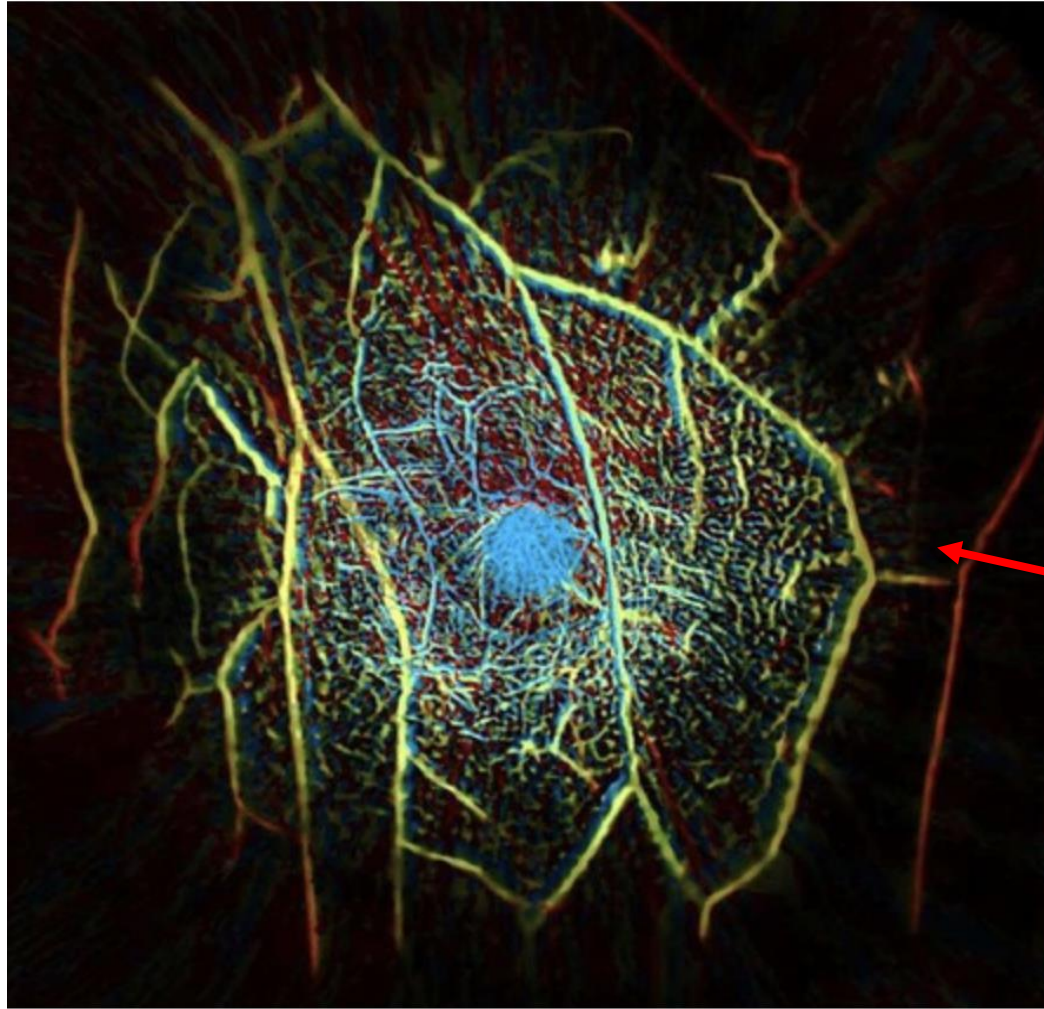
Photons absorbed by bio-molecules

Absorbed energy → to heat

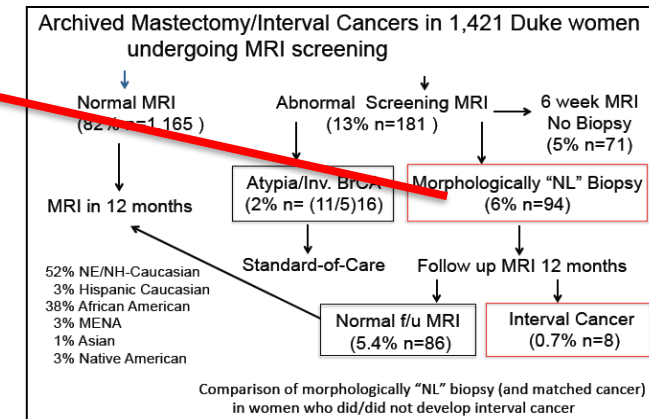
Heat-induced pressure wave propagates as ultrasound wave

US wave detected. Image reconstructed

Vascular/Metabolic Imaging - Photoacoustic Tomography (PACT) - Caltech - Lihong Wang, PhD

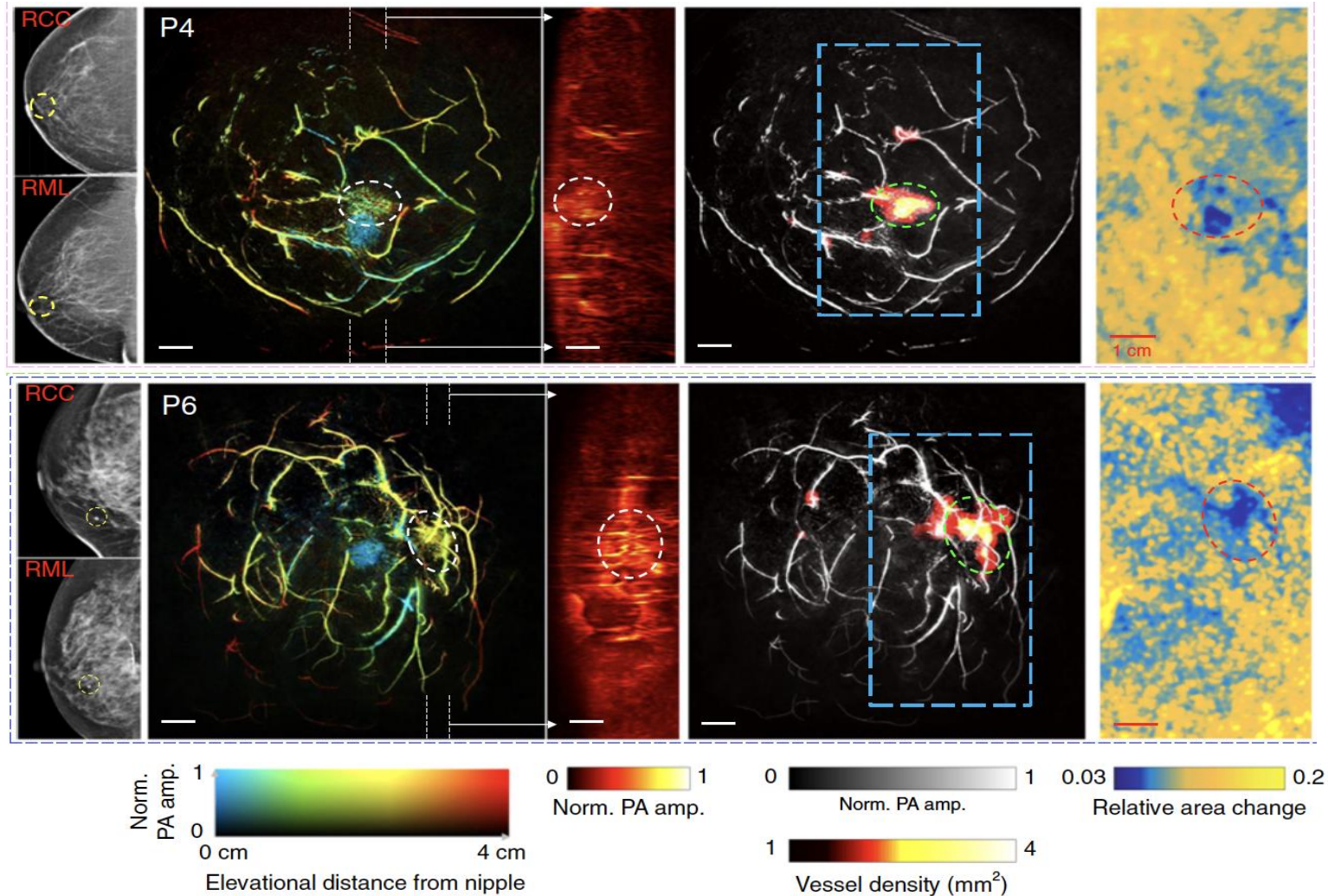


- 15 s image acquisition
- 250 μ in-plane resolution
- Endogenous fluorescence
- Repeat imaging
- Biological read out
- No compression of breast



Visualization of blood vessels by PACT – combined US-optical tomography

Photoacoustic Tomography (PACT) early detection of occult breast cancer and neovascularization



Visualization of blood vessels by PACT – combined US-optical tomography

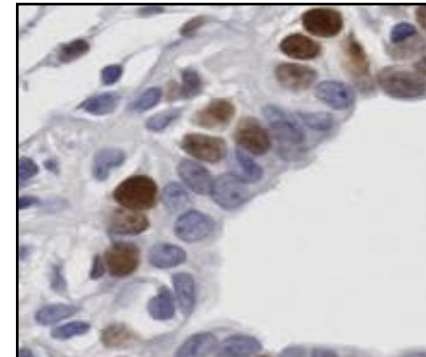
Lin et al. *Nature Communication*, 2018

Insulin resistance, insulin, TNBC

Evidence for insulin-driven aggressive biology

Systems biology

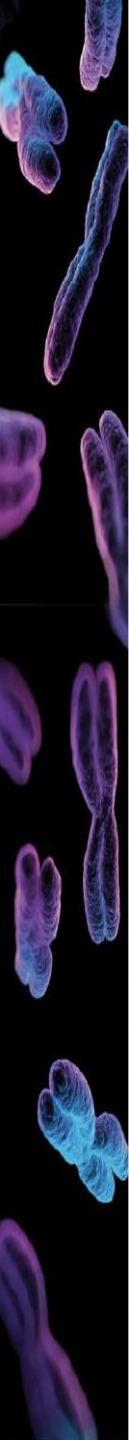
→ epigenetic signaling



Rama Natarajan PhD



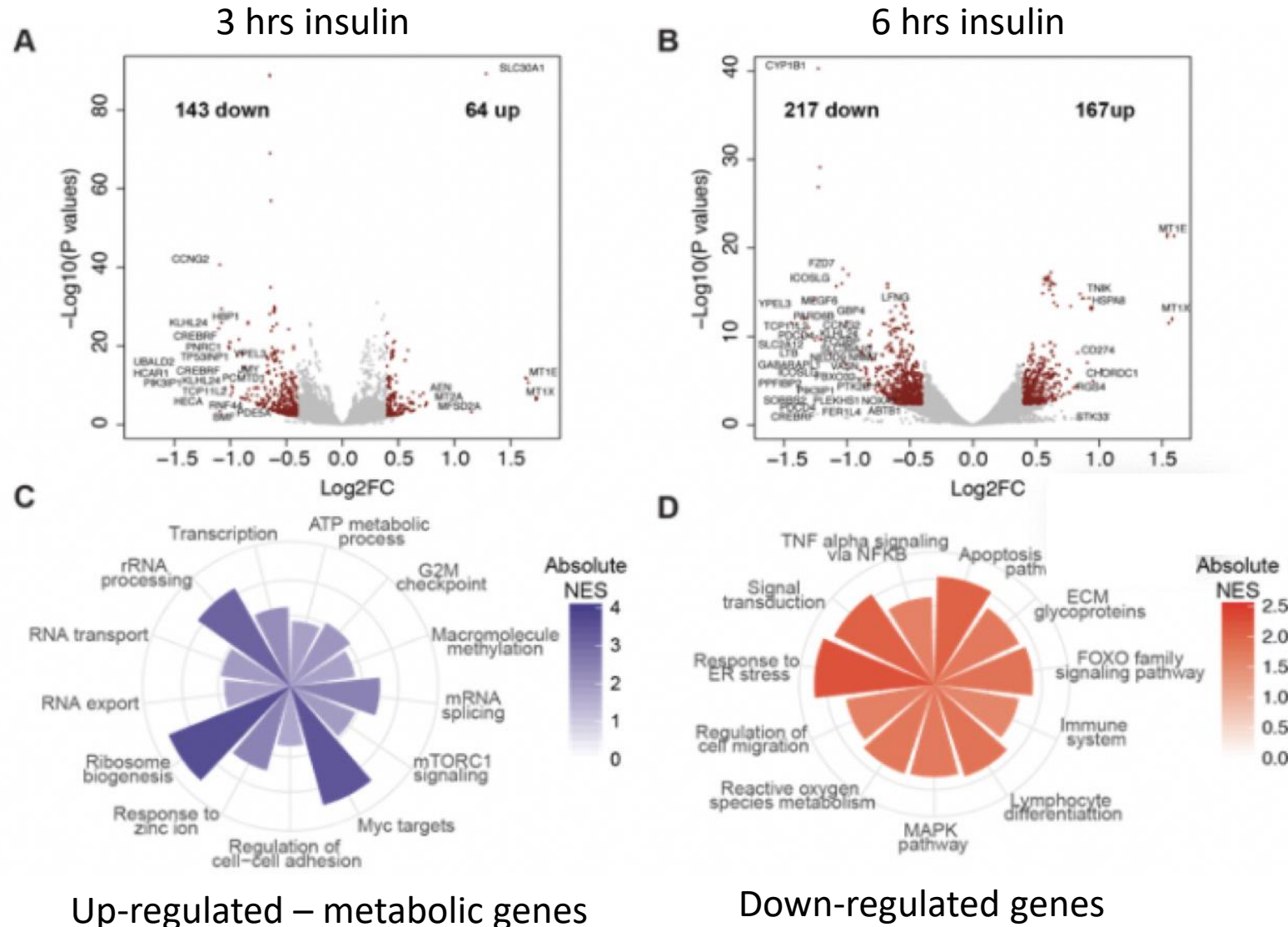
Dustin Schones PhD



Insulin acetylates promotor H3K9Ac - increases transcription

R01CA220693 (Seewaldt, Ann, Schones, Talisman)

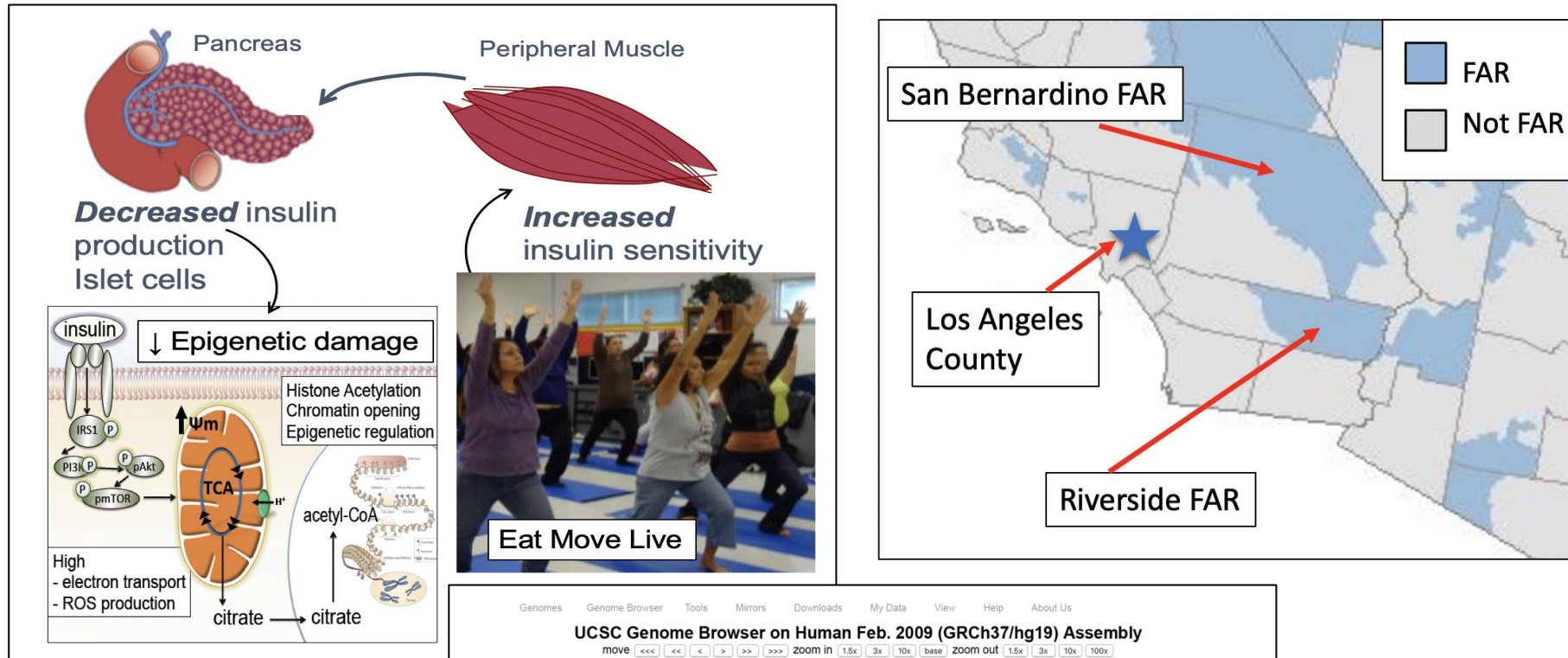
- Senpati et al. *Epigenetics Chromatin* 2019



Can Epigenetic Damage be Reversed?

NIH CCSG Sup. Frontier & Rural Zip Codes Breast CA Survivors
Telehealth Contactless Trial

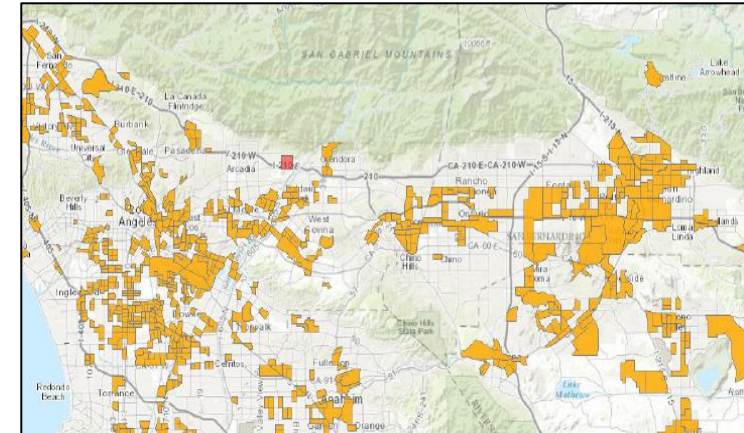
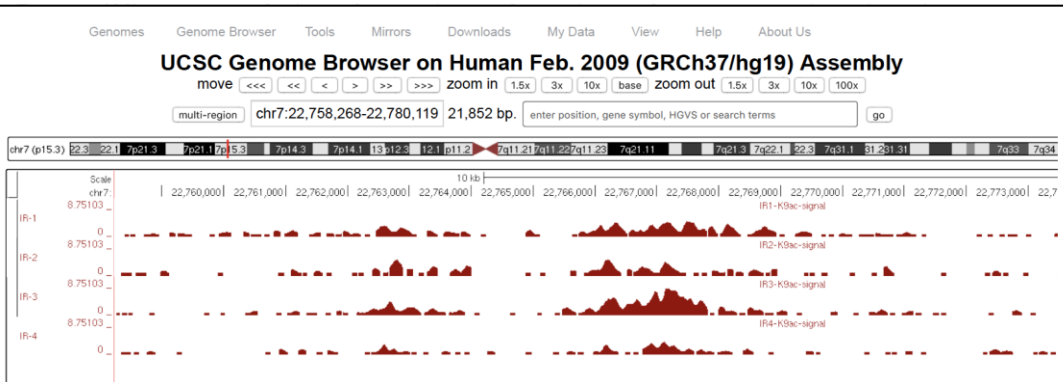
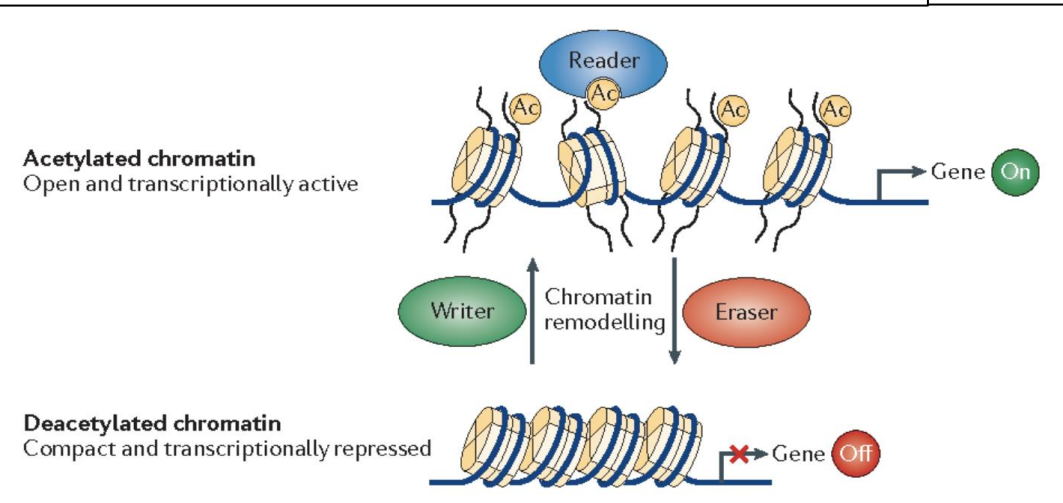
Started Accruing 07/21 - Antelope Valley - Tanyanika Phillips MD



Does Living in a Food Desert Census Tract Promote Epigenetic Damage - 521 women enrolled

R01CA220693 (Seewaldt, Ann, Schones, Talisman)

High Insulin Drives Chromatin Acetylation



Insulin Resistant Women ChIP Seq - Cytokine

Top Hits WBC:

- IL6
- TNFalpha
- IL1-beta
- CXCL1

Yee et al. *Frontiers Endocr.* 2020; Senapati et al. *Epigenetics & Chromatin*, 2020
 Ramos et al. *iScience*, 2020; Dietze et al. *Cancers*, 2021 in revision

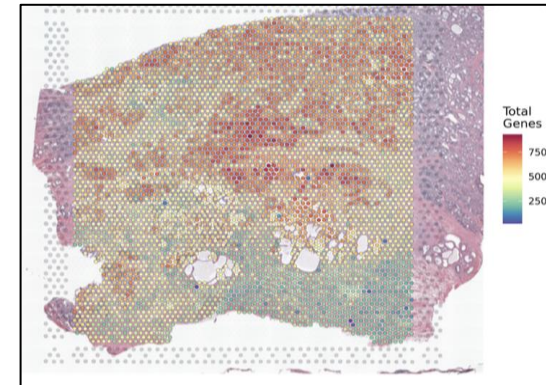
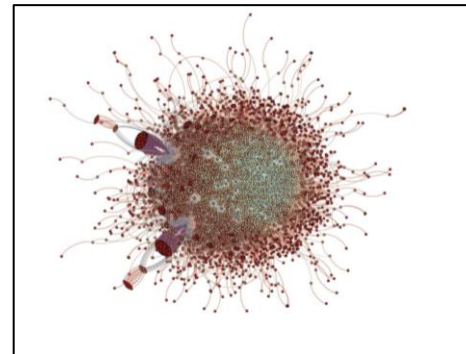
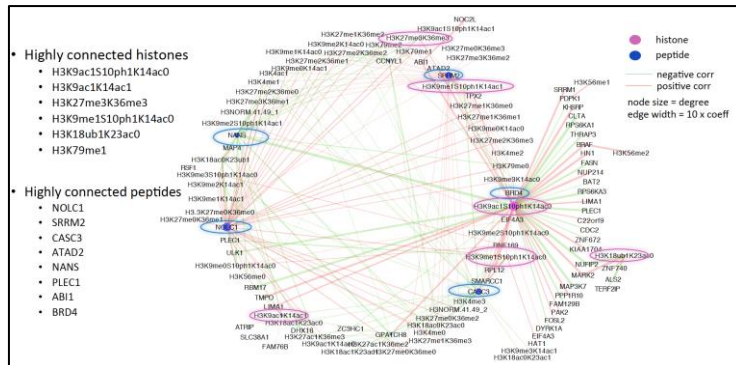
Insulin resistance, insulin, TNBC

Evidence for insulin-driven aggressive biology

Systems biology



microenvironment – single cell and spatial transcriptomics



Systems Biology

UC San Diego

JACOBS SCHOOL OF ENGINEERING

Shankar Subramanian PhD



BrCA Biology



Veronica Jones MD



Immunology



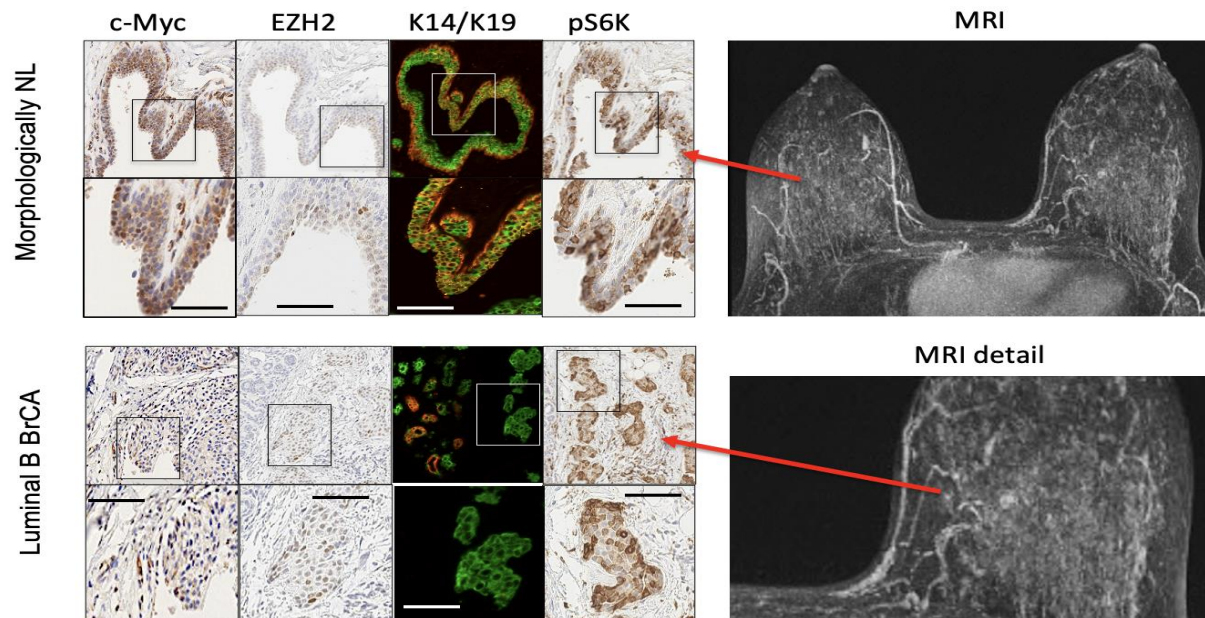
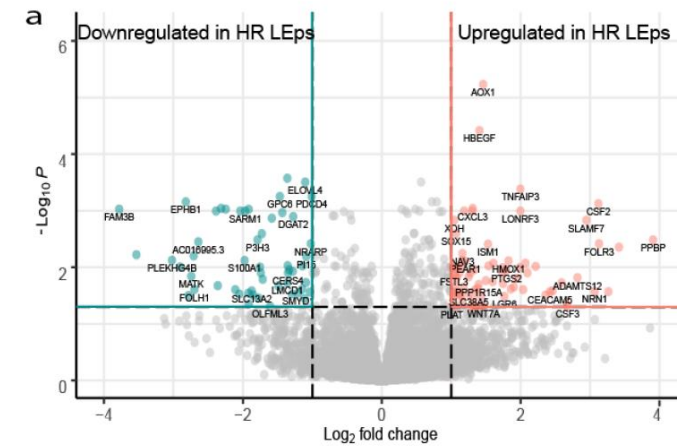
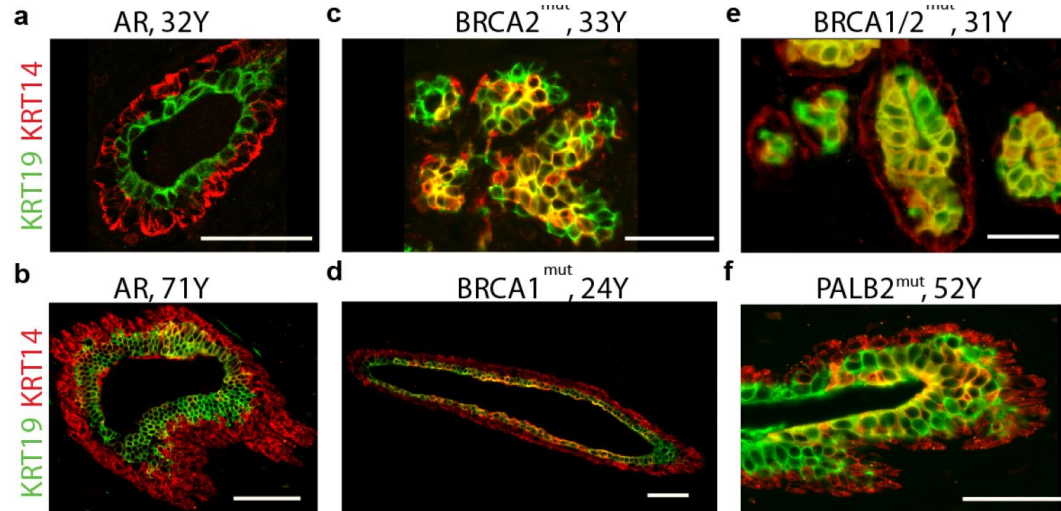
Augusto Ochoa MD
Maria Sanchez-Pino

Insulin-Driven Pre-Cancerous Biopsy

U01CA189283 - prospective (Duke, OSU, UT, USC)



Sundus Shalabi MD PhD



Shalabi S. et al.
Seewaldt/LaBarge *Nature Aging* 2021 in press

Frankhouser et al.
PLoS Medicine
2021 in revision

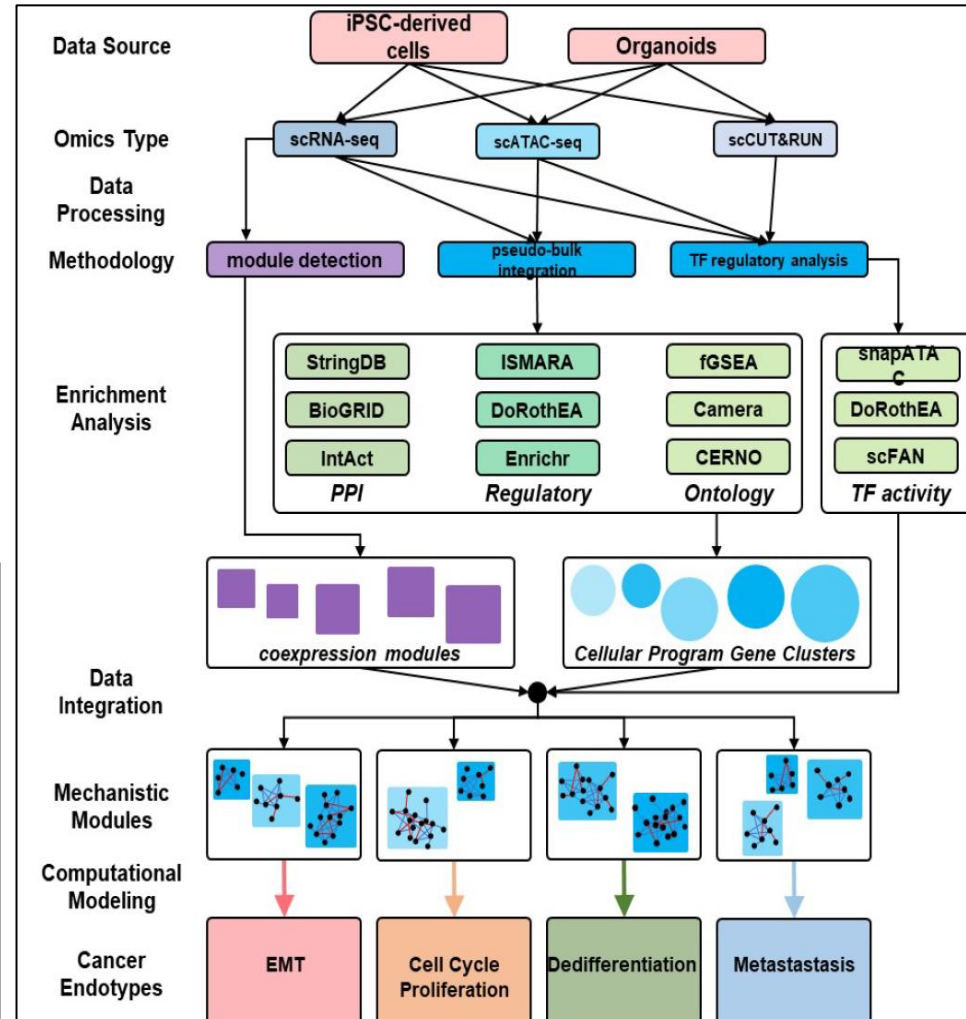
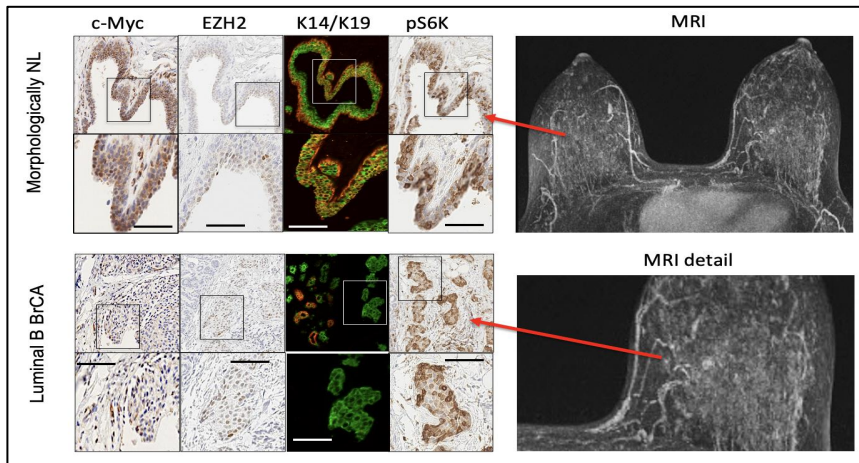
Welcome Trust – Delta Tissue – TNBC

Focus on women of African Ancestry

Shankar Subramaniam UCSD, Augusto Ochoa LSU

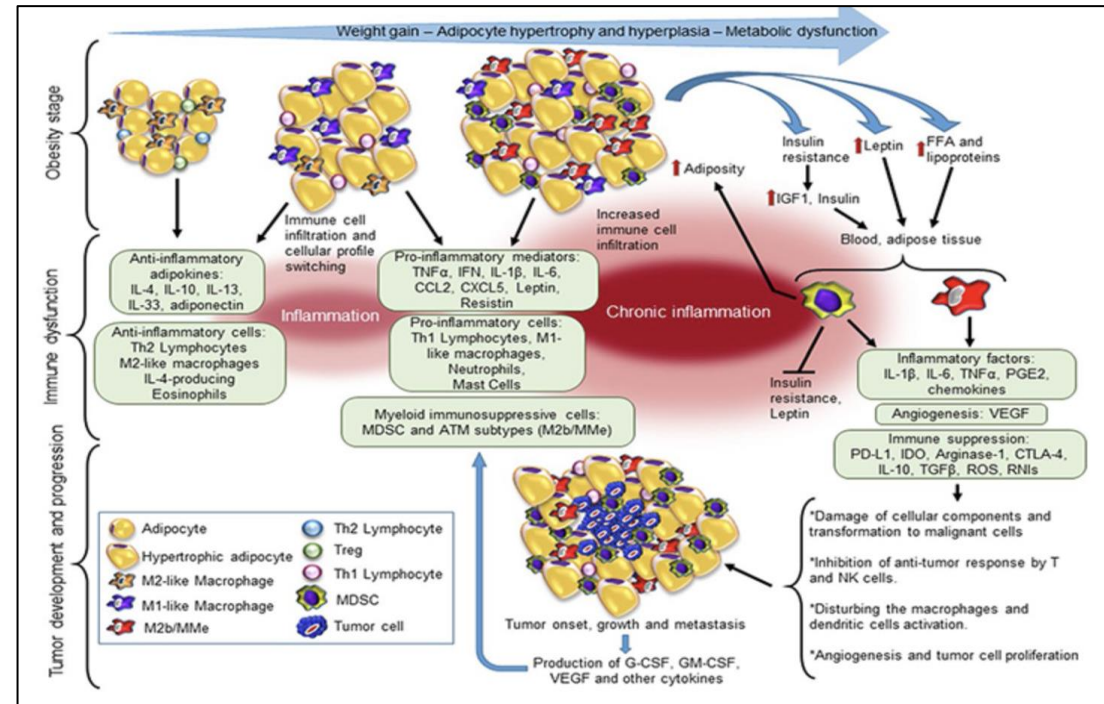
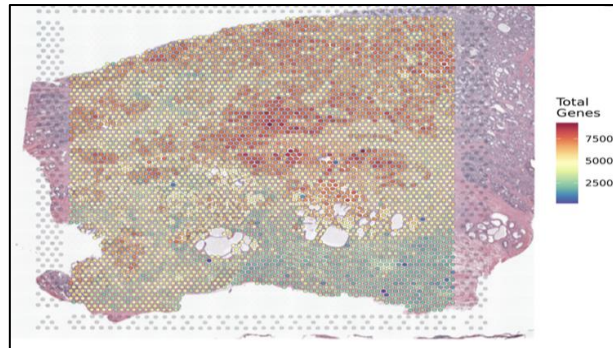
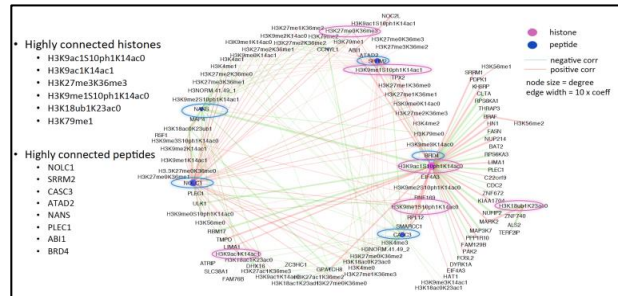
Single Cell Analysis Spatial Transcriptomics

- Is aggressive biology hardwired in premalignant tissue?
- Impact of insulin/cholesterol innate immunity/inflammation



Welcome Trust – Delta Tissue – TNBC

- Obesity, metabolism, and immunosuppressive environment
- Contribution immunosuppressive MDS to chemo-resistance



Systems Biology
 UC San Diego
 JACOBS SCHOOL OF ENGINEERING
 Shankar Subramanian PhD



BrCA Biology
 City of Hope
 Veronica Jones MD



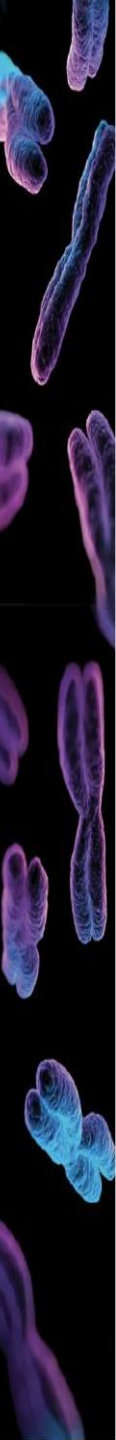
Immunology
 LSU Health
 NEW ORLEANS
 Augusto Ochoa MD
 Maria Sanchez-Pino

Summary

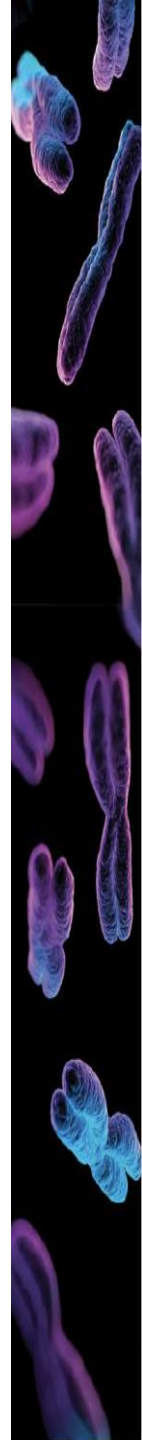
- Pre-diabetes and insulin counts
- Early evidence of aggressive biology
- Evidence for intersection of Wnt/EZH2 and pAKT signaling

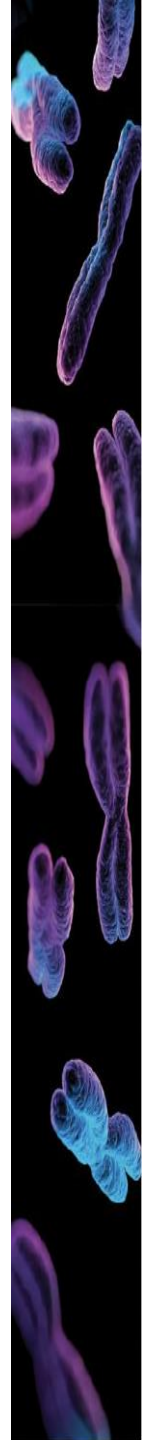
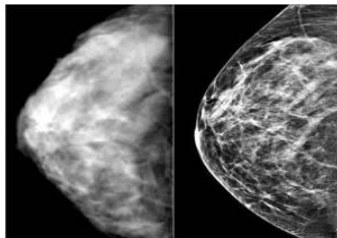
Future Directions

- Integration of single cell analysis, spatial transcriptomics, and metabolic imaging



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





Serial analysis neoadjuvant chemotherapy tx breast cancer

