RESEARCH ON TAP

Genomes in the 21st Century

Monday, October 24, 2022

bu.edu/research/events

BOSTON UNIVERSITY

Boston University Office of Research

Agenda

- Welcome Remarks
- Presentations
  - Charles DeLisi
  - Trevor Siggers
  - Joshua Campbell
  - Juan Fuxman Bass
  - Camron D. Bryant
  - Christopher A. Schmitt
  - Sarah W. Davies
  - Rick Sherva
  - Rachel Flynn
- Closing Remarks

The Profound Implications of Genomics Beyond the Animal Kingdom

Charles DeLisi

Arthur Metcalf Professor of Science and Engineering
College of Engineering

From Humans to Plants

- Cancer Genomics and Immunology (largely historical)
- Data Mining Development and Network Inference
- Planetary Climate
  - Mechanisms of Planetary Energy Balance Regulation on Geologic Time Scales
  - Agrigenomics and Climate Change (main current activity)

    Engineering RuBisCO (the problem of photorespiration)

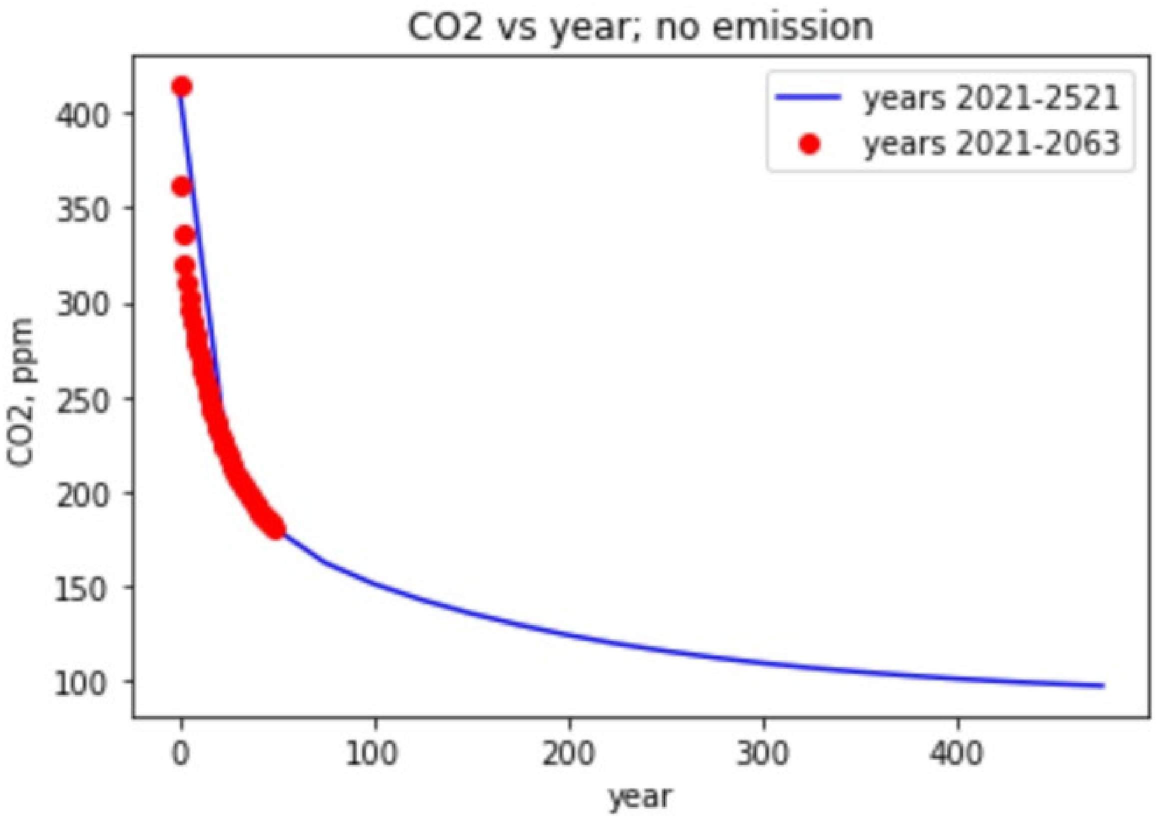
    Activities With The Gates Foundation

Mitigating and Adapting to Climate Change Through Agrigenomics

Three numbers place the magnitude of the problem in perspective

- Energy Imbalance: ~ 2.3 W m^{-2} (Equivalent to the rate of energy release by 5 Hiroshima bombs per second)
- Current Concentration of Atmospheric CO2 Exceeds Preindustrial Level by ~ 1 Trillion tonnes.
- CO2 Remains in the Atmosphere for Centuries

Some 20 - 25 % of CO2 now in the Atmosphere Will Still be There in 500 Years



Trees Engineered for Increased Yield Can Dramatically Reduce Atmospheric Carbon

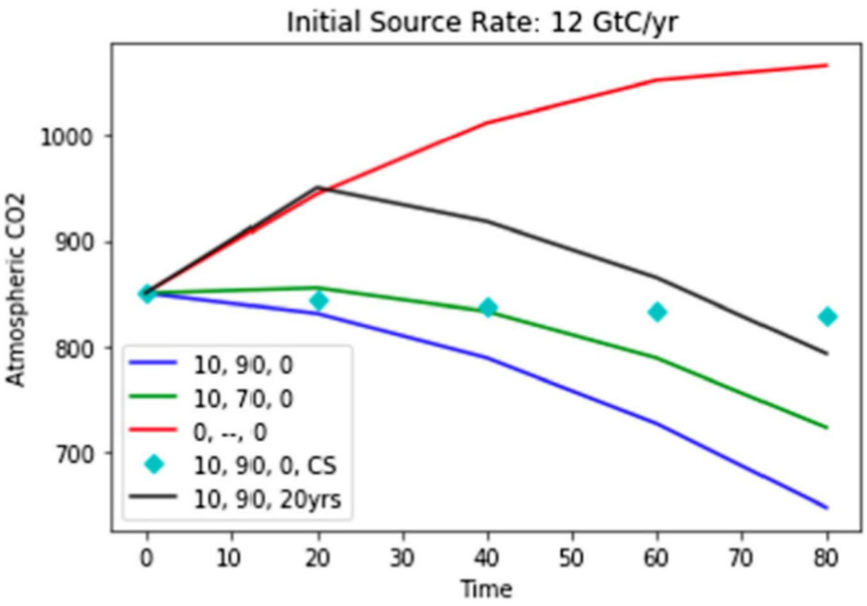


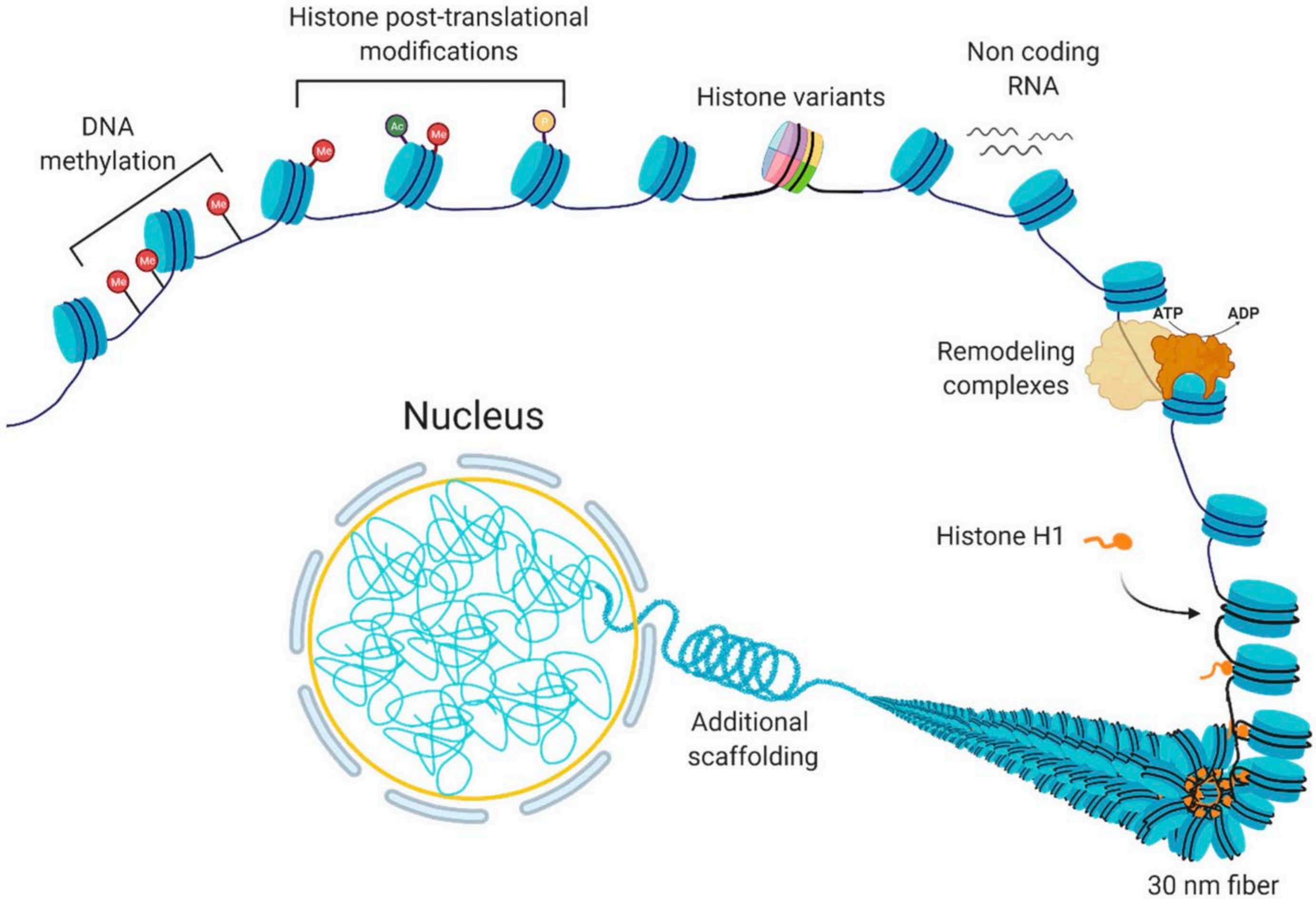
Fig. 2 Atmospheric carbon dioxide as a function of time in years. The triplets in the legend represent the percentage of engineered trees, their efficiency, and the mitigation start time. The last entry (black) shows the course of atmospheric CO2 when mitigation is delayed 20 years. CS indicates that the source remains constant at 12 GtC/year; in all other cases it decreases uniformly to zero over an 80-year period

Who's Regulating the Genome?

Trevor Siggers

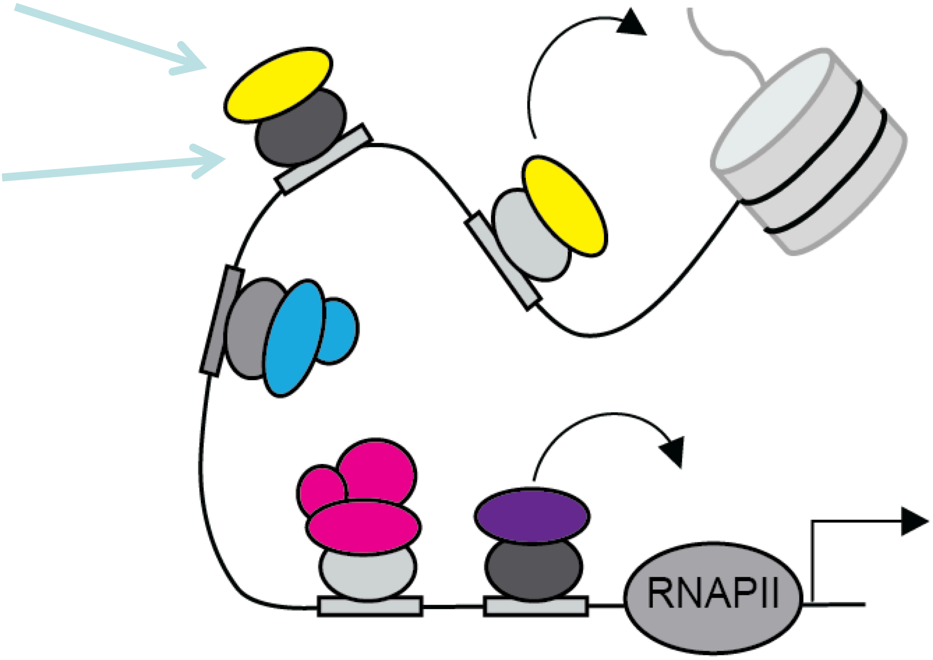
Associate Professor
Biology, CAS

Genomic DNA exists in complex with proteins



Alspoy et al. (2021) Biology 10(4):272

Transcription factors recruit cofactors to regulate the genome


Cofactor (COF)

Transcription factor (TF)

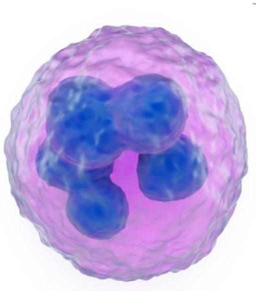
CASCADE approach to characterize TF-COF complexes

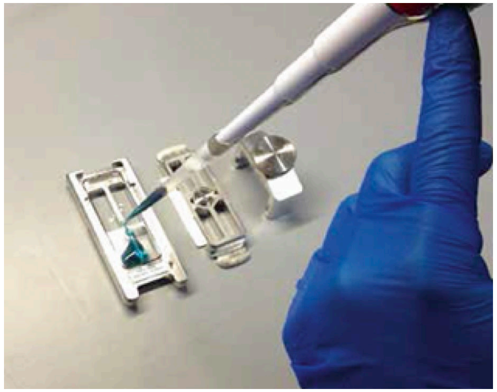
Cell
extracts

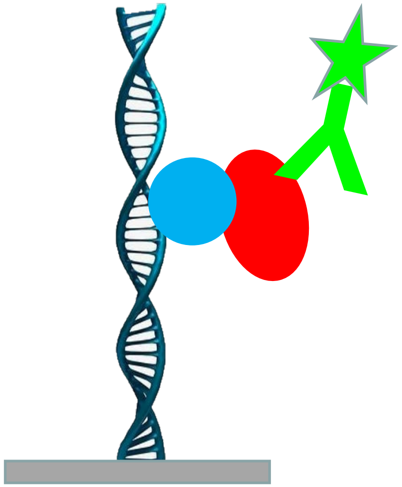
Apply to
microarray

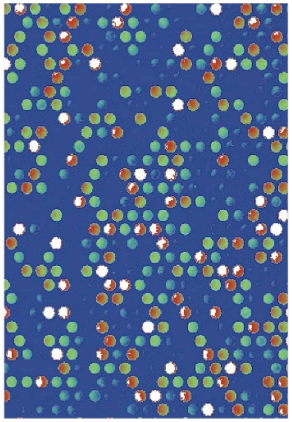
Label bound
proteins

Quantify thousands
of binding events





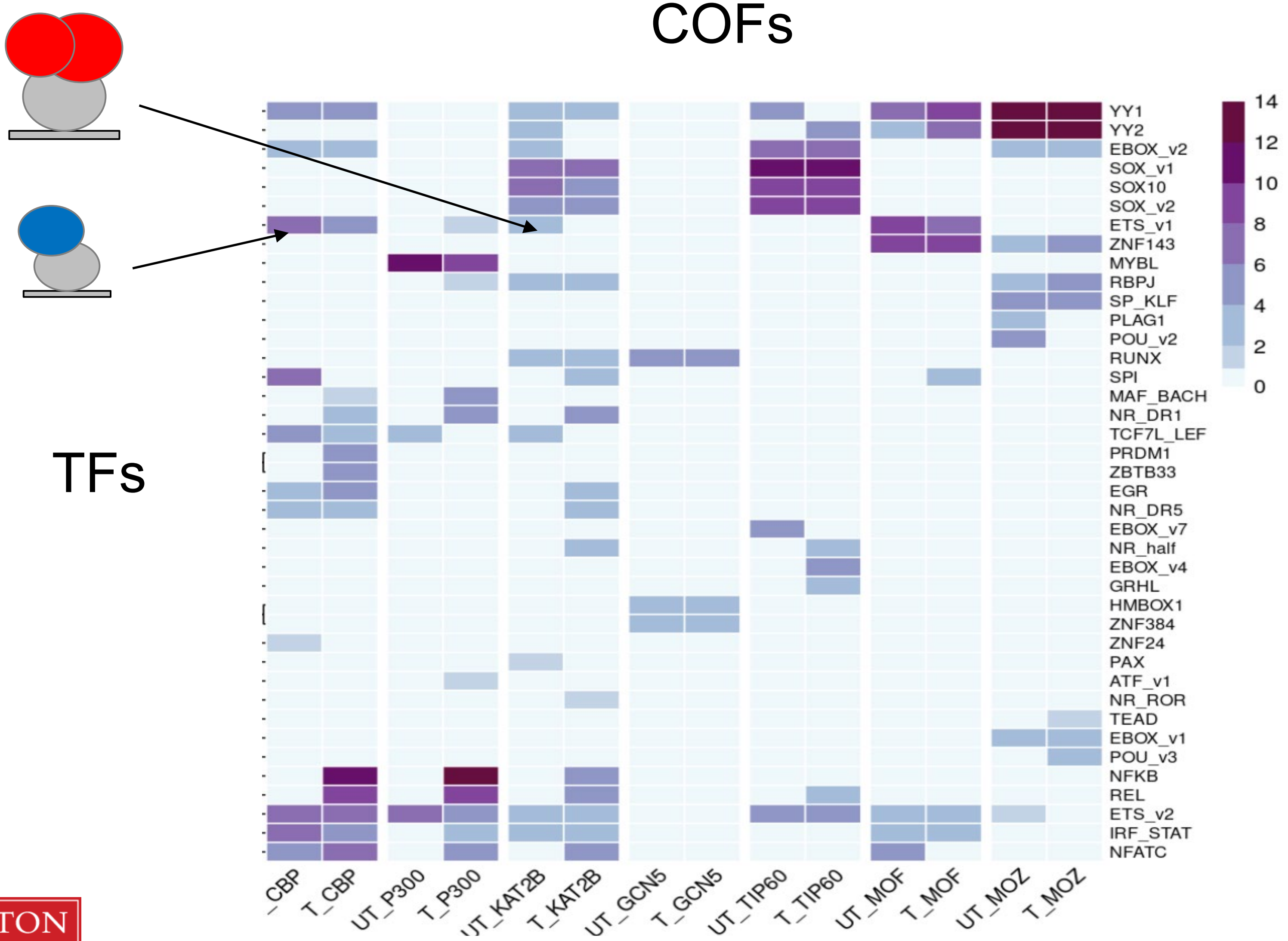




Bray & Hook *et al.* (2022) Cell Genomics

Mapping TF-COF complexes to study genome regulation

COFs

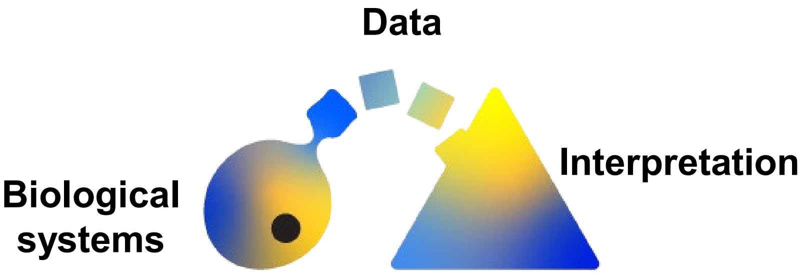


TFs

Examining Genomic Differences in Prostate Cancer Between African American and European Men

Joshua Campbell

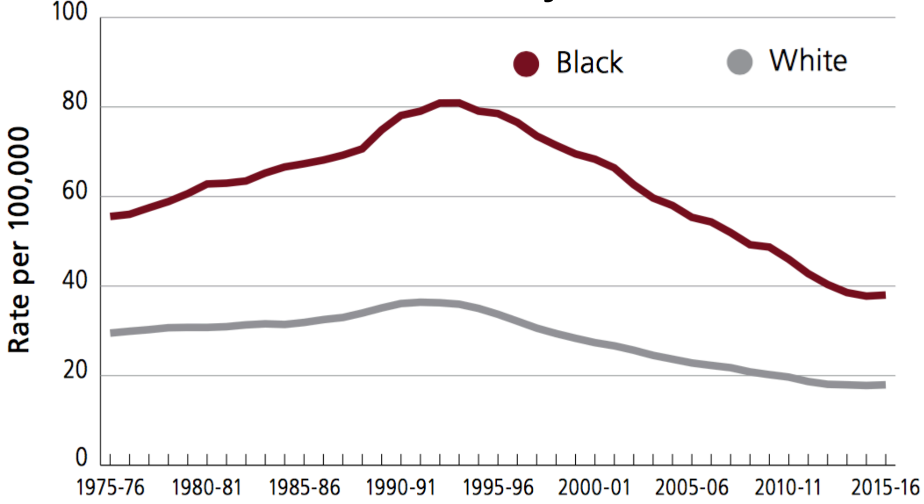
Associate Professor
Section of Computation Biomedicine, Dept. of Medicine
Boston University School of Medicine



camplab.net
@camplab1

African American (AA) men have worse clinical outcomes compared to European American (EA) men in prostate cancer.

- 1.5-fold higher incidence rate
- 2-fold higher mortality rate
- Diagnosed at a younger age
- More aggressive disease at time of diagnosis



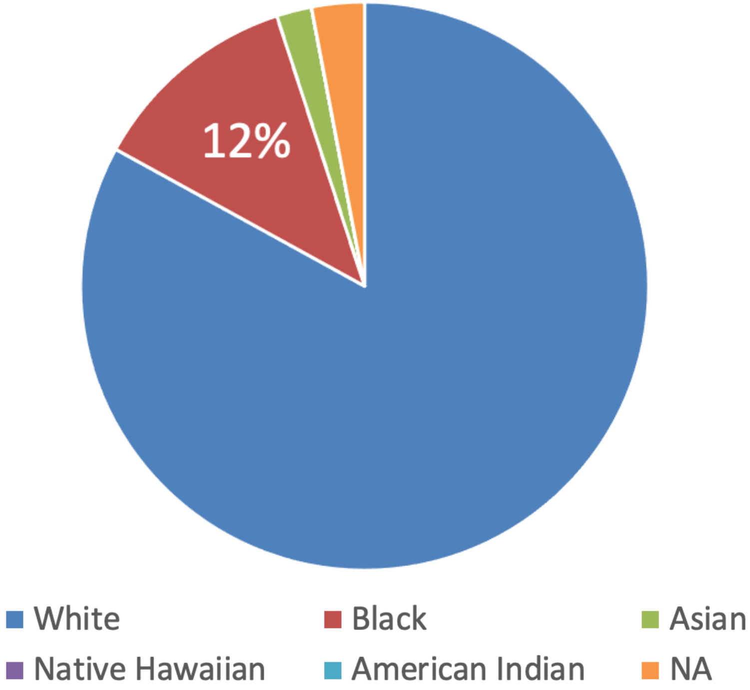
Prostate cancer mortality

American Cancer Society. *Cancer Facts & Figures for African Americans 2019-2021*.

AA men are underrepresented in genomic studies.

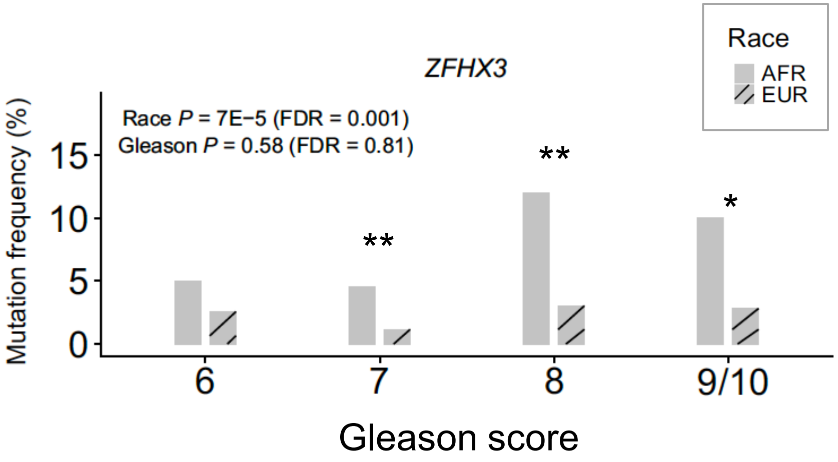
Cell Resource

The Molecular Taxonomy of Primary Prostate Cancer

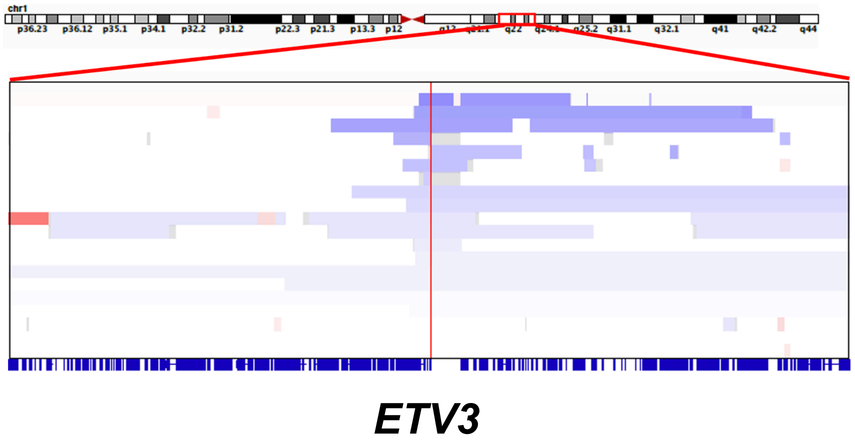


A meta-analysis across four cohorts revealed gene alterations frequencies associated with self-reported race.

ZFHX3 mutations were more frequent in AA men.



ETV3 was significantly recurrently deleted only in AA men.

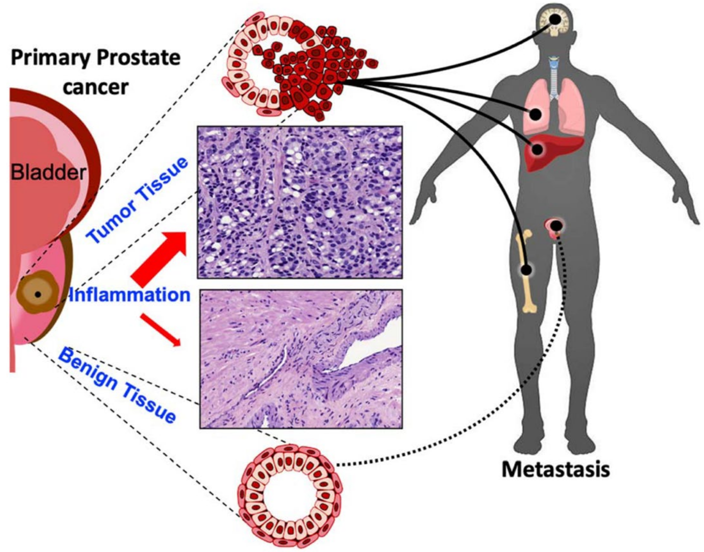


Koga, Song et al, *Clinical Cancer Research,* 2020

Yusuke Koga
(BU)

Franklin Huang
(UCSF)

Genome sequencing of primary tumors from African American patients at Boston Medical Center (BMC).



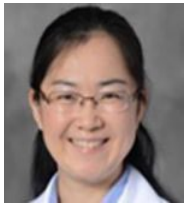
Archer et al, *Cancers*, 2020

NCI Center to Reduce Cancer Health Disparities (R01)
Whole-exome sequencing (300 AAM, 200 EAM)

BU CTSI & BU Shipley (Pilot award)
Whole-genome sequencing (25 AAM, 25 EAM)

Pathology

Zhichun Lu



Liz Duffy

Chris Andry

Hematology & Medical Oncology

Chris Heaphy

Joakin Mori

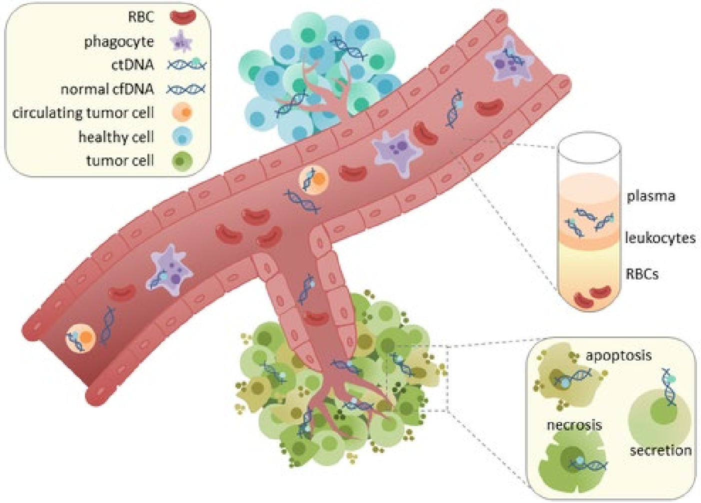
Pharmacology

Rachel Flynn

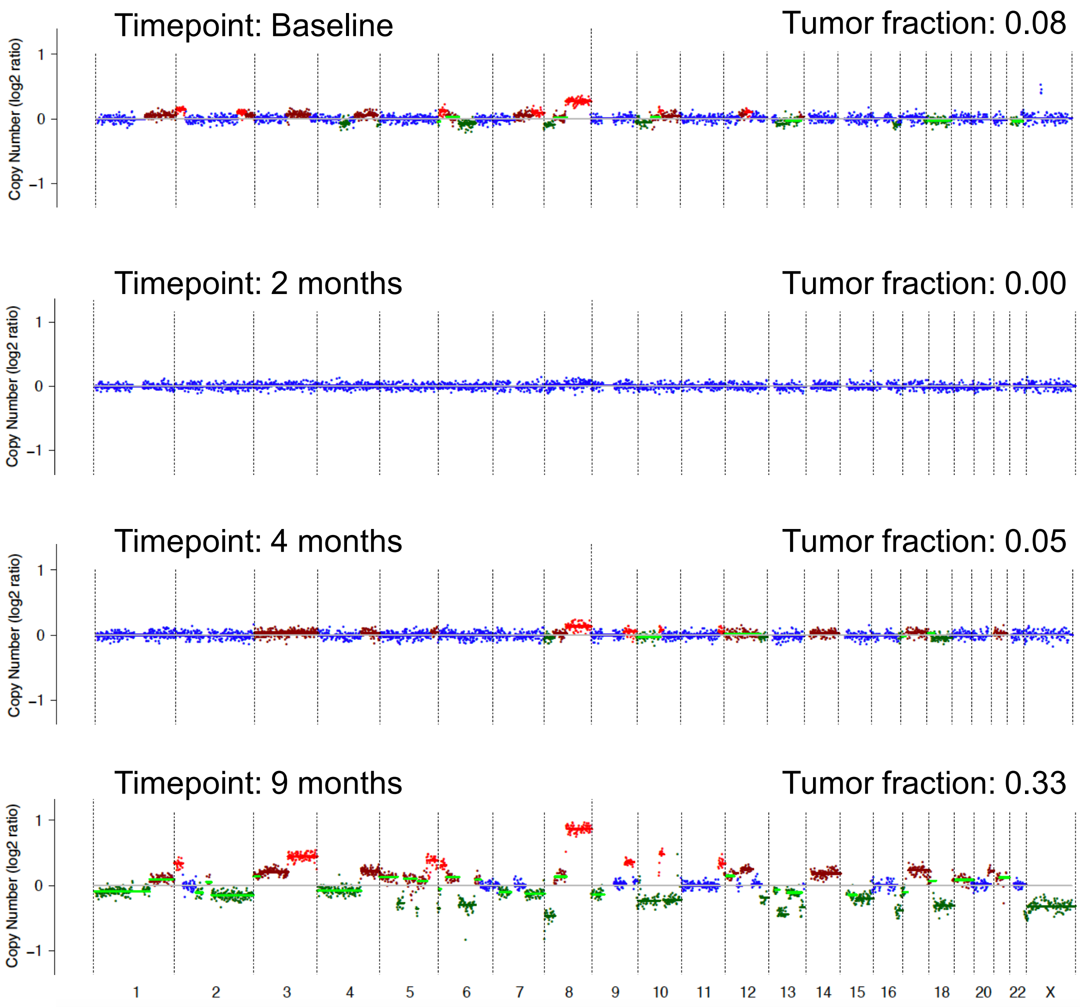
Biochemistry

Alla Grishok

Genome sequencing of cell-free DNA from African American patients at BMC with metastatic disease.



https://en.wikipedia.org/wiki/Circulating_tumor_DNA



Timepoint: Baseline Tumor fraction: 0.08

Timepoint: 2 months Tumor fraction: 0.00

Timepoint: 4 months Tumor fraction: 0.05

Timepoint: 9 months Tumor fraction: 0.33

Hematology & Oncology

Gretchen Gignac

Matthew Kulke

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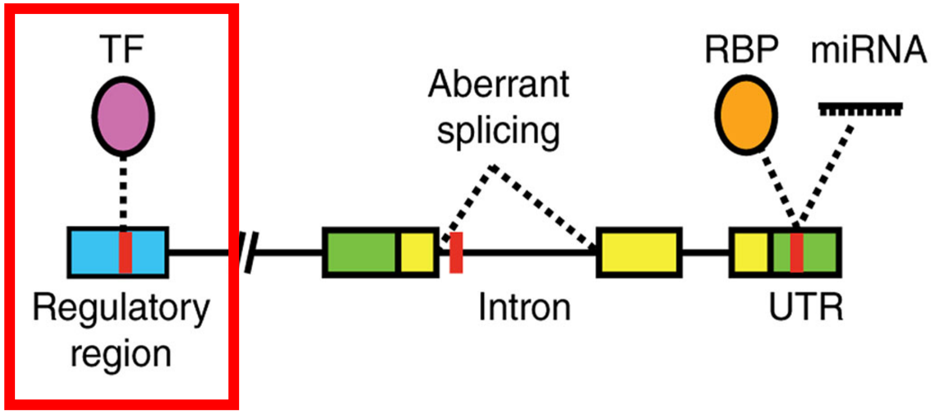
Identification and Characterization of Cancer Driver Mutations in Non-Coding Regions

Juan Fuxman Bass

Assistant Professor
Biology, CAS

Cancer driver mutations in non-coding regions

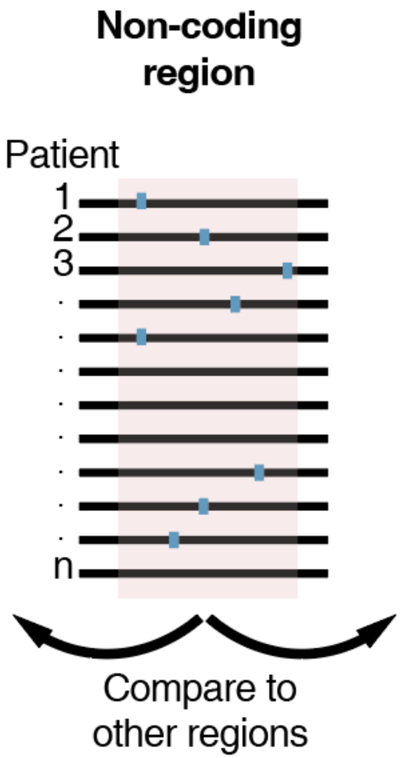
- Millions of mutations have been identified in cancer patients.
- >95% of cancer mutations reside in non-coding regions.
- It is challenging to identify functional non-coding mutations
  → **only ~70 known drivers**



Gan et al, *Frontiers in Genetics* 2018

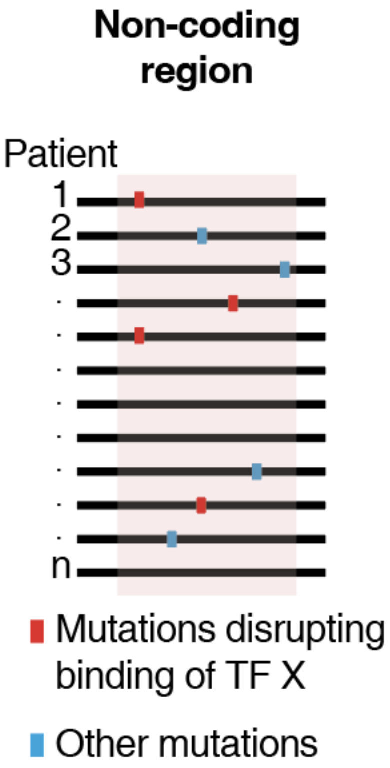
Which non-coding mutations are cancer drivers?

Traditional burden tests



- Identify regions with increased mutational frequency across patients.
- Background mutational frequencies are derived from other genomic regions.

TF-aware burden test

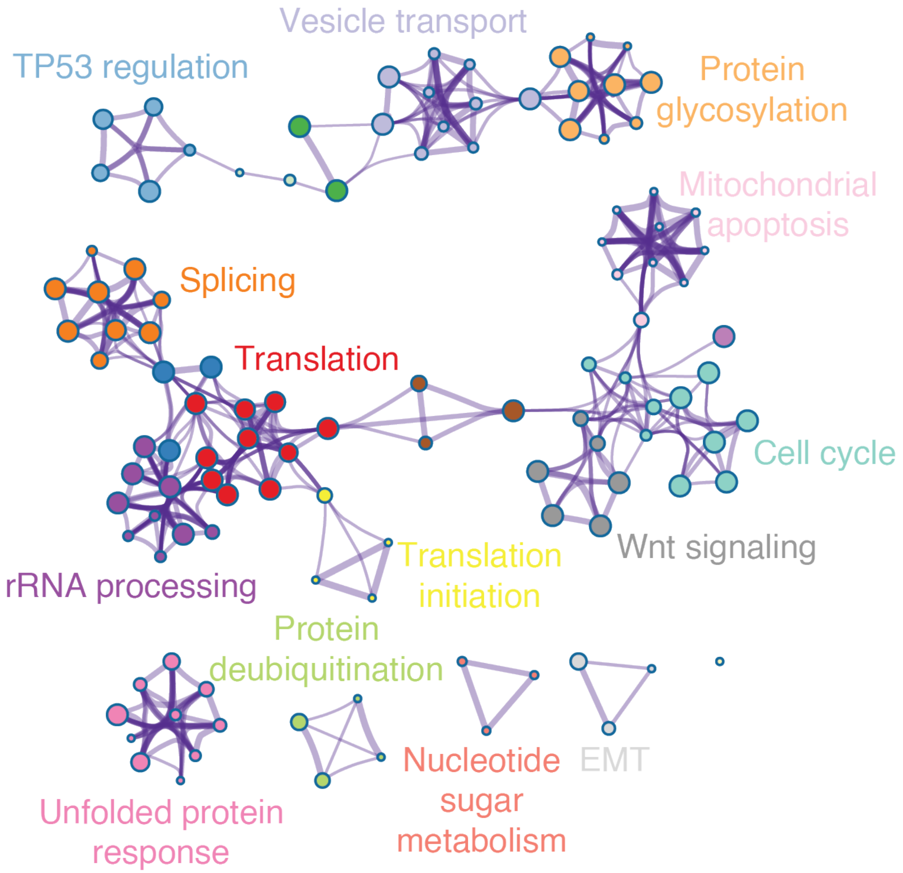


- Finds mutations that share mechanism.
- Increases statistical power.

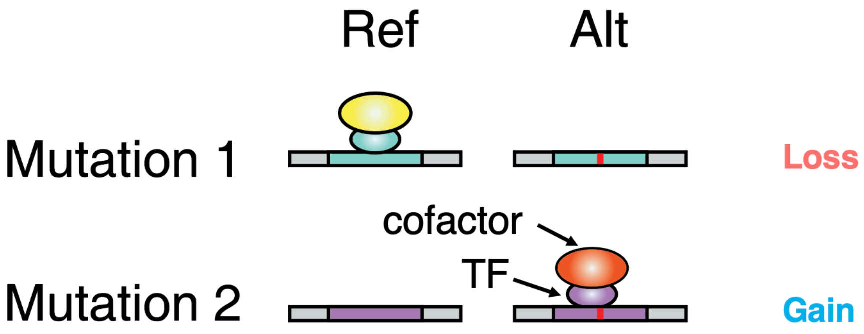
Predicted non-coding mutations are functional

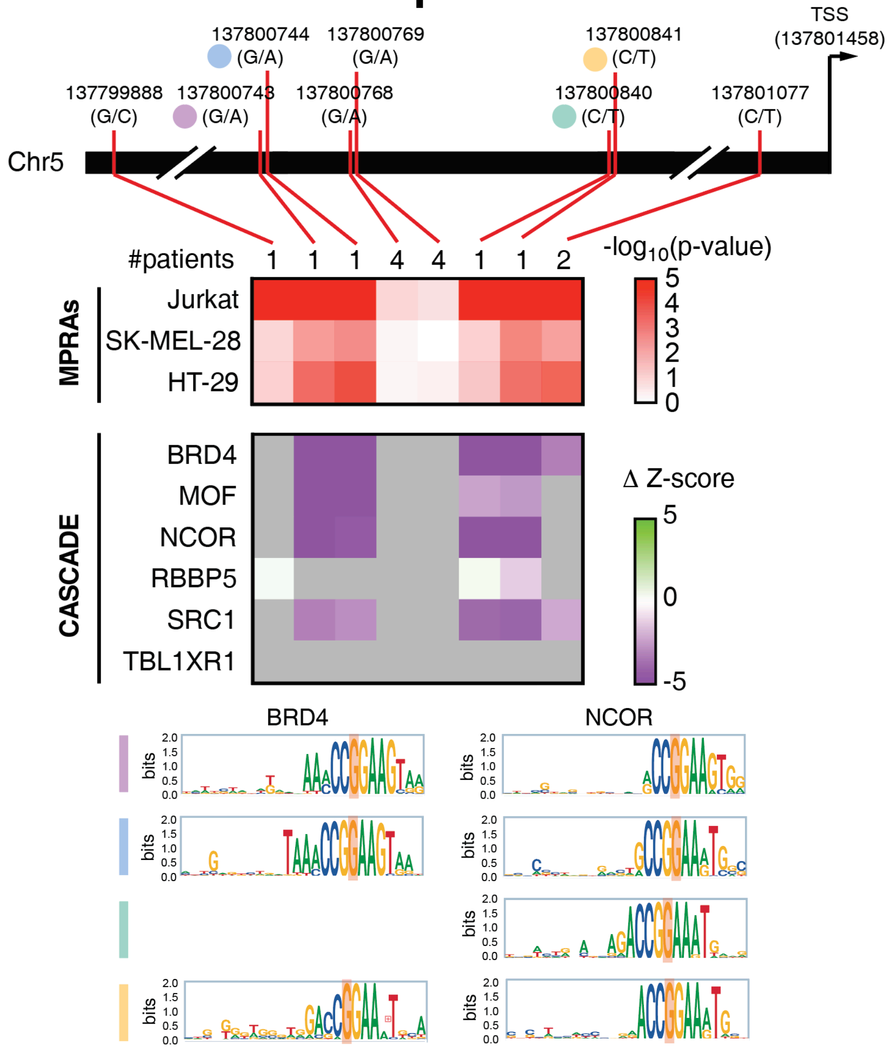
- We predicted 2,555 driver non-coding mutations in 813 genes.
- Genes are associated with housekeeping and cancer-related functions.
- Hundreds of mutations affect transcriptional activity.

How do these mutations affect gene expression?



Non-coding mutations alter cofactor recruitment




EGR1 promoter

We identified hundreds of cancer driver mutations and their mechanisms.

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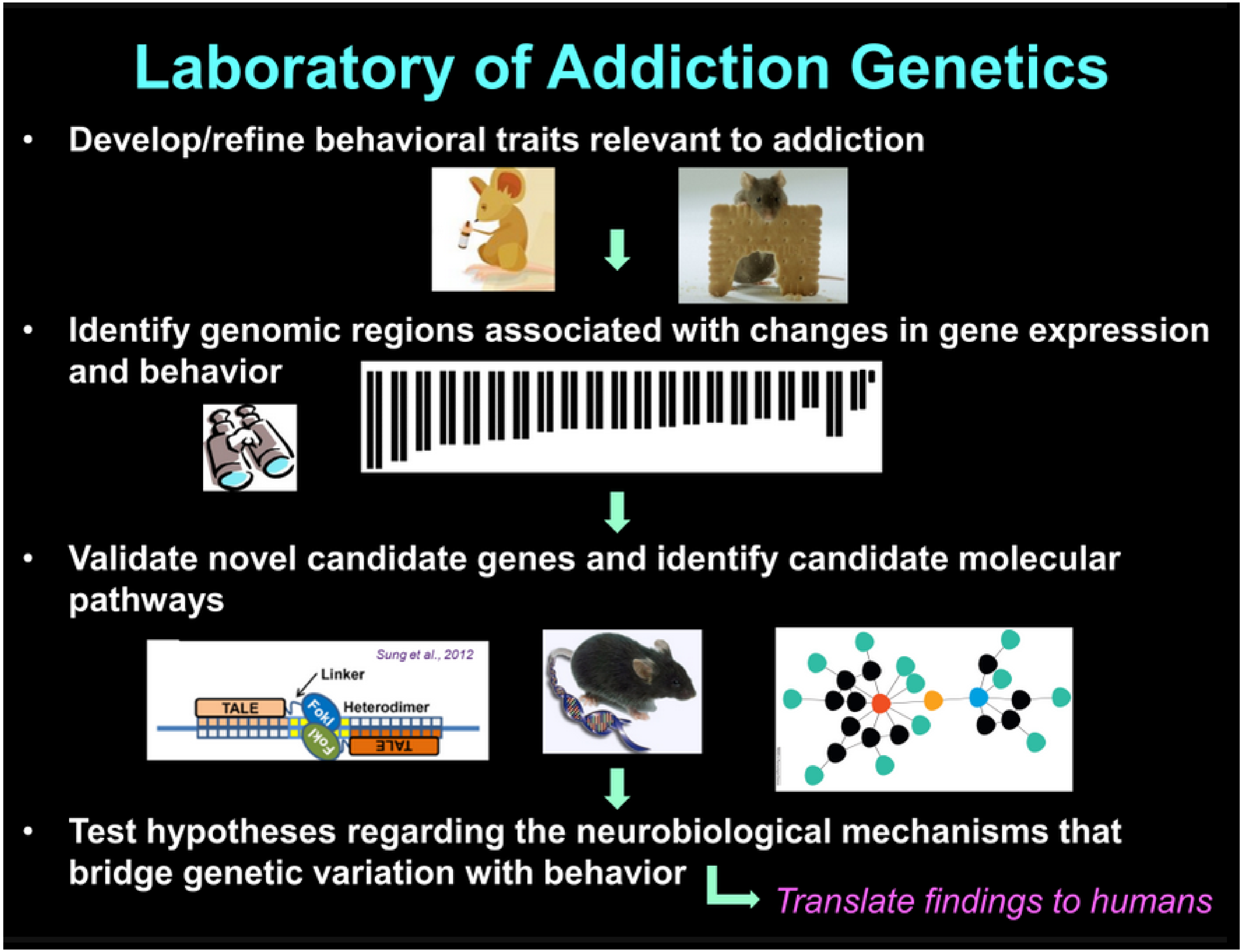
Catching the Drift: Exploiting Near-Isogenic Genomes for Rapid Gene Discovery for Neurobehavioral Traits

Camron D. Bryant, Ph.D.

Associate Professor
Department of Pharmacology & Experimental Therapeutics and Psychiatry
Boston University School of Medicine

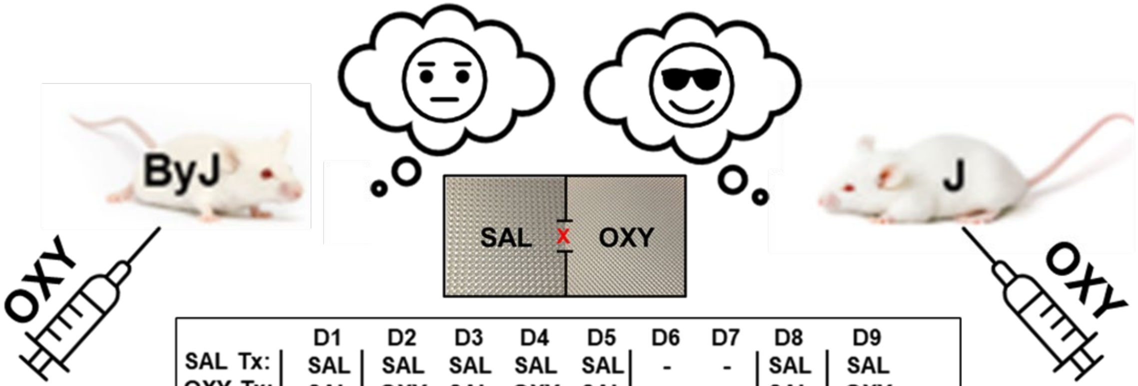


Laboratory of Addiction Genetics

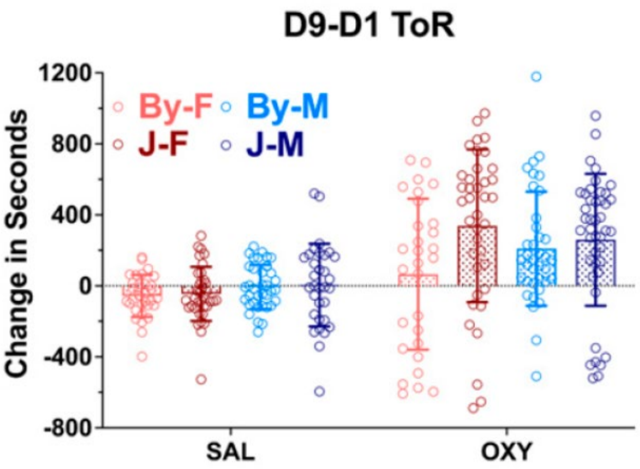
- Develop/refine behavioral traits relevant to addiction
- Identify genomic regions associated with changes in gene expression and behavior
- Validate novel candidate genes and identify candidate molecular pathways
- Test hypotheses regarding the neurobiological mechanisms that bridge genetic variation with behavior

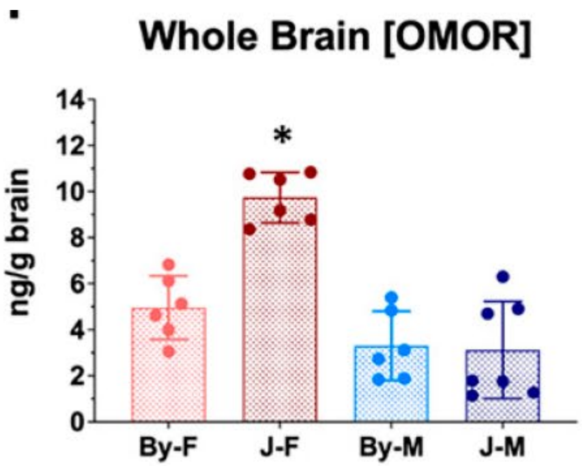
↳ *Translate findings to humans*

BALB/c substrain differences in oxycodone reward learning and oxymorphone brain concentration

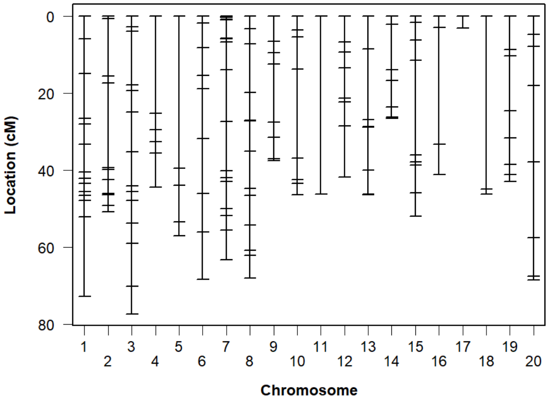


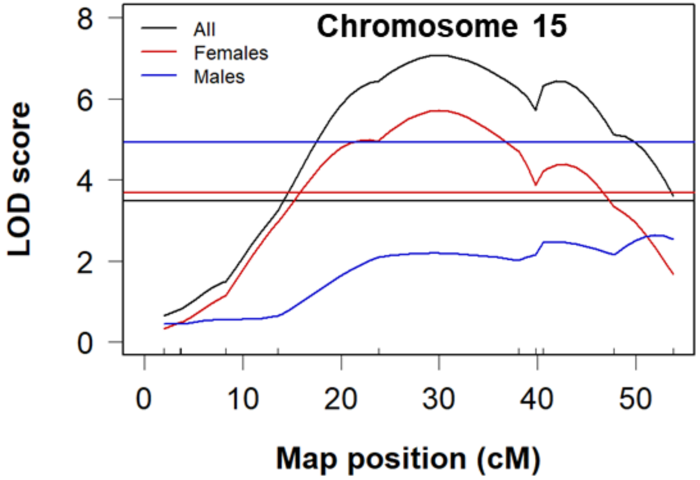
	D1	D2	D3	D4	D5	D6	D7	D8	D9
SAL Tx:	SAL	SAL	SAL	SAL	SAL	-	-	SAL	SAL
OXY Tx:	SAL	OXY	SAL	OXY	SAL	-	-	SAL	OXY
	Initial Pref.	Training				Consolid.		CPP	State-Dep. CPP

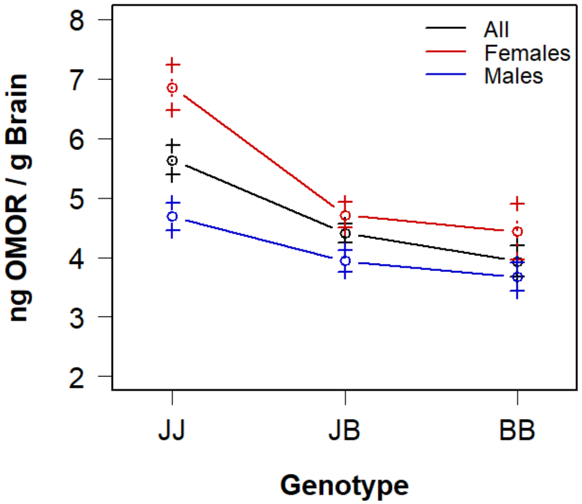




QTL, eQTL, & proteomic analysis identify *Zhx2* as a candidate gene underlying brain [oxymorphone]







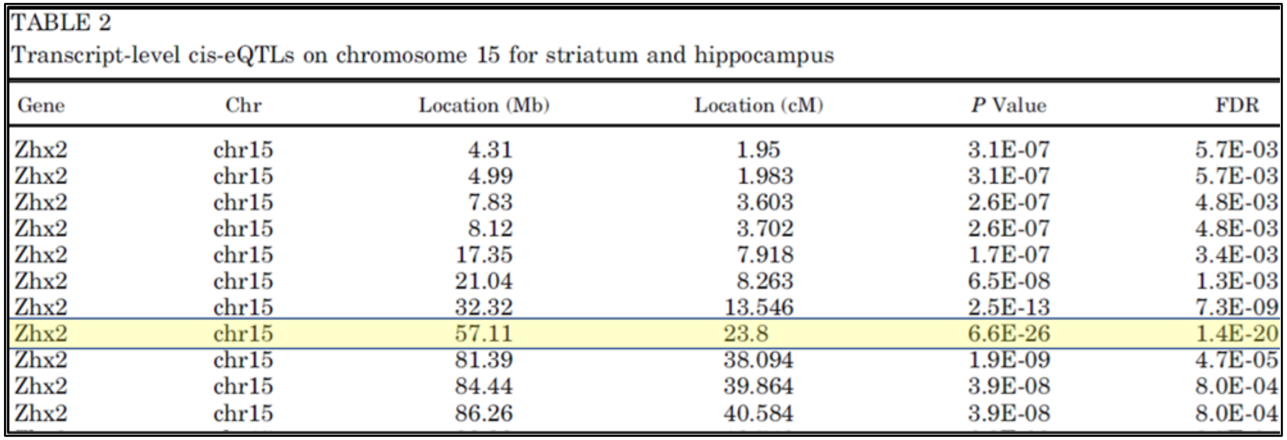
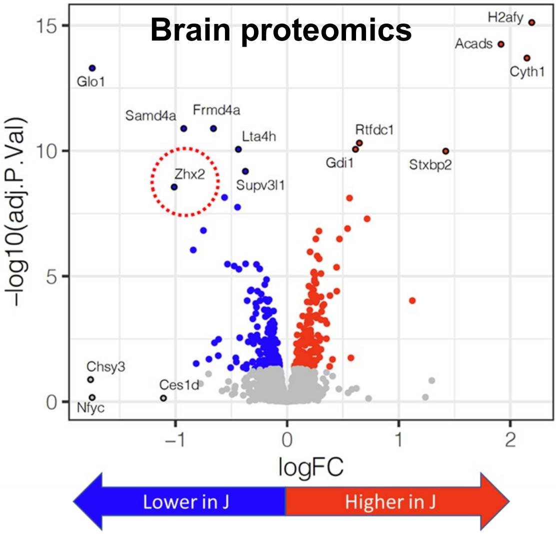


TABLE 2

Transcript-level cis-eQTLs on chromosome 15 for striatum and hippocampus

Gene	Chr	Location (Mb)	Location (cM)	*P* Value	FDR
Zhx2	chr15	4.31	1.95	3.1E-07	5.7E-03
Zhx2	chr15	4.99	1.983	3.1E-07	5.7E-03
Zhx2	chr15	7.83	3.603	2.6E-07	4.8E-03
Zhx2	chr15	8.12	3.702	2.6E-07	4.8E-03
Zhx2	chr15	17.35	7.918	1.7E-07	3.4E-03
Zhx2	chr15	21.04	8.263	6.5E-08	1.3E-03
Zhx2	chr15	32.32	13.546	2.5E-13	7.3E-09
Zhx2	chr15	57.11	23.8	6.6E-26	1.4E-20
Zhx2	chr15	81.39	38.094	1.9E-09	4.7E-05
Zhx2	chr15	84.44	39.864	3.9E-08	8.0E-04
Zhx2	chr15	86.26	40.584	3.9E-08	8.0E-04



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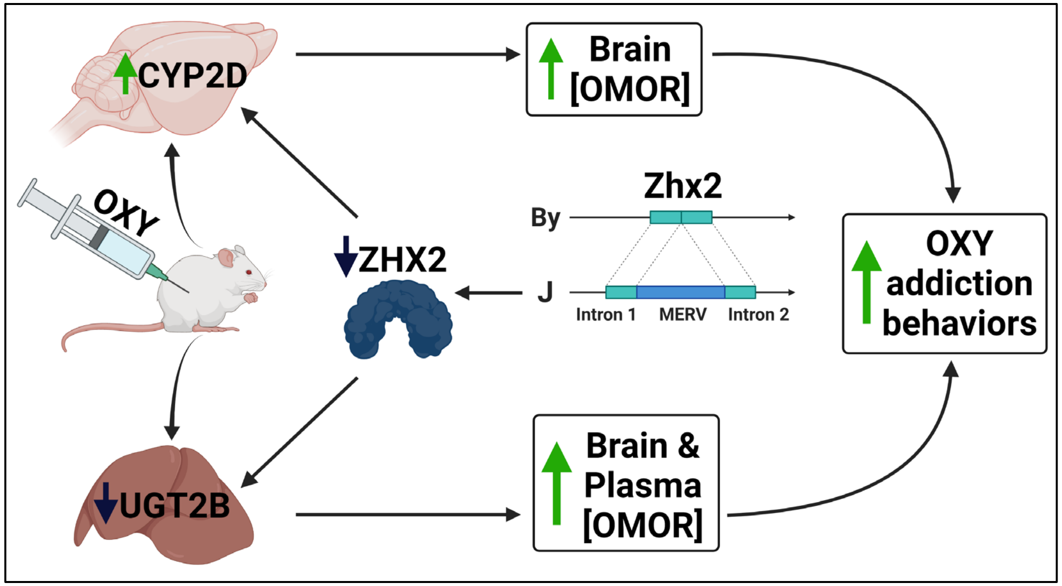
Zhx2 hypothesis linking brain [OMOR] with OXY behavior

Dr. Jacob A. Beierle



↑ CYP2D

↑ Brain [OMOR]

OXY

↓ ZHX2

Zhx2

By

J

Intron 1

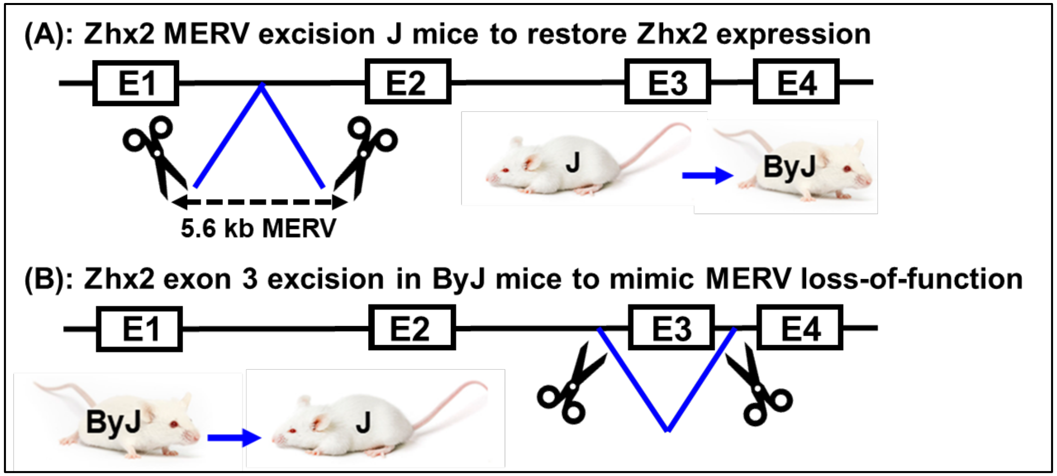
MERV

Intron 2

↑ OXY addiction behaviors

↓ UGT2B

↑ Brain & Plasma [OMOR]



(A): Zhx2 MERV excision J mice to restore Zhx2 expression

E1 E2 E3 E4

5.6 kb MERV

J → ByJ

(B): Zhx2 exon 3 excision in ByJ mice to mimic MERV loss-of-function

E1 E2 E3 E4

ByJ → J

William B. Lynch

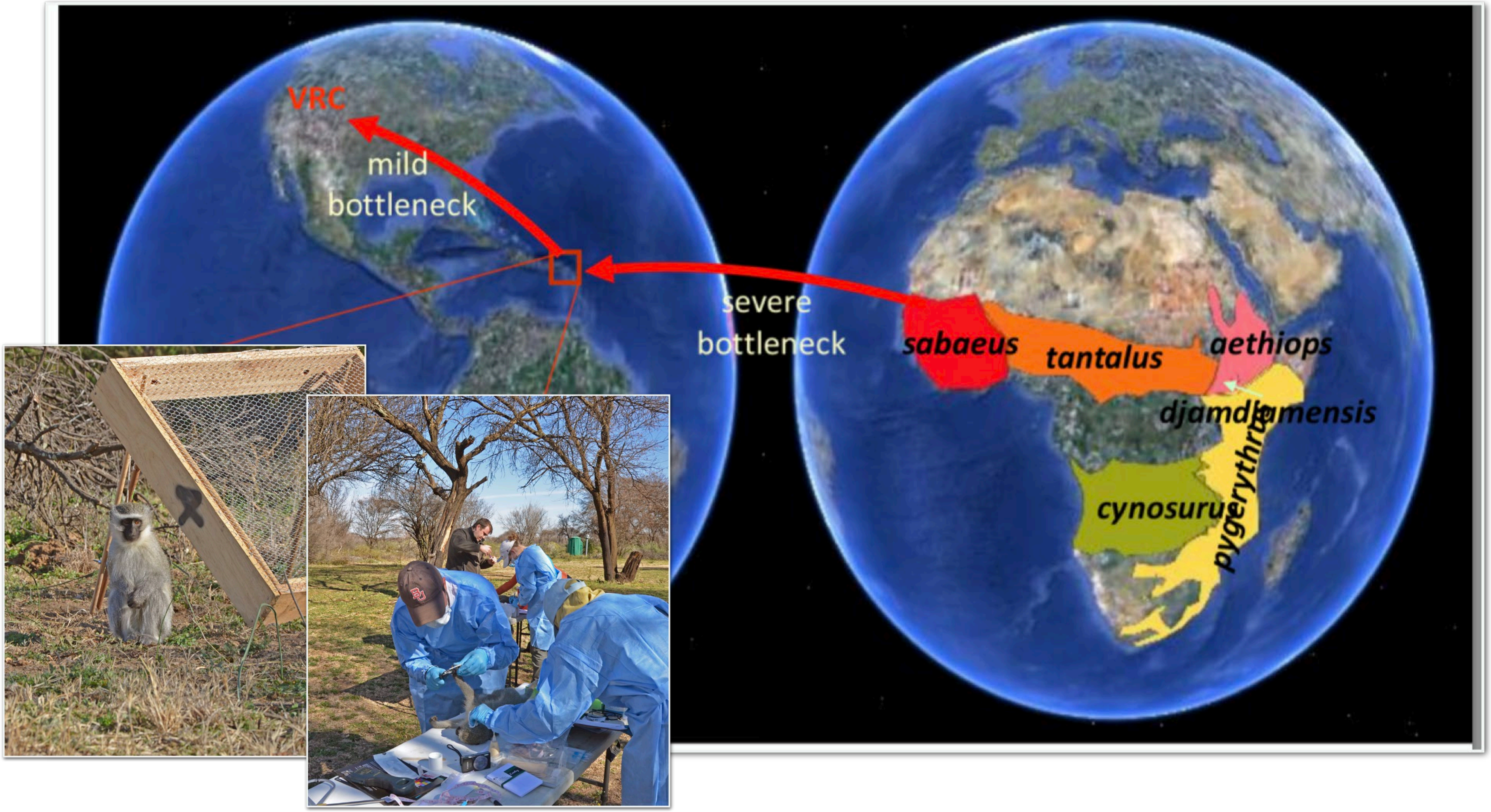
BOSTON UNIVERSITY

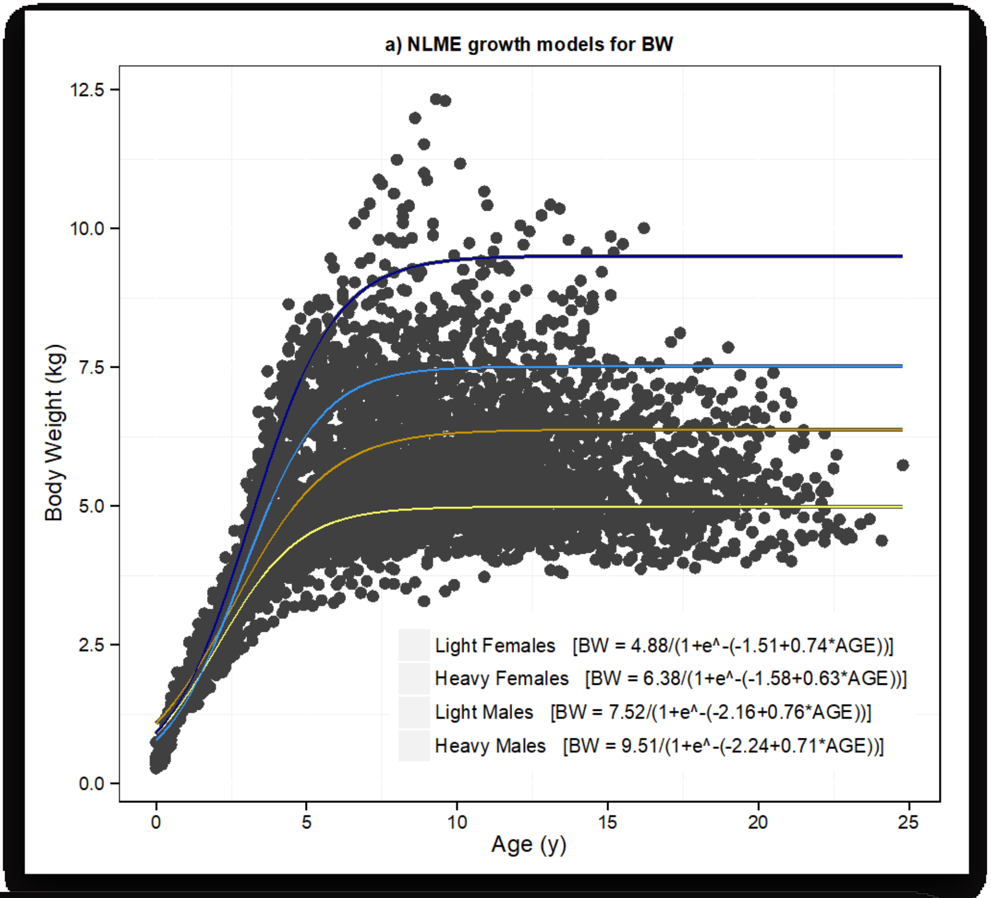
Using the Genome to Model the Evolutionary Origins of Obesity

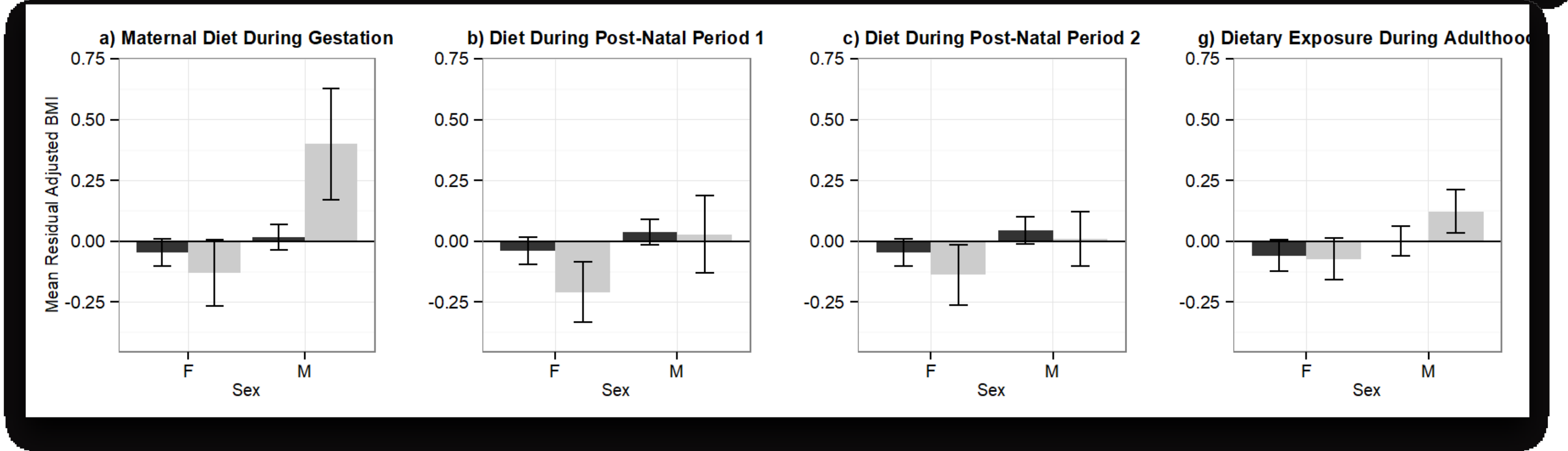
Christopher A. Schmitt

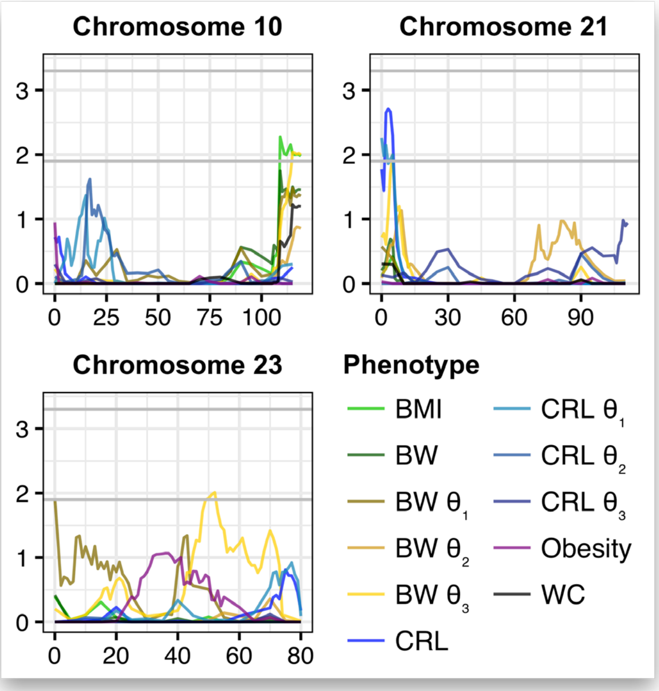
Assistant Professor
Departments of Anthropology, Biology, and WGS
College of Arts & Sciences

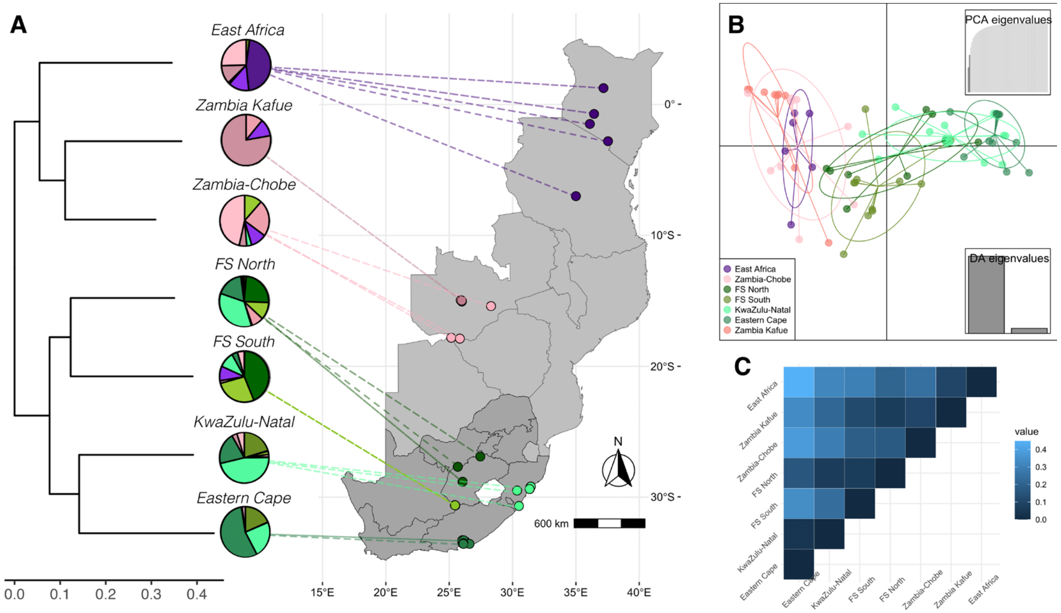
Humans Aren't the Best Models… *But Monkeys*…

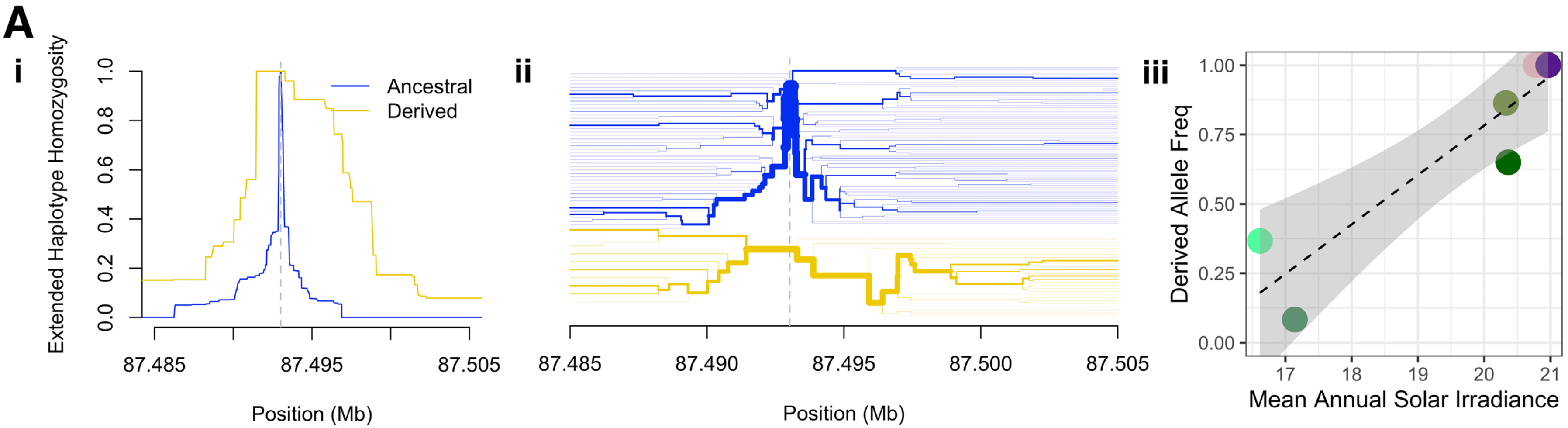



a) NLME growth models for BW
Body Weight (kg)
0.0
2.5
5.0
7.5
10.0
12.5
Age (y)
0
5
10
15
20
25
Light Females [BW = 4.88/(1+e^-(-1.51+0.74*AGE))]
Heavy Females [BW = 6.38/(1+e^-(-1.58+0.63*AGE))]
Light Males [BW = 7.52/(1+e^-(-2.16+0.76*AGE))]
Heavy Males [BW = 9.51/(1+e^-(-2.24+0.71*AGE))]

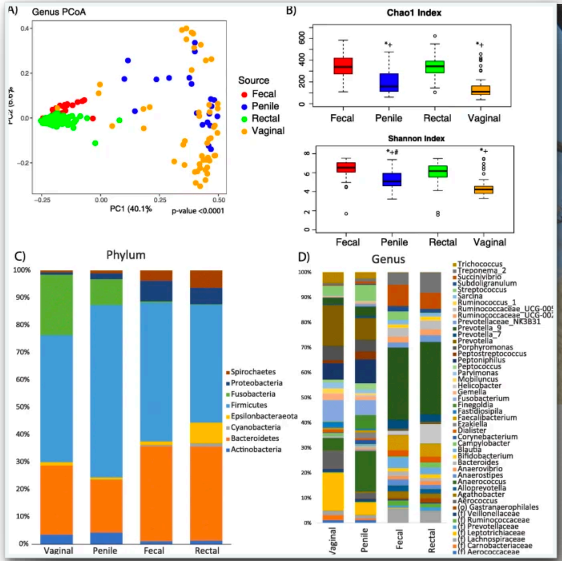

a) Maternal Diet During Gestation
b) Diet During Post-Natal Period 1
c) Diet During Post-Natal Period 2
g) Dietary Exposure During Adulthoo
Mean Residual Adjusted BMI
0.75
0.50
0.25
0.00
-0.25
F
M
Sex


Chromosome 10
Chromosome 21
Chromosome 23
3
2
1
0
0
25
50
75
100
0
30
60
90
0
20
40
60
80
Phenotype
BMI
BW
BW θ1
BW θ2
BW θ3
CRL
CRL θ1
CRL θ2
CRL θ3
Obesity
WC

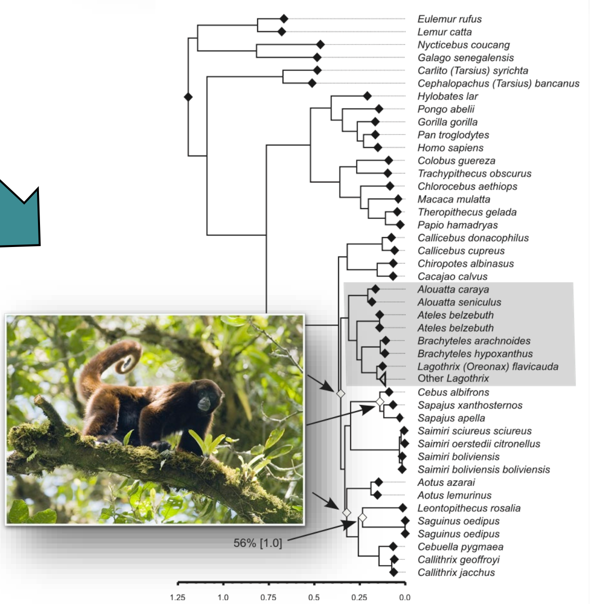

A
East Africa
Zambia Kafue
Zambia-Chobe
FS North
FS South
KwaZulu-Natal
Eastern Cape
0.0
0.1
0.2
0.3
0.4
0°
10°S
20°S
30°S
15°E
20°E
25°E
30°E
35°E
40°E
N
600 km
B
PCA eigenvalues
DA eigenvalues
East Africa
Zambia-Chobe
FS North
FS South
KwaZulu-Natal
Eastern Cape
Zambia Kafue
C
value
0.4
0.3
0.2
0.1
0.0
East Africa
Zambia Kafue
Zambia-Chobe
FS North
FS South
KwaZulu-Natal
Eastern Cape


A
i
Extended Haplotype Homozygosity
0.0
0.2
0.4
0.6
0.8
1.0
Ancestral
Derived
87.485
87.495
87.505
Position (Mb)
ii
87.485
87.490
87.495
87.500
87.505
Position (Mb)
iii
Derived Allele Freq
0.00
0.25
0.50
0.75
1.00
17
18
19
20
21
Mean Annual Solar Irradiance


minipcr
SONY
VAIO


A) Genus PCoA
PC2 (9.5%)
PC1 (40.1%)
p-value <0.0001
Source
Fecal
Penile
Rectal
Vaginal
B) Chao1 Index
Fecal
Penile
Rectal
Vaginal
Shannon Index
C) Phylum
Spirochaetes
Proteobacteria
Fusobacteria
Firmicutes
Epsilonbacteraeota
Cyanobacteria
Bacteroidetes
Actinobacteria
Vaginal
Penile
Fecal
Rectal
D) Genus
Trichococcus
Treponema_2
Succinivibrio
Subdoligranulum
Streptococcus
Sarcina
Ruminococcus_1
Prevotella_9
Prevotella_7
Prevotella
Porphyromonas
Peptostreptococcus
Peptoniphilus
Peptococcus
Parvimonas
Mobiluncus
Helicobacter
Gemella
Fusobacterium
Finegoldia
Fastidiosipila
Faecalibacterium
Ezakiella
Dialister
Corynebacterium
Campylobacter
Blautia
Bifidobacterium
Bacteroides
Anaerovibrio
Anaerostipes
Anaerococcus
Alloprevotella
Agathobacter
Aerococcus


Soetdoring
!Gariep
Pre-D
Peak-D
Pre-D
Peak-D

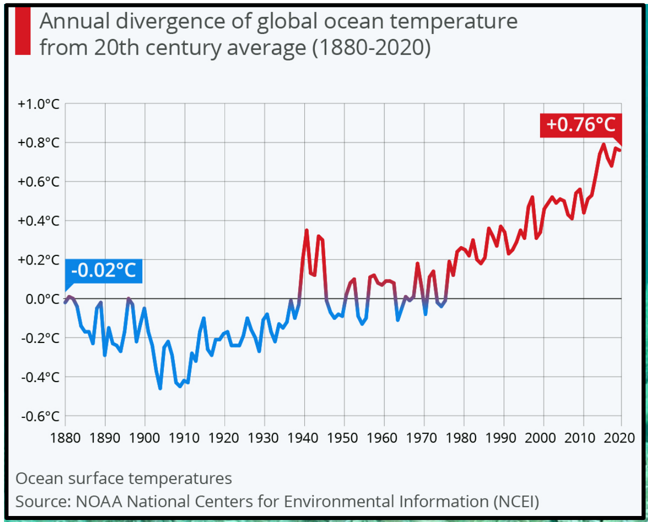

Eulemur rufus
Lemur catta
Nycticebus coucang
Galago senegalensis
Carlito (Tarsius) syrichta
Cephalopachus (Tarsius) bancanus
Hylobates lar
Pongo abelii
Gorilla gorilla
Pan troglodytes
Homo sapiens
Colobus guereza
Trachypithecus obscurus
Chlorocebus aethiops
Macaca mulatta
Theropithecus gelada
Papio hamadryas
Callicebus donacophilus
Callicebus cupreus
Chiropotes albinasus
Cacajao calvus
Alouatta caraya
Alouatta seniculus
Ateles belzebuth
Ateles belzebuth
Brachyteles arachnoides
Brachyteles hypoxanthus
Lagothrix (Oreonax) flavicauda
Other Lagothrix
Cebus albifrons
Sapajus xanthosternos
Sapajus apella
Saimiri sciureus sciureus
Saimiri oerstedii citronellus
Saimiri boliviensis
Saimiri boliviensis boliviensis
Aotus azarai
Aotus lemurinus
Leontopithecus rosalia
Saguinus oedipus
Saguinus oedipus
Cebuella pygmaea
Callithrix geoffroyi
Callithrix jacchus
56% [1.0]
1.25
1.0
0.75
0.5
0.25
0.0

Understanding Coral Diversity in the Era of Genomics

Sarah W. Davies

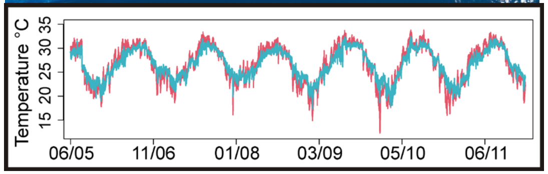
Assistant Professor
Department of Biology, College of Arts and Sciences

Coral Bleaching- Urgent issue as climate change accelerates

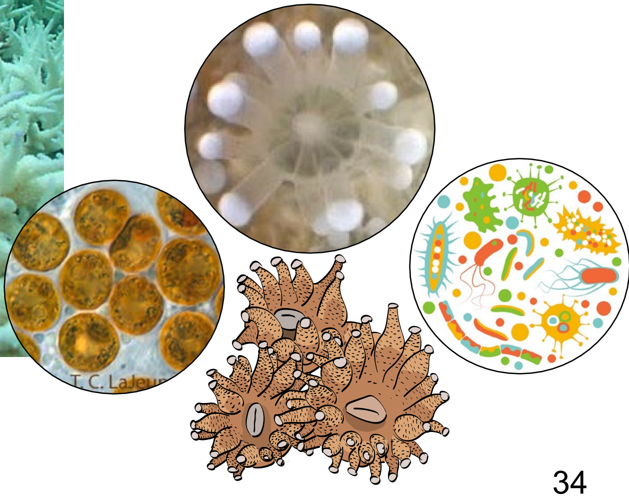


Annual divergence of global ocean temperature from 20th century average (1880-2020)

Ocean surface temperatures
Source: NOAA National Centers for Environmental Information (NCEI)

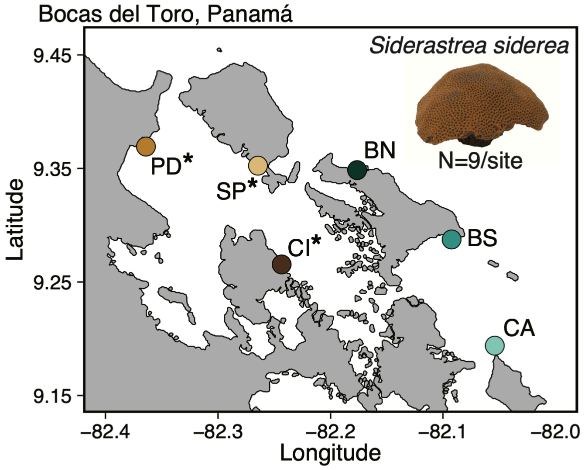


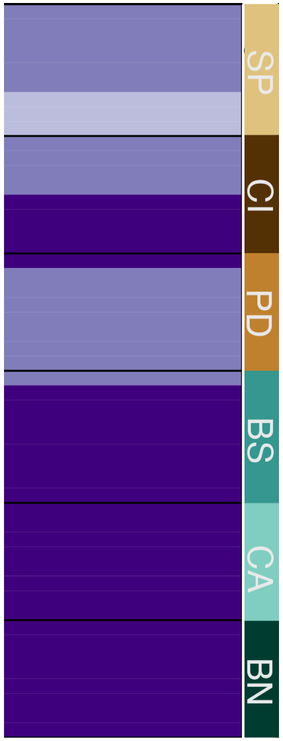
Coral Holobiont

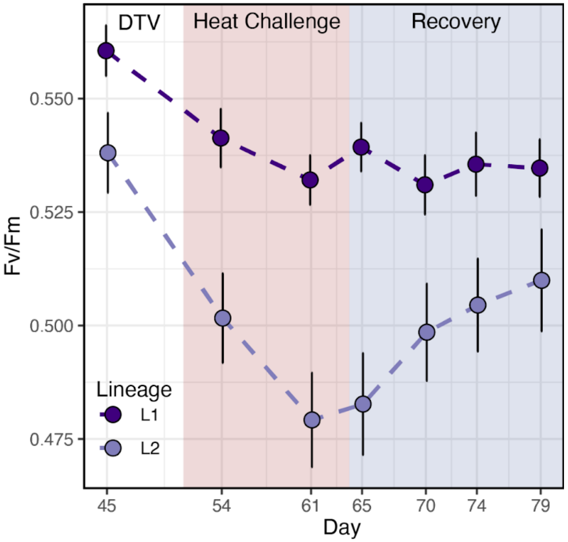


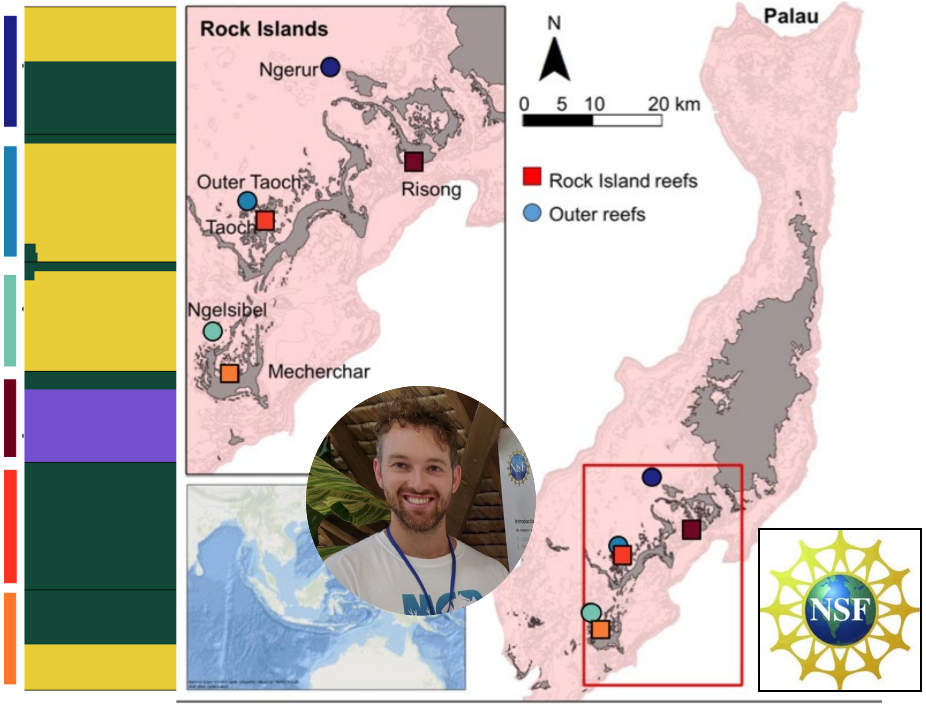
Boston University Office of Research

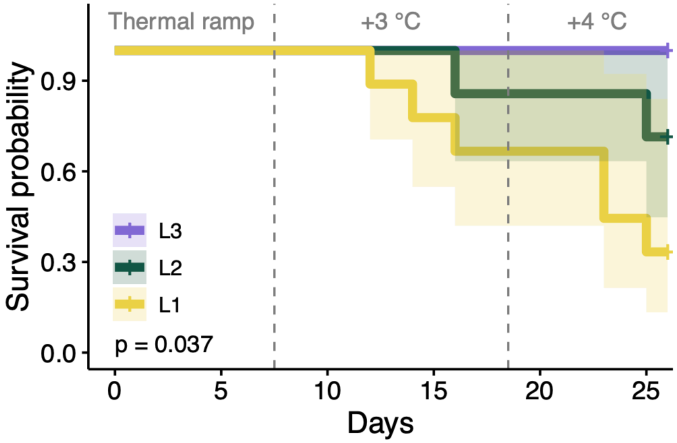
Cryptic species make predicting thermal tolerance challenging











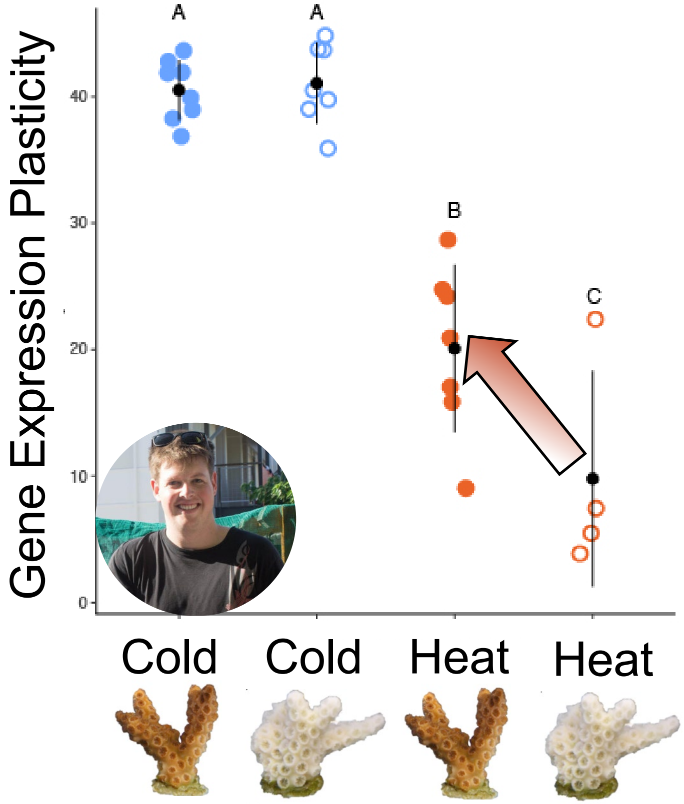
Using facultative corals to understand bleaching mechanisms

Aposymbiotic Host

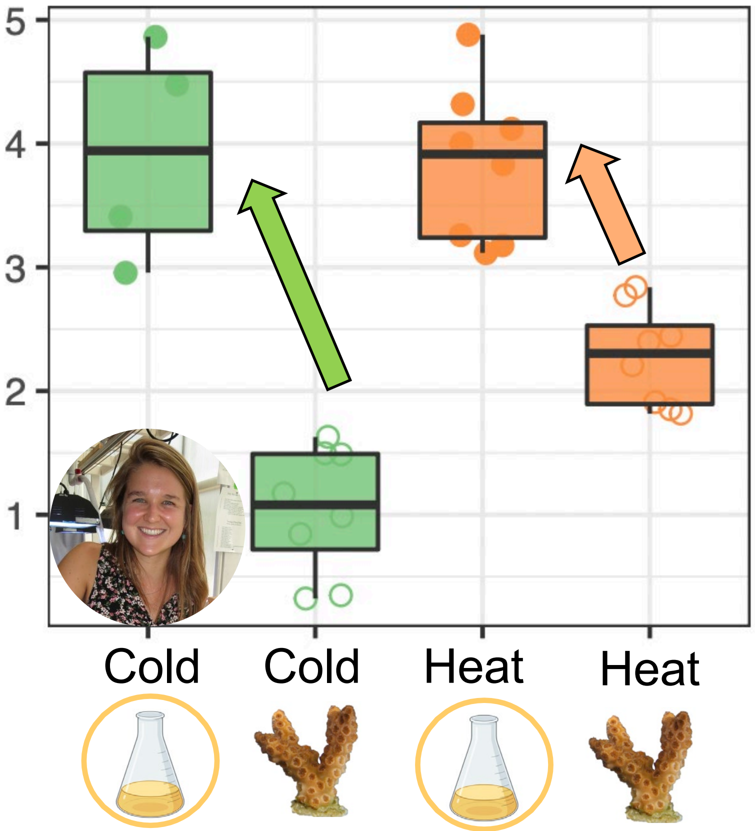
Symbiotic

Aposymbiotic Algae

Host: symbiosis leads to stronger response in heat

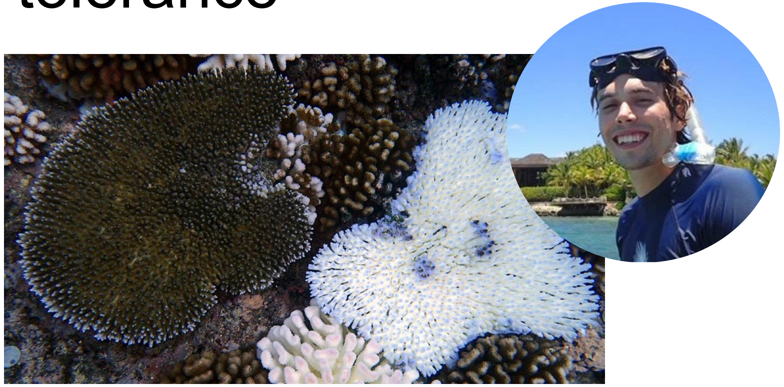


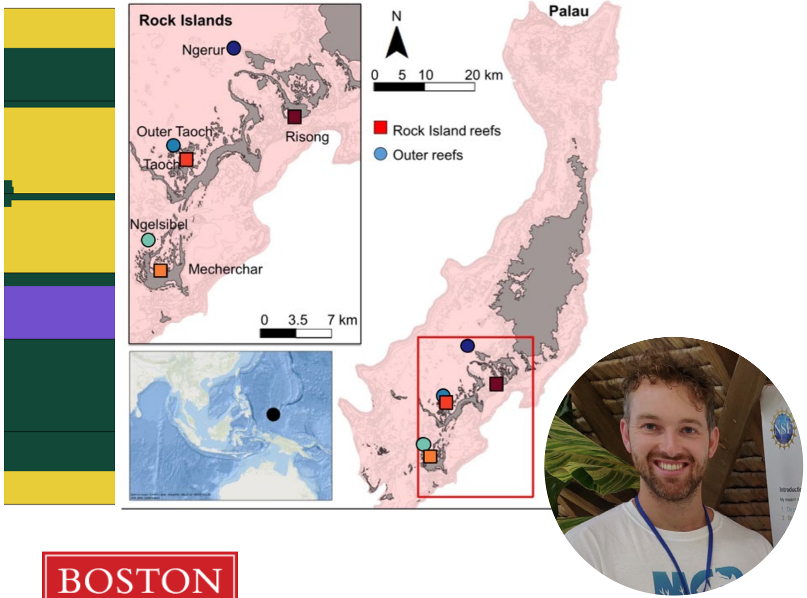
Algae: symbiosis leads to muted response



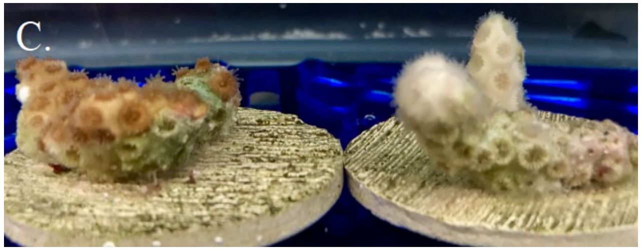
BOSTON UNIVERSITY

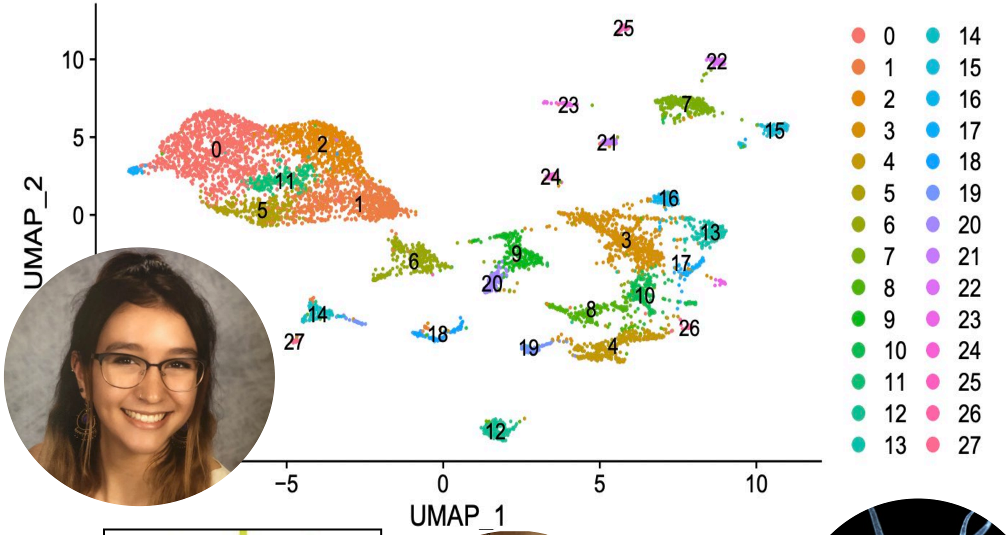
Future work: Genomic architecture of thermal tolerance





Future work: Tradeoffs between innate immunity and symbiosis

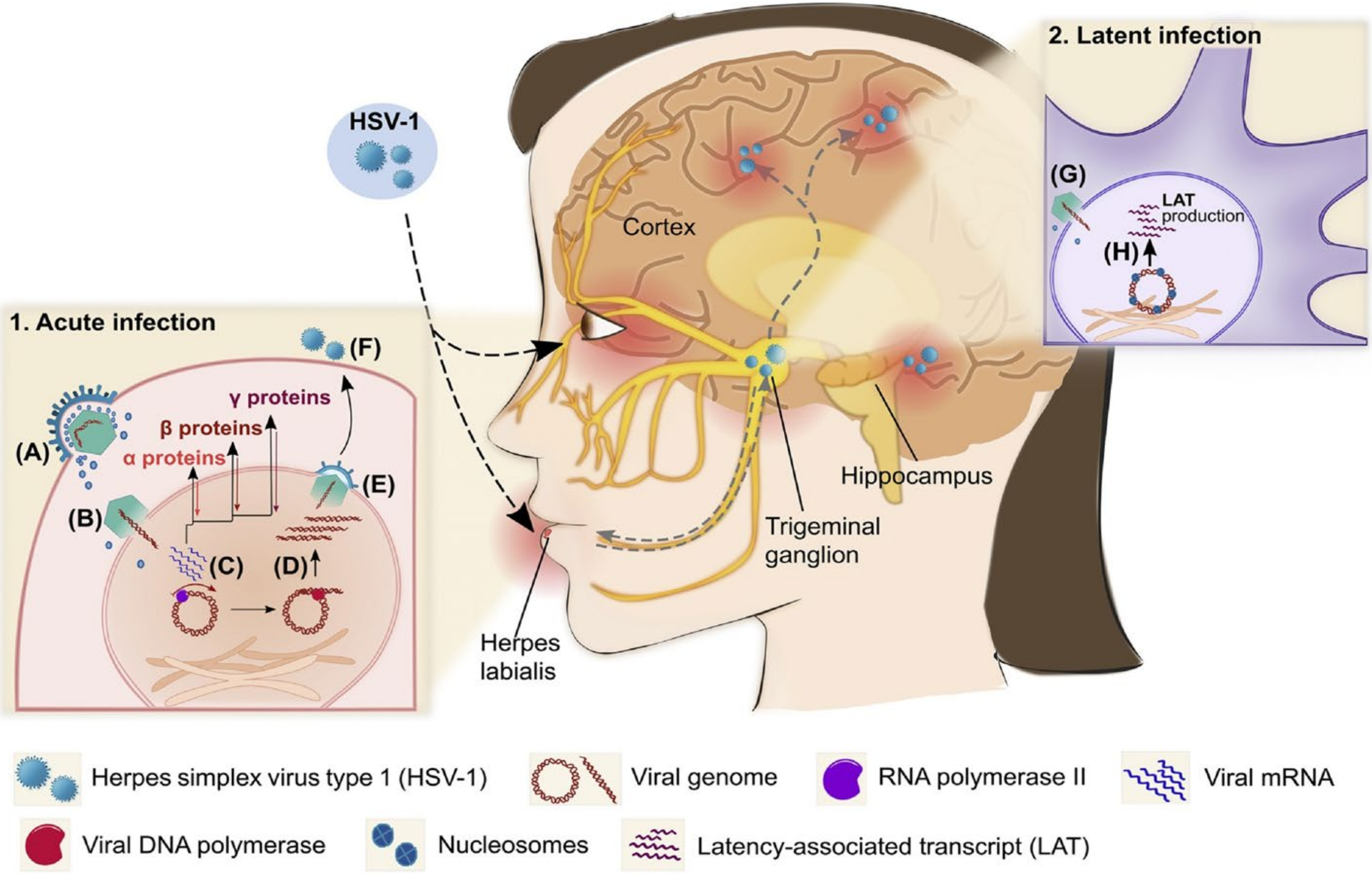




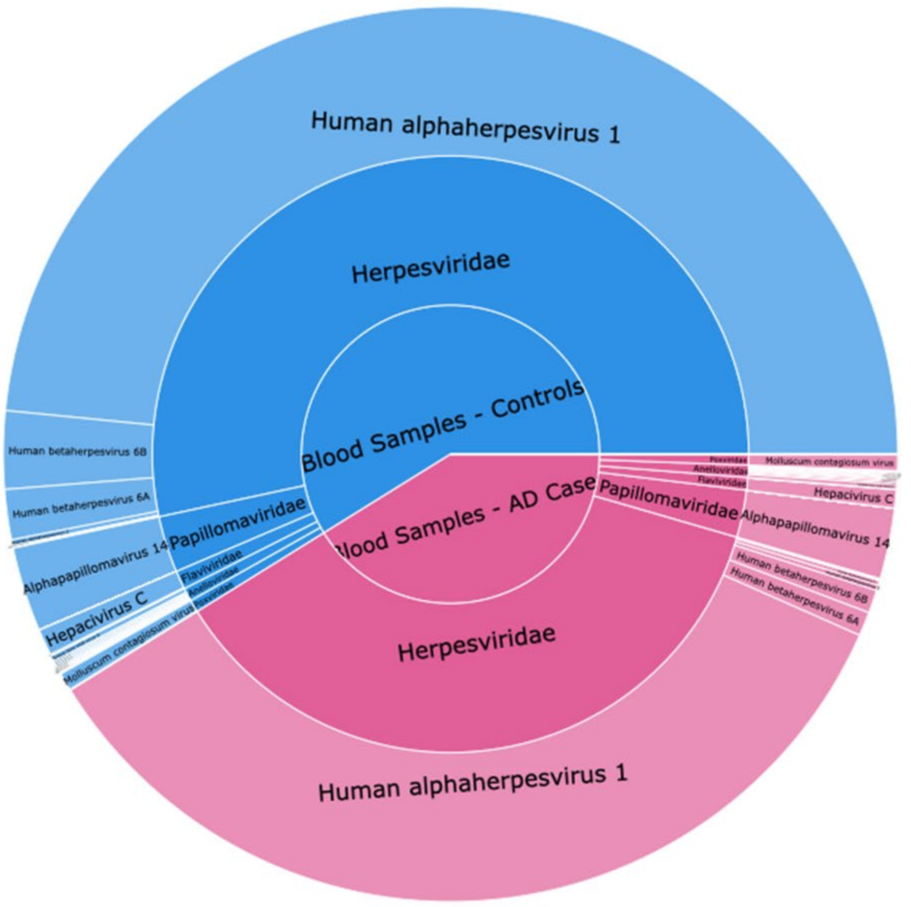
The Viral Etiology of Alzheimer’s Disease

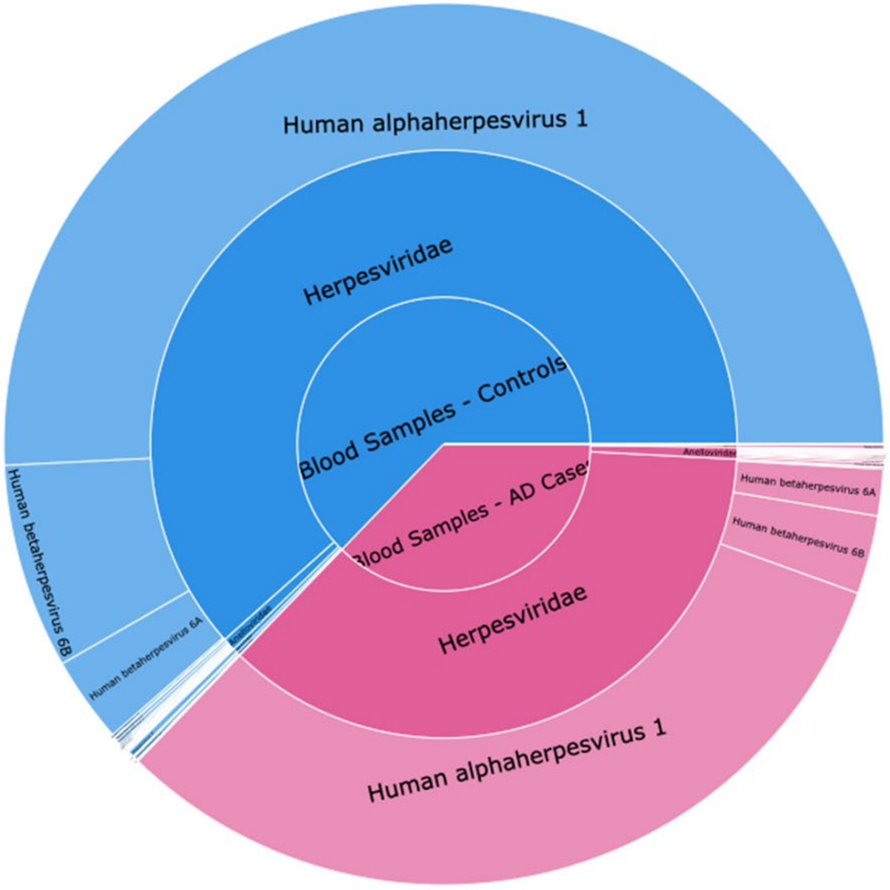
Rick Sherva

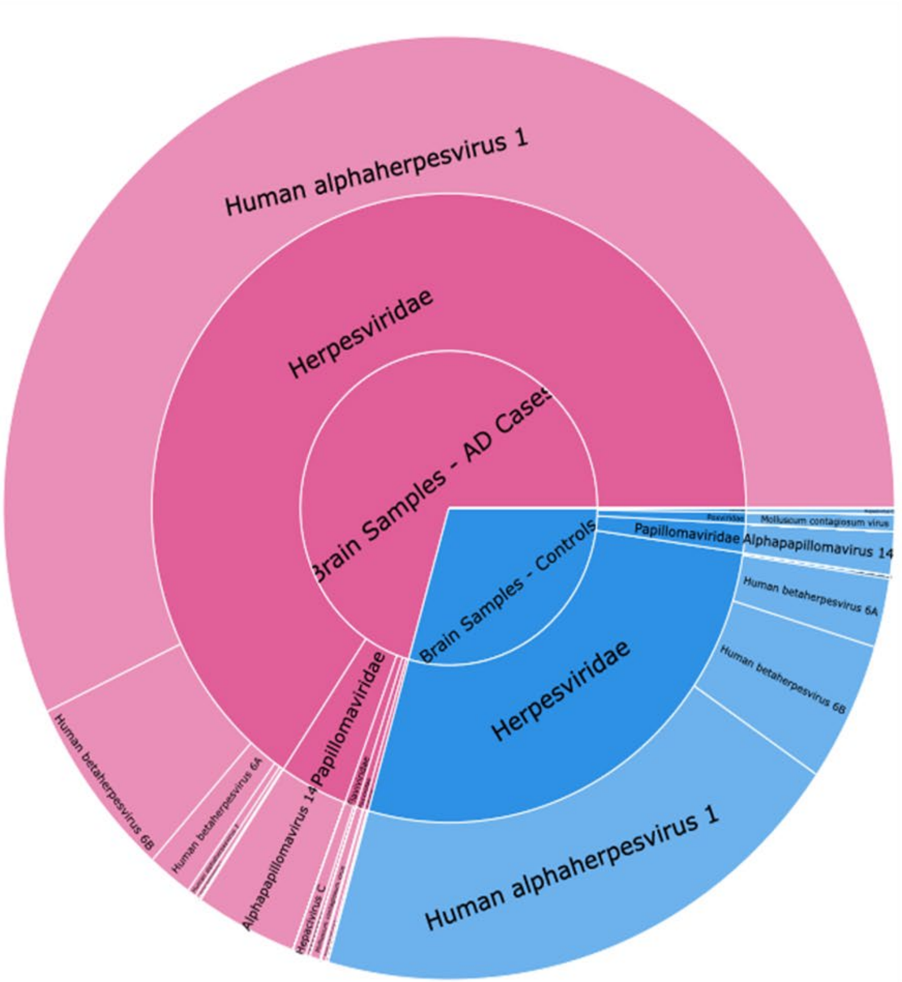
Assistant Professor
Biomedical Genetics, School of Medicine



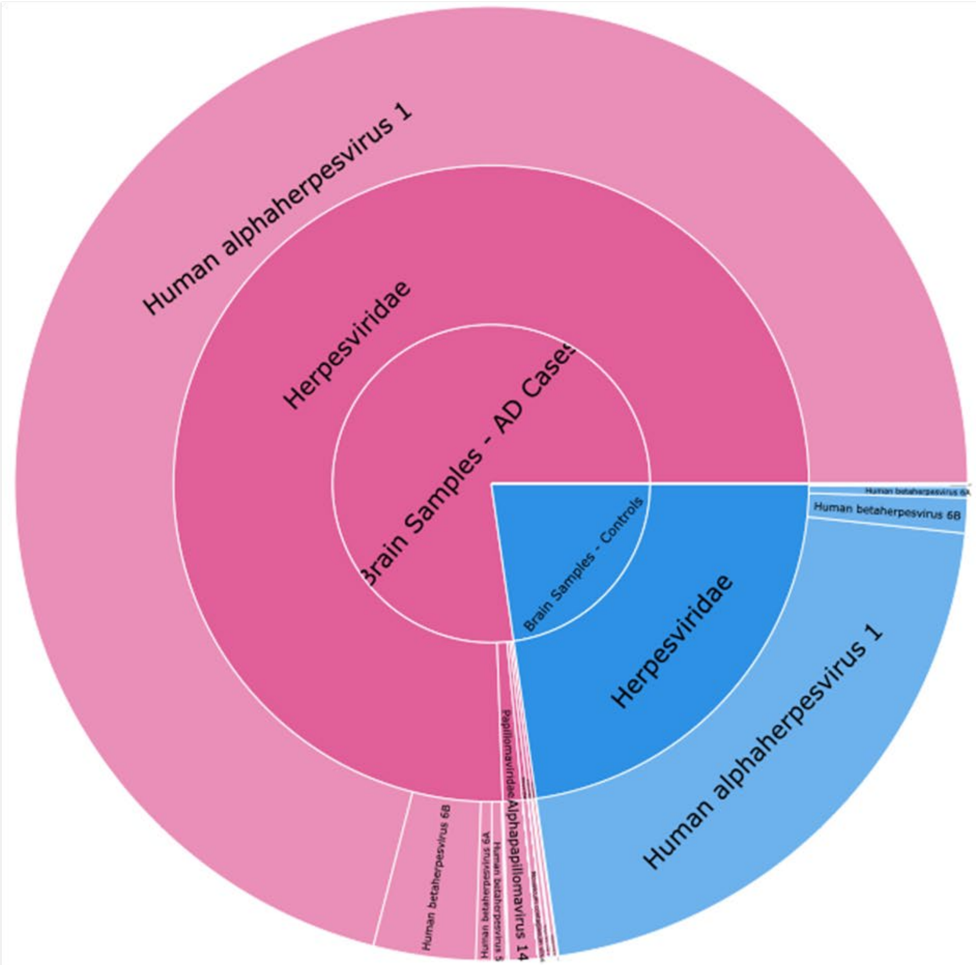
Trends in Microbiology


Human alphaherpesvirus 1
Herpesviridae
Blood Samples - Controls
Human betaherpesvirus 6B
Human betaherpesvirus 6A
Papillomaviridae
Alphapapillomavirus 14
Flaviviridae
Anelloviridae
Poxviridae
Hepacivirus C
Molluscum contagiosum virus
Blood Samples - AD Case
Herpesviridae
Human alphaherpesvirus 1
Papillomaviridae
Poxviridae
Anelloviridae
Flaviviridae
Molluscum contagiosum virus
Hepacivirus C
Alphapapillomavirus 14
Human betaherpesvirus 6B
Human betaherpesvirus 6A

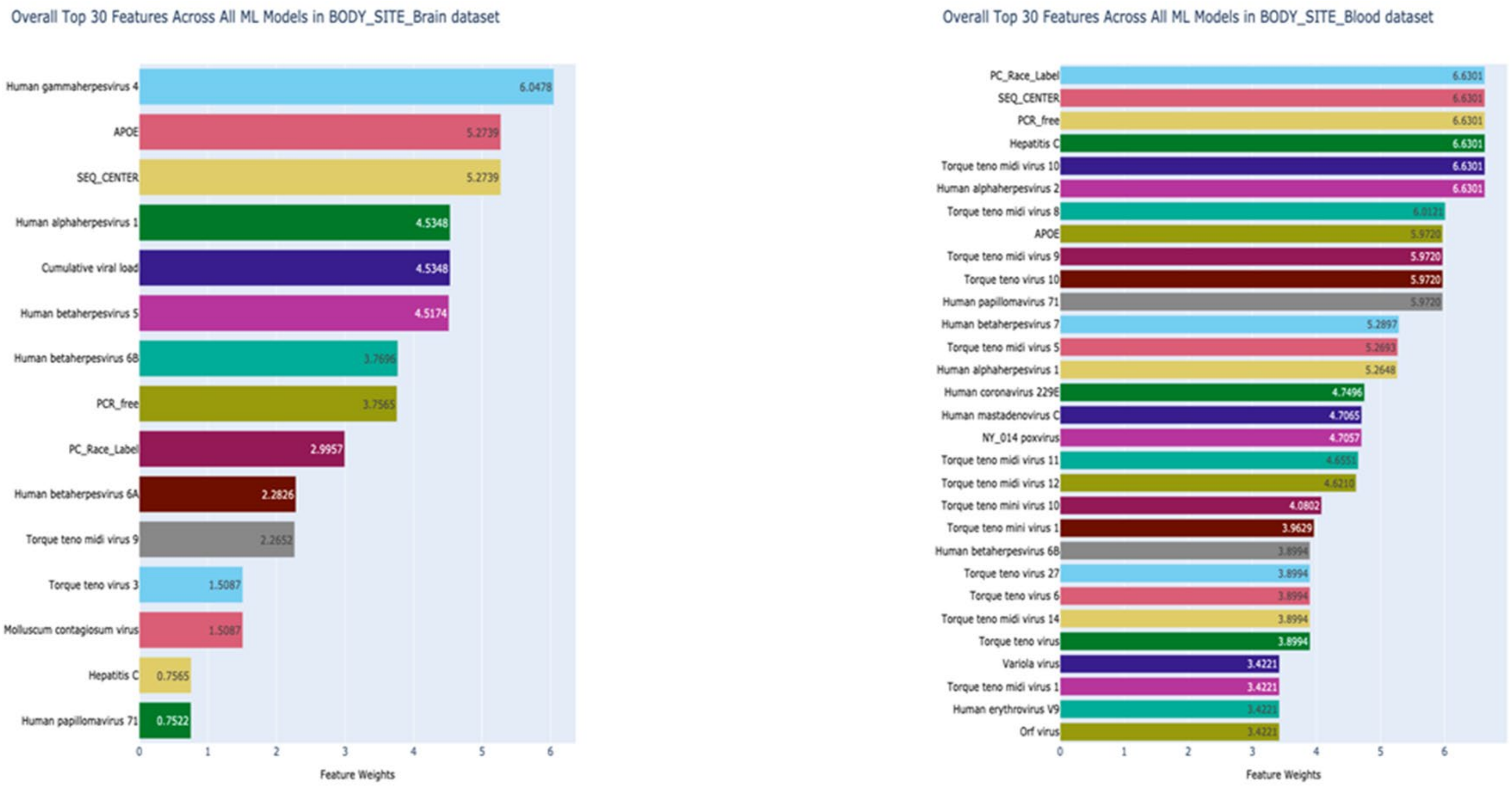

Human alphaherpesvirus 1
Herpesviridae
Blood Samples - Controls
Human betaherpesvirus 6B
Human betaherpesvirus 6A
Anelloviridae
Blood Samples - AD Case
Herpesviridae
Human alphaherpesvirus 1
Anelloviridae
Human betaherpesvirus 6A
Human betaherpesvirus 6B



(c) WES Brain



(d) WGS Brain



(a) Brain

(b) Blood

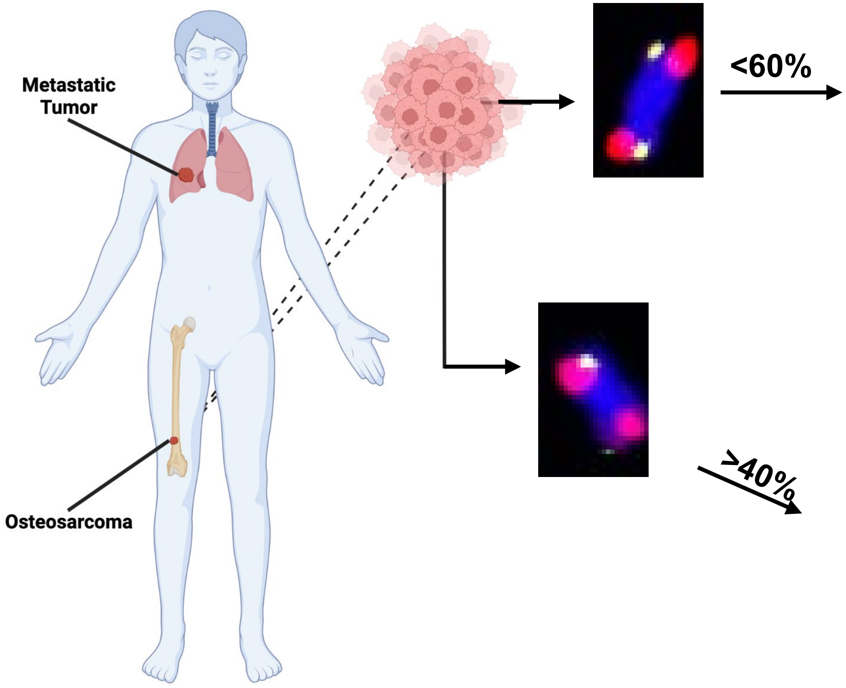
Figure 3: WGS Feature Importance

Defining the Alternative Lengthening of Telomeres Pathway in Osteosarcoma

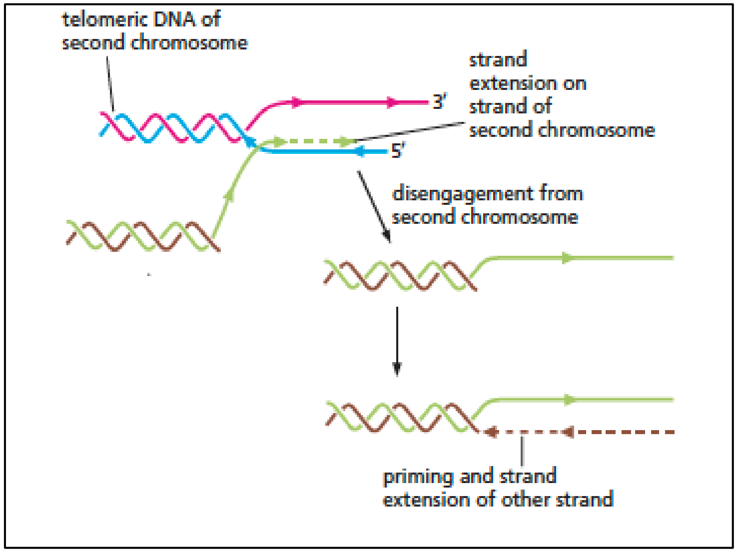
Rachel Flynn

Associate Professor of Pharmacology and Medicine
Department of Pharmacology
Boston University School of Medicine

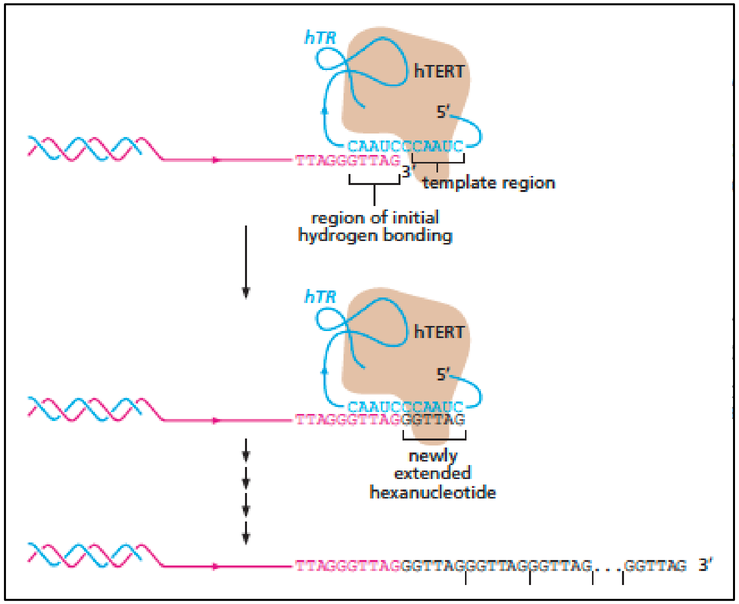
Telomere Maintenance in Osteosarcoma



Alternative Lengthening of Telomeres

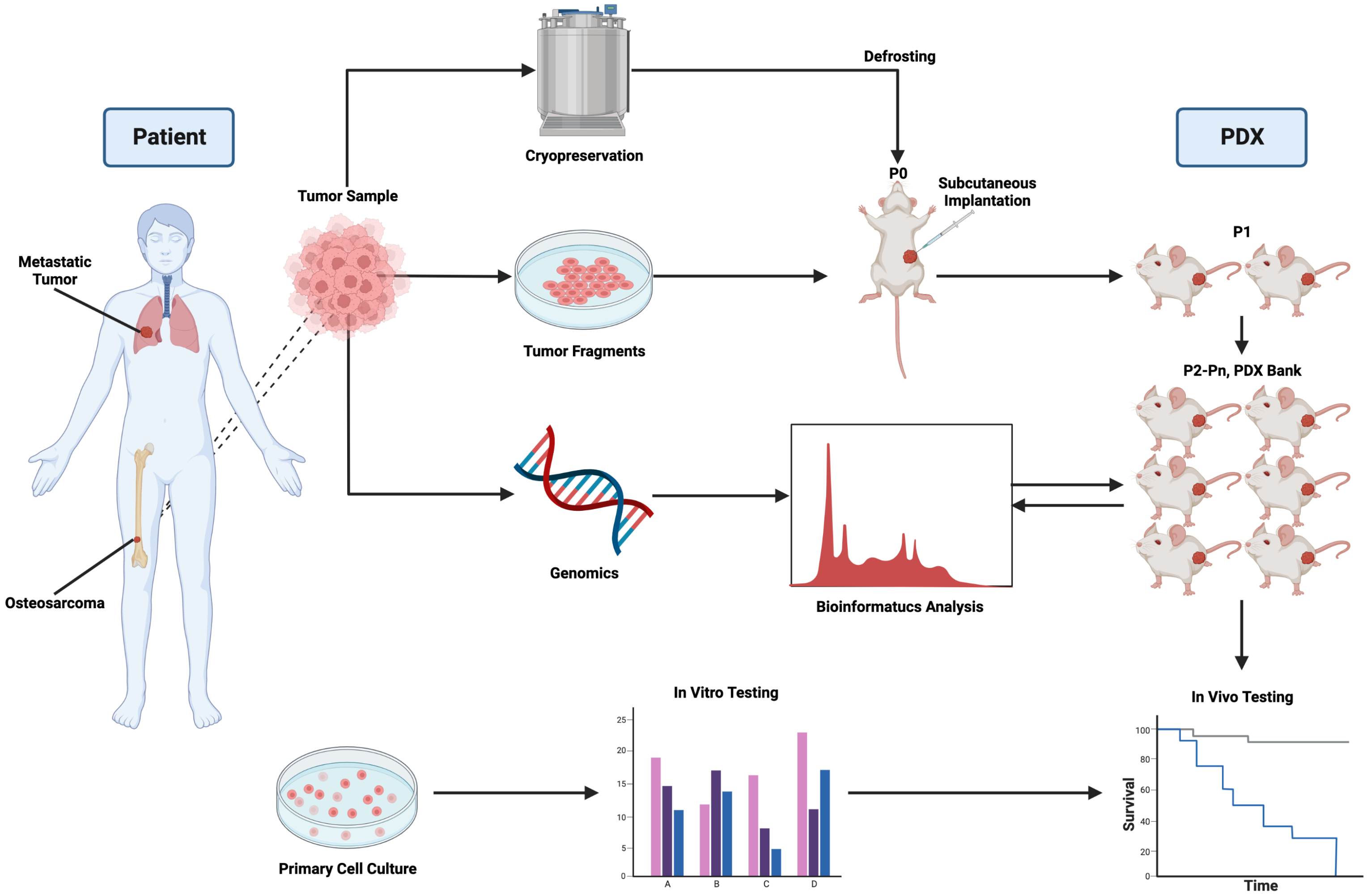


Telomerase

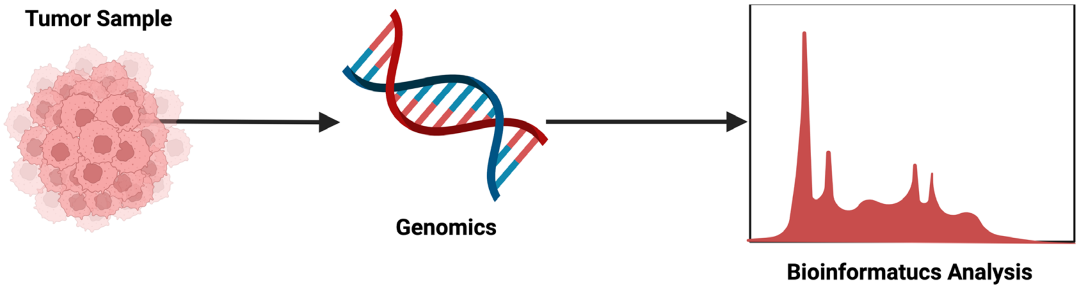


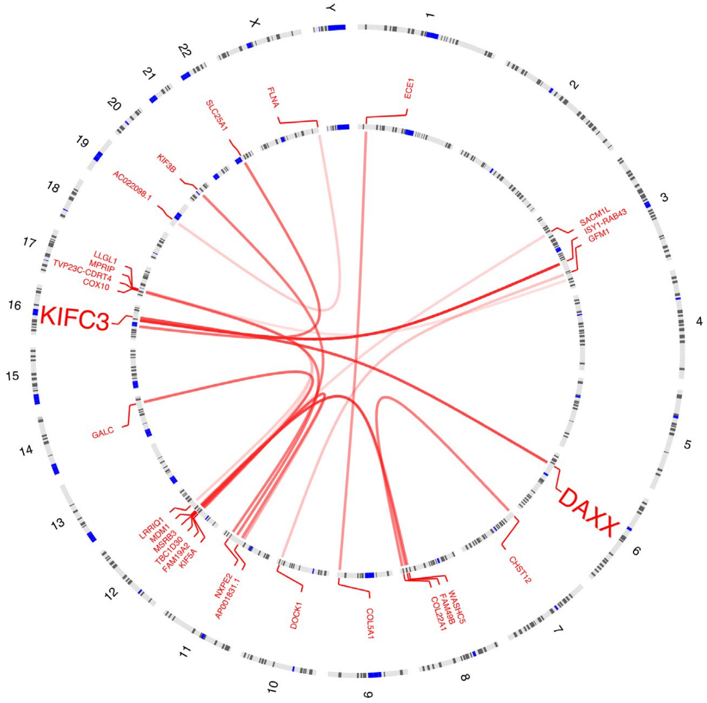
Weinberg 2014

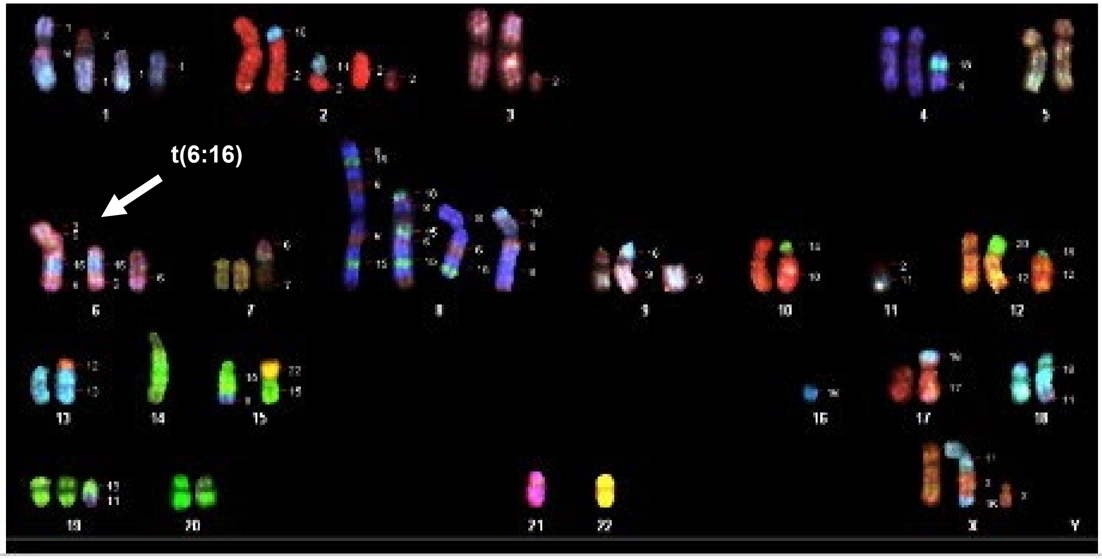
Defining ALT in Ostoesarcoma



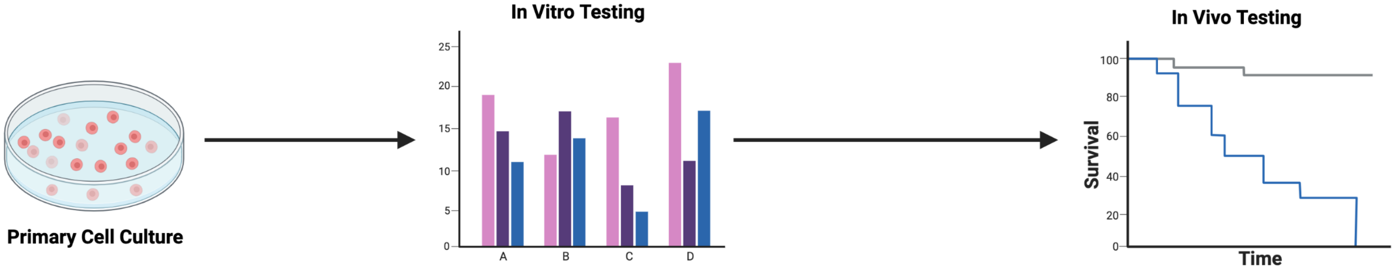
Identification of Genetic Mutations in ALT

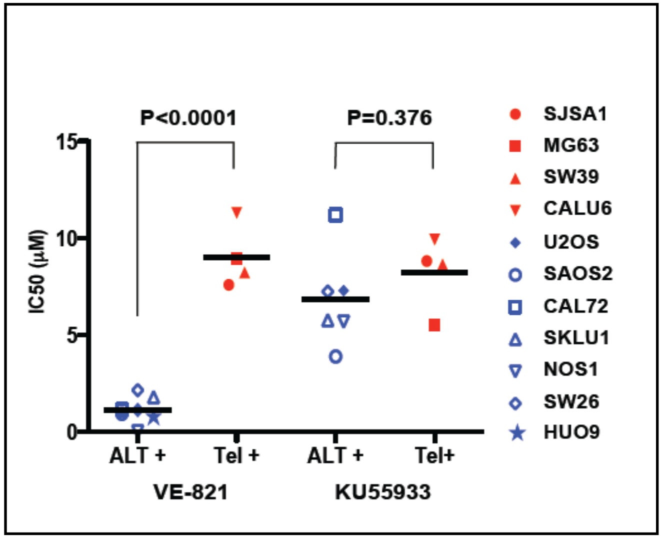




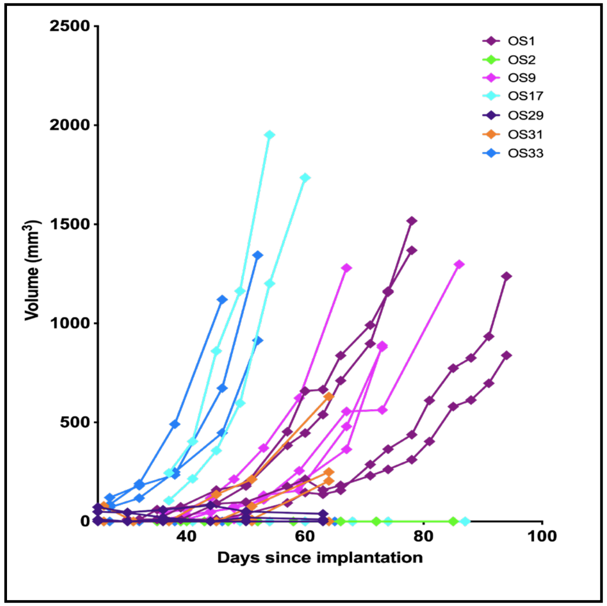


Targeting ALT in PDX Models of Osteosarcoma





In Vitro



In Vivo

Flynn Lab

Kelli Cox

Emily Mason-Osann

Jess Floro

Jane Lock

Matt Reiss

Lisa Carson

Josh Keegan

NIH NATIONAL CANCER INSTITUTE

1R01CA201446

1R01CA214880

THANK YOU!

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Topic ideas & feedback: bu.edu/research/topic-ideas

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Artificial Intelligence for Biomedicine and Healthcare
November 9, 2022 | 4-6 pm

Developing Technologies for a Sustainable Future
Wednesday, December 7, 2022 | 4-6 pm

RESEARCH HOW-TO

Find a Collaborator: Making Research Connections at Boston University
Tuesday, November 1, 2022 | 1-3 pm

Meet the American Lung Association
Wednesday, November 2, 2022 | 12-1 pm