UCI 趙 Chao Family Comprehensive Cancer Center

Cancer Center Update

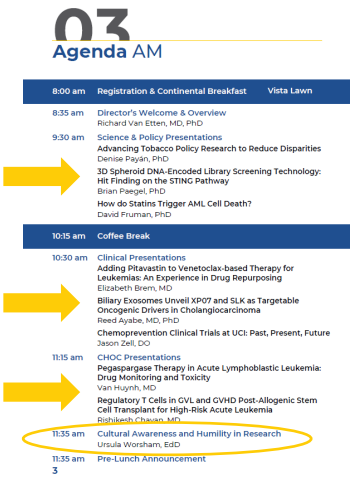
Rick Van Etten, MD PhD
Director, Chao Family Comprehensive Cancer Center
Senior Associate Dean and Associate Vice Chancellor for Cancer
University of California, Irvine

Today's Retreat

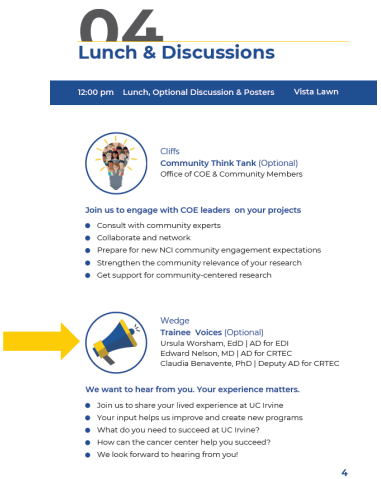
- We're glad you're here!
- > 350 participants!
- The Retreat goals are communication and interaction
- Agenda
  - Science & Policy
  - Clinical presentations
  - CHOC
  - Cultural Awareness & Humility in Research
  - Lunch with discussions
  - Concurrent Breakout Sessions
    - AI
    - Implementation Science
    - Tumor Immunology
  - Community Outreach & Engagement
  - Shared Resources
  - Posters & Flash Talks ($$$)

We want your input! Your feedback is important!

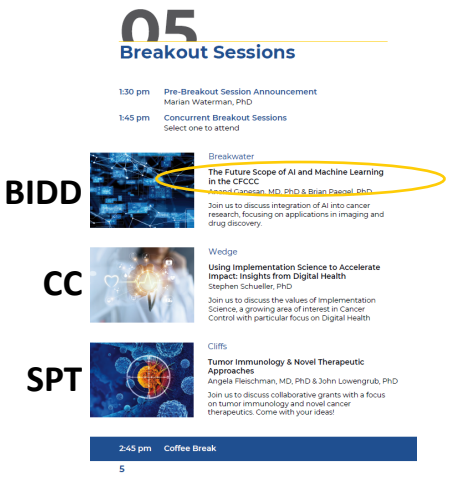
- **More science talks**



- **Opportunities for student input**



- **Program-focused Breakout Sessions**



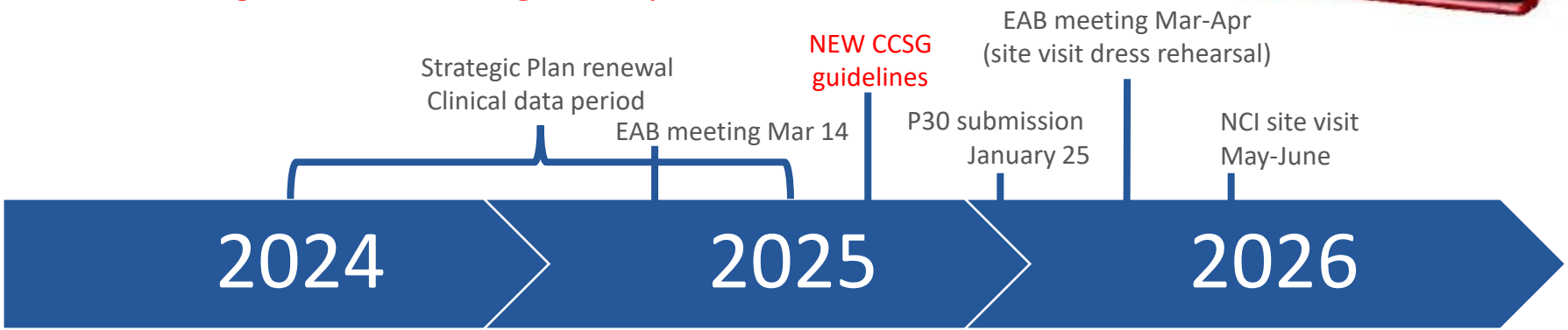
- **Shorter Flash Talks**

- **Cultural appropriateness**

- **Presentation on AI**

CFCCC P30 renewal status

- Received official notification of renewal of CCSG on Feb. 25, 2022
  - *Outstanding* ratings in 4 of the 6 Essential Characteristics
- Five-year funding period is through Jan. 31, 2027
- We are finishing our third year on the current grant
- Next competing renewal application will be due Jan. 25, 2026
- New CCSG guidelines coming out September 2025



UCI 趙 Chao Family Comprehensive Cancer Center

Physical Space (*Outstanding*)

CFCCC laboratory space

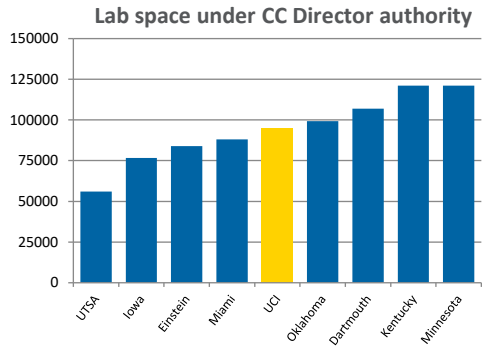
Sprague Hall (Irvine campus)

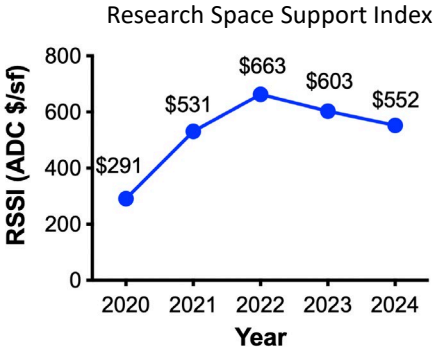
- 83,000 sf, vivarium in basement
- 3rd floor: Genomics Research and Technology Hub (**GRTHub**) and Biobehavioral Shared Resource (**BBSR**)
- Current occupants: 25 CFCCC members

Shanbrom Hall (Orange campus)

- Second floor assigned to CFCCC
- ~12,000 sf, vivarium in basement
- Current occupants: Fruehauf (**SPT**), Zi (**CC**), Uchio (**CC**), Cozen (**CC**), Yu (HSCT)
- ETR TMA facility, Cell Processing Lab for HSCT Program

- Current CFCCC space comparable to other NCI CCs
- Space managed by CFCCC Administration
- Additional lab space of CFCCC members ~140,000 sf
- Open space for recruitments: 6 bays, ~4,000 sf
- 20,500 sf of new space in FLF-MIB in 2025
- Commitment of additional 5,000 sf for next 5 yrs.





Falling Leaves Foundation – Medical Innovation Building

cGMP Facility

UCI Medical Center-Irvine

HSCT & Cellular Therapy Program

Samueli Integrative Health Institute

Integrative Nutrition Center

Genomics Research & Technology Hub

GRTH

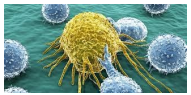
FLF-MIB
Gross Stem Cell Center
Translational Vision & Neuroscience
Pharmaceutical Sciences
Precision Omics
Skin Biology Center

In Vivo Functional Onco-Imaging

IVFOI

Phase I & Infusion Center

Alpha Stem Cell Clinic



Immuno-Oncology

Precision Oncology

College of Health Sciences investigators

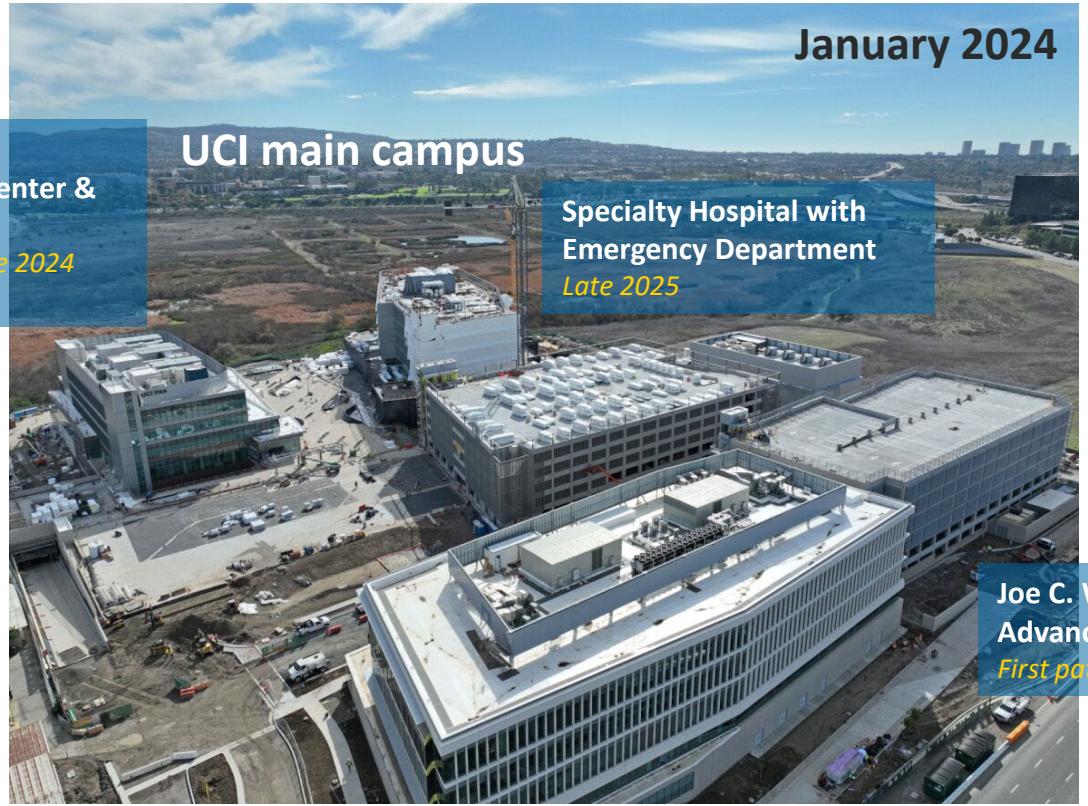
UCI Chao Family Comprehensive Cancer Center

UCI Susan & Henry Samueli College of Health Sciences

Cancer Center clinical & clinical research footprint across Orange County

UCI Medical Center - Irvine

Chao Family Comprehensive Cancer Center & Ambulatory Care
Infusion Center opened: June 2024
All Services: July 2024



New Cancer Center Building on Irvine Campus

- 200,000 sf
- Radiation Oncology
- Advanced imaging
- Outpatient specialty pharmacy
- Multidisciplinary clinics
- 50 exam rooms
- Infusion Center (42 stations)
- Clinical research space
- Shelled floor for growth

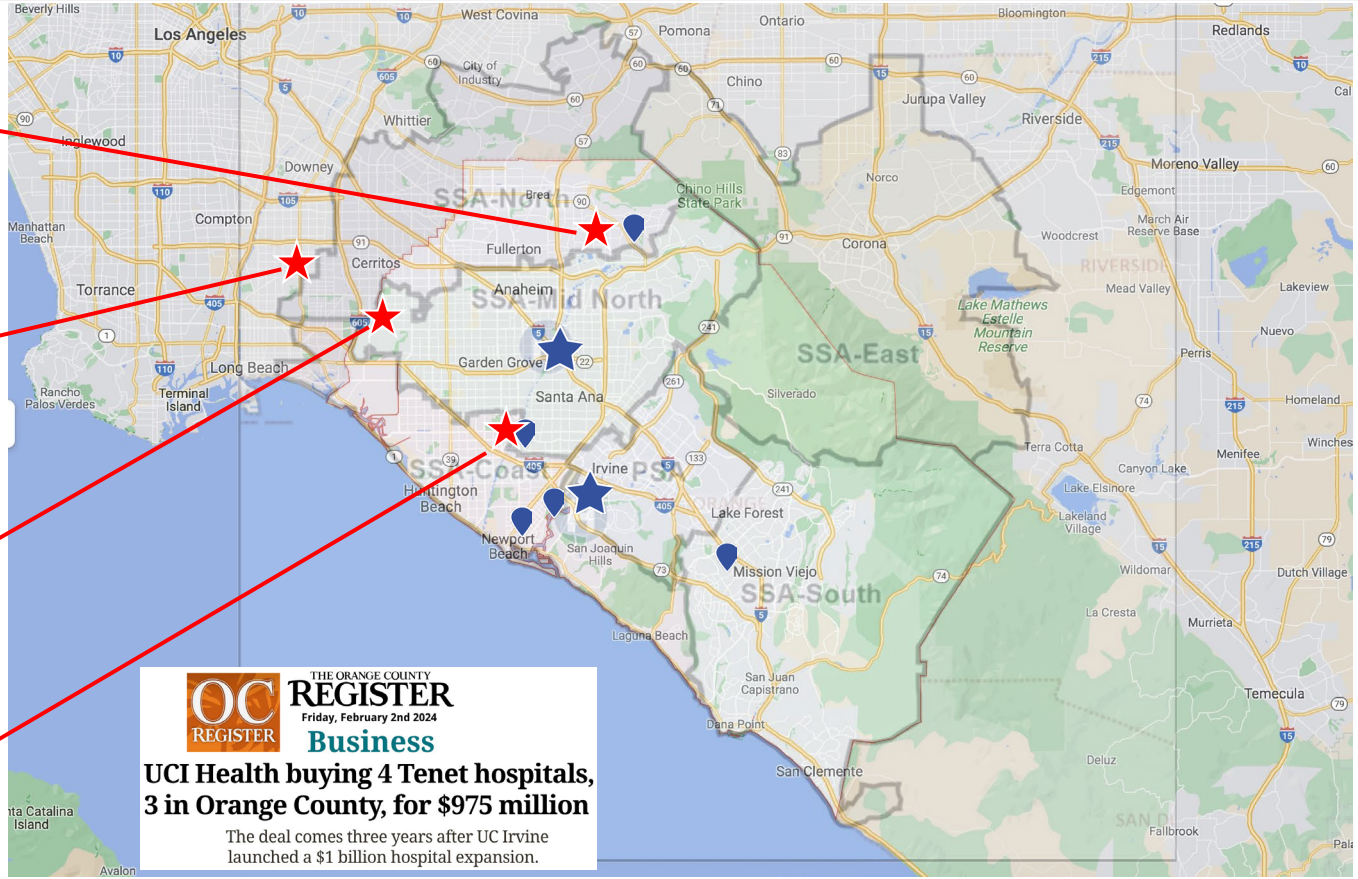
UCI Health – Tenet Hospital Acquisition

Placentia-Linda Hospital (114 beds)

Lakewood Hospital (172 beds)

Los Alamitos Hospital (172 beds)

Fountain Valley Hospital (400 beds)



THE ORANGE COUNTY REGISTER
Friday, February 2nd 2024
Business

UCI Health buying 4 Tenet hospitals, 3 in Orange County, for $975 million

The deal comes three years after UC Irvine launched a $1 billion hospital expansion.

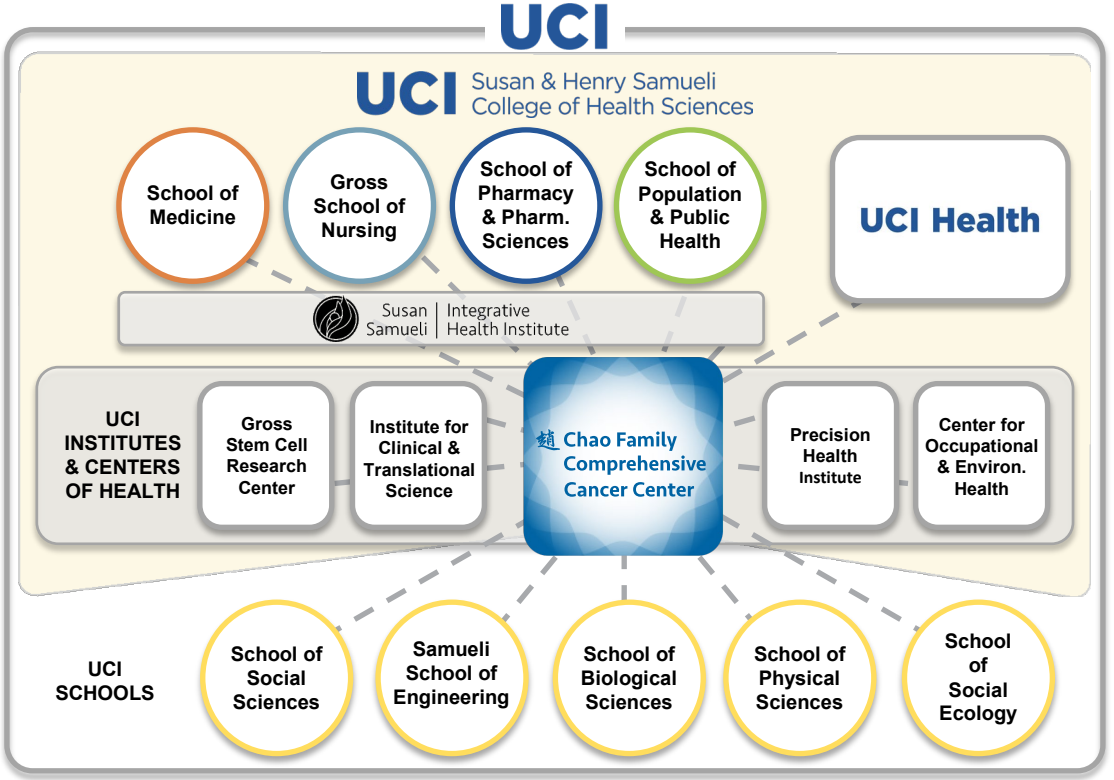
UCI 趙 Chao Family Comprehensive Cancer Center

Organizational Capabilities (*Outstanding*)

CFCCC Institutional Status

趙 Chao Family Comprehensive Cancer Center

- A Center within Samueli College of Health Sciences
- Status superior to a Department
- Many members in the four COHS Schools:
  - Medicine
  - Nursing
  - Pharmacy & Pharmaceutical Sciences
  - Population & Public Health
- Numerous members in five other UCI Schools
- Cancer clinicians & clinical investigators practice within UCI Health
- CFCCC Director Van Etten serves as Associate Vice Chancellor for Cancer



Transitions in CFCCC Leadership

Miguel Villalona-Calero, MD
Deputy Director (Chief, Heme/Onc Divison)

Farshid Dayyani, MD, PhD
Associate Director for Translational Science

Gary Deng, MD, PhD
Associate Director for Integrative Oncology

Ursula Worsham, PhD
Associate Director for Equity, Diversity & Inclusion

Marian Waterman, PhD
interim **Associate Director for Shared Resources**

CFCCC LEAD Program

inaugural **Deputy Associate Directors**

Claudia Benavente, PhD
CRTEC

Wendy Cozen, DO, MPH
Pop Sci & Cancer Control

Aimee Edinger, PhD
Basic Science

inaugural **Assistant Program Leaders**

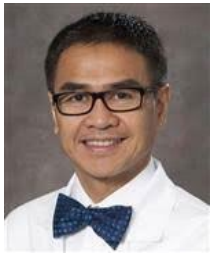
Xiaoyu Shi, PhD
BIDD

Roberto Tinoco, PhD
SPT

Gelareh Sadigh, MD
CC

New members of External Advisory Board

Louis Weiner, MD Chair
Georgetown Lombardi CCC



Primo (Lucky) Lara, MD
UC Davis CCC

Cheryl Willman, MD
Mayo CCC

Christopher Flowers, MD
MD Anderson CC

Kit Lam, MD PhD
UC Davis CCC

John Bushweller, PhD
U Virginia CC

Anita Kinney, PhD
Rutgers CINJ

John Pounardjian, MBA
Case Western CCC

Roshan Bastani, PhD
UCLA Jonsson CCC

Amelie Rameriz, DrPH MPH
UT Health San Antonio CC

Samuel Achilefu, PhD
UT Southwestern CC

Michael Birrer, MD PhD
Univ Arkansas CI

Kevan Shokat, PhD
UCSF Diller CCC

Clinician workforce recruitment for UCI Health network

Estimated need for cancer clinicians/clinical investigators: ~36 faculty
Heme-Onc: 22
Surg Onc: 8
Rad Onc: 6

Sayeh Lavasani, MD MS
Breast Medical Oncology
City of Hope (faculty)

Ann Arter, MD
HO/Thoracic Oncology
UCI (fellow)

Reza Nabavizadeh, MD
Urology
Mayo (faculty)

Poorya Vaidya, MD
HO/Melanoma
UCSD (fellow)

Michael O'Leary, MD
Surgery/Hepatobiliary
Loma Linda (faculty)

April Choi, MD
HO/GI cancer
Tufts (fellow)

Quoc-Anh Ho, MD
Radiation Oncology
Stanford (faculty)

Jorge Ramos-Perez, MD
Hematology/HSCT
City of Hope (fellow)

Jerica Lomax, MD
Neuro-oncology
UCI (fellow)

Brian Sworder, MD PhD
HO/Lymphoma
Stanford (faculty)

Nicole Foley, MD
HO/lymphoma-HSCT
Wash U (fellow)

Miguel Villalona-Calero, MD
HO/Thoracic Oncology
City of Hope (faculty)

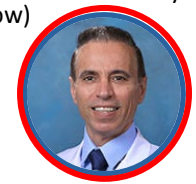
Priya Mitra, MD
Rad Onc
USC (faculty)

Shynam Srinivas, MD PhD
Interventional Radiology
UPMC (faculty)

Holly Yong, MD
Breast Surgical Oncology
Kaiser Permanente

Shirin Attarian, MD
HO/Head & Neck
LI Jewish (faculty)

Kelly Fairbairn, DO
Thoracic Surgical Oncology
MSKCC (fellow)



Mohammad Ziari, MD
Heme/Onc
City of Hope (faculty)

Polina Bellman, MD
HO/HSCT
U Kansas (fellow)

Eric Chen, MD
Rad Onc
Case Western (fellow)

Ongoing / Future Recruitments

- Precision Medicine / Early Phase Clinical Trials Leader
- Cancer Control faculty member
- GU oncology translational researcher
- Institute for Precision Health Director
- Pathology Chair
- Radiation Oncology Chair
- Otolaryngology Chair

UCI 趙 Chao Family Comprehensive Cancer Center

Cancer Focus (*Excellent to Outstanding*)

CFCCC extramural funding, AY 2021 vs. 2024

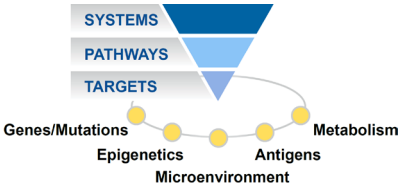
Funding Source	2021		2023		2024 (YTD)	
	Direct Costs	No. of Projects	Direct Costs	No. of Projects	Direct Costs	No. of Projects
Peer-Reviewed Projects						
NCI	$10.7M	65	$12.5M	85	$13.5M*	86
Other NIH	$13.8M	81	$13.3M	86	$14.8M	98
Other non-NIH	$6.6M	52	$7.0M	47	$5.7M	37
Subtotal Peer-Reviewed	$31.1M	198	$32.8M	218	$34.0M*	221
Non Peer-Reviewed Projects						
Industry	$10.5M	139	$10.8M	238	$10.0M	237
Other	$2.5M	31	$2.2M	27	$3.8M	38
Subtotal Non-Peer-Reviewed	$13.0M	170	$12.9M	265	$13.8M	275
Grand Total	$44.1M	368	$45.7M	483	$47.8M	496

* excluding P30 CCSG

CFCCC Research Programs

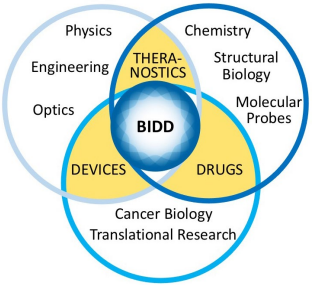
Systems, Pathways & Targets (SPT) Program (*Outstanding to Excellent*)

- 88 members across 6 UCI Schools and 19 Departments
- $18.6M in grant funding, $5.3M from the NCI
- Recruitment of numerous new members
- New research initiatives in Cancer Systems Biology, Cancer Metabolism



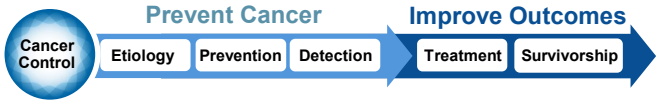
Biotechnology, Imaging & Drug Development (BIDD) Program (*Outstanding*)

- Merger of previous OIB and MDT Programs
- 90 members across 6 UCI Schools and 22 Departments
- $16.5M in grant funding, $5.0M from the NCI
- Emphasis on UCI excellence in “oncology physical sciences”
- Need to identify new program co-leader



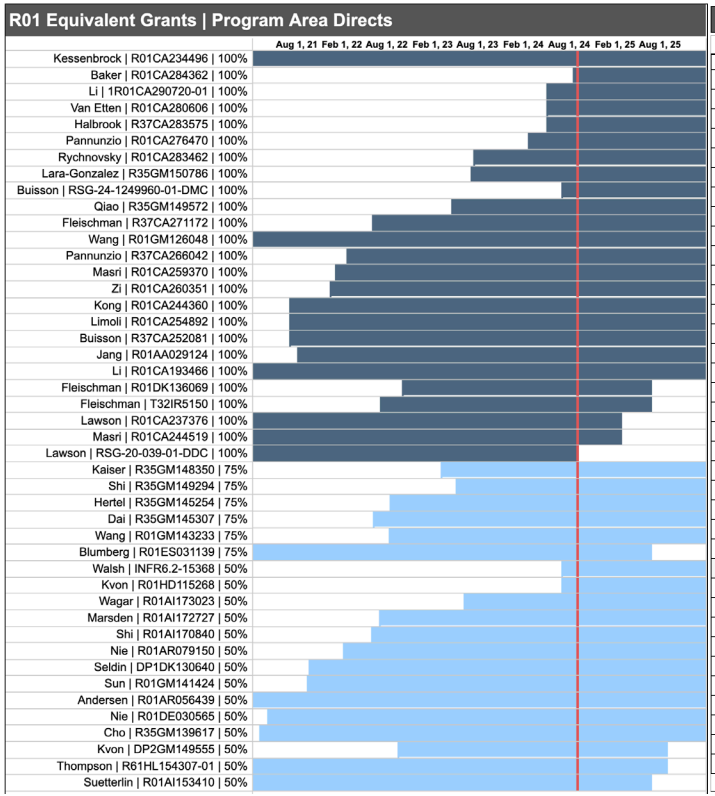
Cancer Control (CC) Program (*Excellent to Very Good*)

- Refocused from previous Cancer Prevention, Outcomes & Survivorship (CPOS) Program
- 55 members across 7 UCI Schools and 18 Departments
- $8.1M in grant funding, $2.6M from the NCI
- New focus on cancer prevention and outcomes

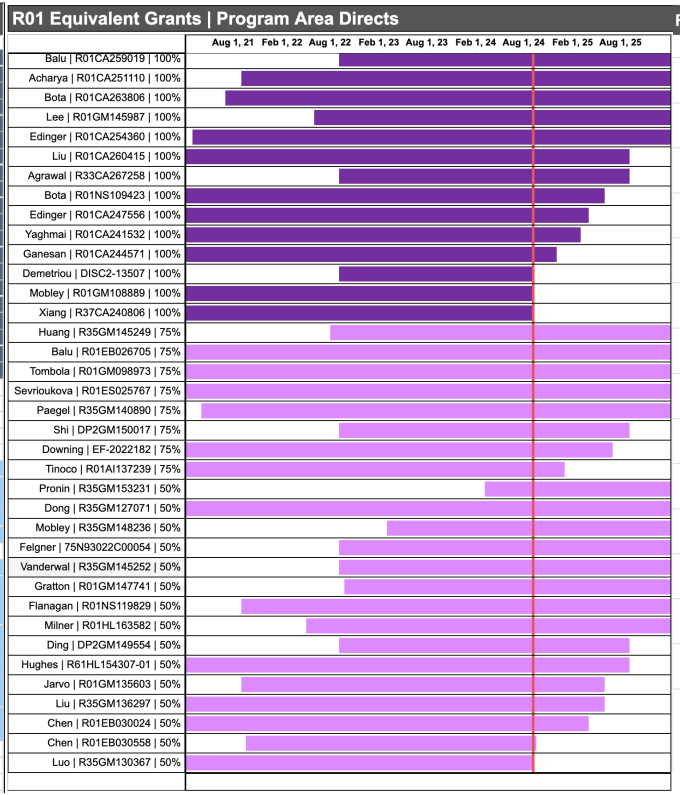


Extramural Funding Profiles of CFCCC Research Programs

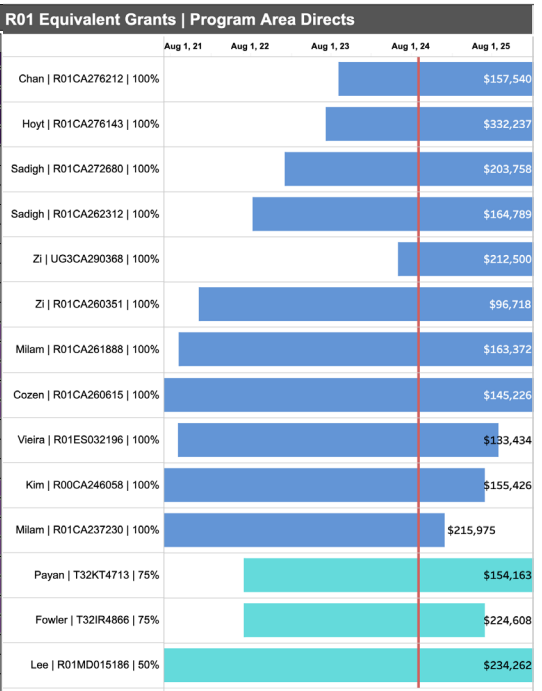
SPT (45)



BIDD (43)



CC (14)



Strategies to increase extramural peer-reviewed funding

- Assist current faculty, particularly early stage investigators, to get new extramural grants

Selma Masri, PhD
Assistant Professor
Biological Chemistry

ACC Pilot Project Awards 2018 & 2020

UCI Anti-Cancer Challenge

→ NIH NATIONAL CANCER INSTITUTE **R01 CA259370**

Chris Halbrook, PhD
Assistant Professor
Mol Biol & Biochem

ACC Pilot Project Award 2021

UCI Anti-Cancer Challenge

→ NIH NATIONAL CANCER INSTITUTE **R01 CA283575**

Kristen Kelly, MD
Professor
Dermatology

ACC Pilot Project Award 2020

UCI Anti-Cancer Challenge

→ NIH NATIONAL CANCER INSTITUTE **R01 CA259019**

NIH BOOT CAMP UC Irvine

- Hire new faculty with existing extramural grants

Wendy Cozen, DO MPH
Professor
Medicine
R01 CA206019
R01 CA260615

Zhuoli Zhang, MD PhD
Professor
Radiological Sciences
R01 CA209886
R01 CA241532

Wei Li, PhD
Professor
Biological Chemistry
R01 CA193466

Program publications

BIDD

	# of Pubs	Inter	Intra	Inter-Inst	High IF (>9.4)
Jan. 2023 - Dec. 2023	170	24%	8%	59%	16%
Apr. 2023 - Mar. 2024	157	24%	7%	59%	16%
Sep. 2023 - Aug. 2024	161	24%	6%	62%	18%

CC

	# of Pubs	Inter	Intra	Inter-Inst	High IF (>9.4)
Jan. 2023 - Dec. 2023	152	20%	13%	72%	13%
Apr. 2023 - Mar. 2024	162	24%	15%	74%	12%
Sep. 2023 - Aug. 2024	174	22%	12%	73%	15%

SPT

	# of Pubs	Inter	Intra	Inter-Inst	High IF (>9.4)
Jan. 2023 - Dec. 2023	261	19%	21%	57%	26%
Apr. 2023 - Mar. 2024	233	23%	21%	59%	26%
Sep. 2023 - Aug. 2024	240	25%	19%	62%	25%

Link to dashboards

Cancer Control Program

- EAB 2024 comments:
  - Program Aims too broad and lack specificity
  - Expand research focused on etiology, risk factors, and cancer screening
  - Focus on priority cancers in the catchment area (CA)
  - Increase the number of funded R01s
  - More interventional research on areas of emphasis
- Need interventional research on cancer prevention
  - RFP for CA-relevant research including clinical trials: 4 proposals funded at $150K/yr x 2

Hari Keshava, MD
Thoracic Surgical Oncology

Low-dose CT scanning and cfDNA screening in nonsmoking relatives of NSCLC patients

- Need to continue to recruit additional extramurally funded members
  - Another mid-career/senior faculty member (FY25 FTE request)

UCI 趙 Chao Family Comprehensive Cancer Center

Transdisciplinary Collaboration & Coordination (*Outstanding*)

Critical CFCCC Cooperative Cancer Grant Renewals

Skin Biology Center (P30 AR075047; PI Andersen, SPT)

- Promoting discoveries in skin biology and disease
- CFCCC supporting a human skin tissue core and Enrichment Program
- Extensive interactions with Skin DOT and Melanoma systems biology group
- Competing renewal application submitted in May 2023, awarded 04/01/24
- CFCCC providing institutional support for pilot projects

UCI SKIN
A Skin Biology Resource Center

Cancer Systems Biology (U54 CA217378; mPI Lander/Lowengrub/Lawson, SPT)

- One of 14 NCI Cancer Systems Biology Consortium Centers
- Focus on tumor heterogeneity and scRNASeq, quantitative models of tumor behavior
- Three interactive projects on breast cancer, melanoma, and leukemia
- U54 program sundowned by the NCI
- P01 grant submitted May 2023: Merit score 36
- P01 A1 version submitted Jan 2024, Merit score 20
- Two R01 applications for leukemia project also submitted:
  - R01 CA280606 (Van Etten)- 3% score, funded 04/01/24
  - R01 CA293425 (Lowengrub & Van Etten)- 18% score

UCI Center for Complex Biological Systems
CaSB@UCI
Cancer Systems Biology

CFCCC Collaborations

CFCCC Affiliates

- CHOC Children's
  - Site of all pediatric cancer care & clinical research
  - COG member, pediatric HCST and Phase I site
  - Active collaborative Working Groups in HSCT, AYA cancer, Education & Training, Research meeting quarterly
- VA Long Beach Health System
  - Joint faculty and CFCCC members
  - Training & educational collaborations
  - Research collaborations: NAVIGATE, Lung Cancer Precision Oncology

Other NCI CCs

- UC Heme Malignancy Consortium
  - Launched in 2014, rapid opening of trials across Consortium
  - 8 trials completed, 9 open to accrual incl. UCHMC1913 from UCI (accrued 24/30 pts)

University of California
Hematologic Malignancies Consortium
UCD UCI UCLA UCSD UCSF

- UC Cancer Consortium
  - Leverage UC Care: ~25,000 new cancer patients annually
  - WGs on clinical pathways, precision oncology, virtual 2nd opinions
  - Disease groups: pancreatic cancer, lung cancer
  - Director Van Etten assumed Deputy UCCC Chair position in Oct. 2024

UNIVERSITY OF CALIFORNIA Cancer Consortium

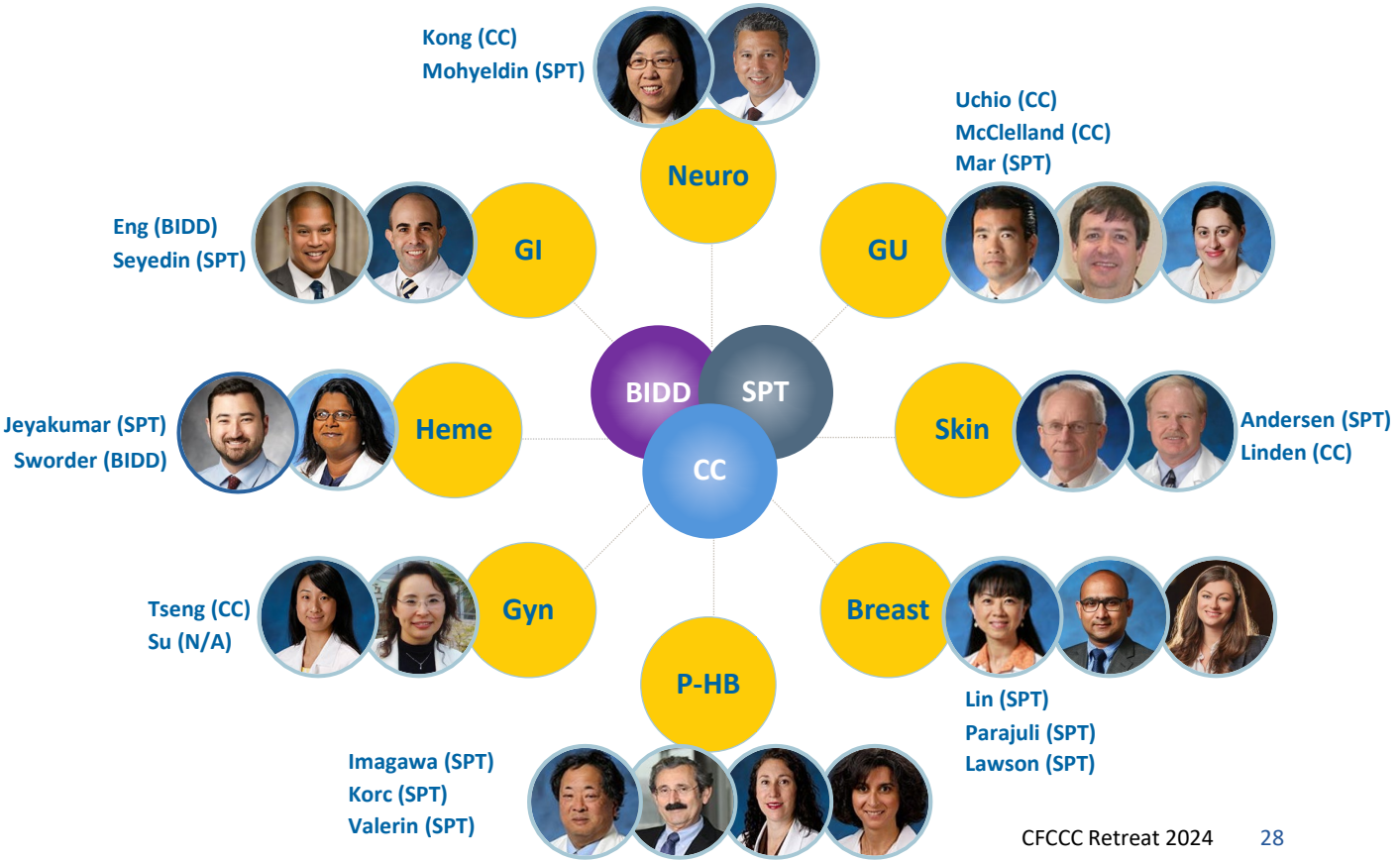
- Other NCI Cancer Centers
  - Partnerships with 12 other NCI-CCs through NCI Cancer Systems Biology Consortium
  - Many multi-PI grants with other centers, incl FLASH Radiotherapy P01

CANCER SYSTEMS BIOLOGY CONSORTIUM

Disease-Oriented Teams: Interface between basic & clinical investigators

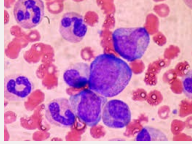
DOT functions

- Quarterly presentations by basic and clinical researchers
- Management of clinical trials portfolio
- Conduct 1st stage of scientific review
- DOT approval required for moving a trial to PRMC/IRB stage
- Bring new trial concepts forward
- Foster investigator-initiated trials



HSCT & Cell Therapy Program

Stefan Ciurea, MD
HSCT Program Leader



- Launched May 2020
- Only adult transplant program in Orange County
- FACT accredited: Mar 2022
- CalOptima Center of Excellence: May 2022
- Cell Processing Lab opened Q2 2024
- Recruited new heme malignancy physicians

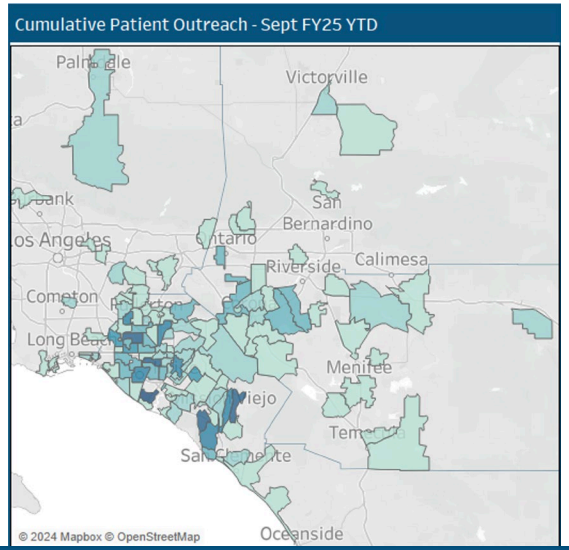
Yaya Chu, PhD
Laboratory Director

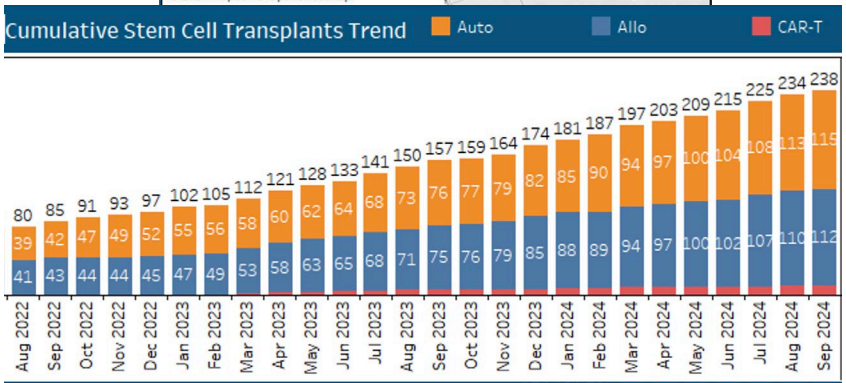
Kiran Naqvi, MD
Myeloid leukemias

Cathy Coombs, MD
CLL

Brian Sworder, MD PhD
Lymphoma

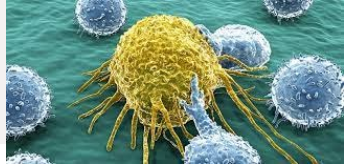
- Continue transplant volume increase towards 100-120/yr
- Obtain COE designation from commercial payers
- Continue faculty recruitments (HSCT, ALL, myeloma)
- First HSCT IITs: ADAPT trial, autologous T cells vs BKV nephritis





UCI Chao Family Comprehensive Cancer Center

Immuno-Oncology



- Approved as designated commercial CAR-T site
- FACT-accredited for cell therapy
- cGMP cell manufacturing facility opened Q4 2023

Mike Demetriou, MD PhD

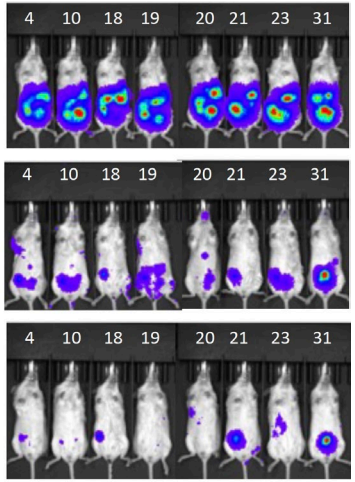
- First CFCCC-developed therapy: novel chimeric antigen receptor targeting cancer-specific carbohydrates

GlyTR

- This therapy cures multiple cancers (breast, ovarian, prostate, lymphoma) in mice
- Accepted into NExT NCI Experimental Therapeutics Program
  – manufacture & testing clinical grade material for first-in-human studies
- Target phase I trial opening: Q2 2025
- Next investigator-initiated trials:
  donor α-BK virus T-cells, haploidentical NK cells
- Recruiting two new immuno-oncology faculty

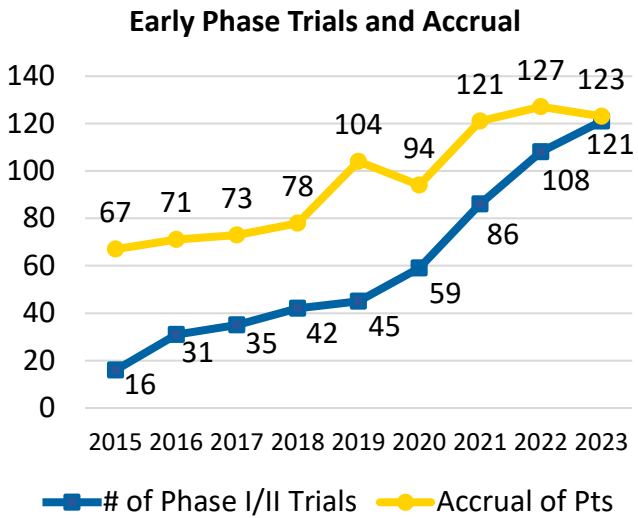
Jianhua Yu, PhD

GlyTR1 + T cells + SKOV3

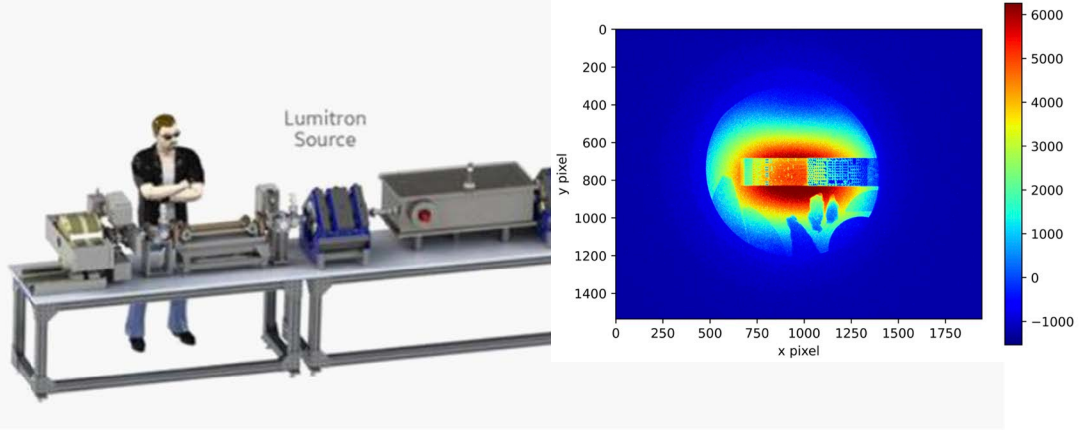


Precision Oncology

- CFCCC & UCI Health have the largest early phase clinical trials program in OC
- Joined NCI ETCTN (with UPitt)
- Joined two industry networks
- Joined the Alliance NCTN group
- Activated genomics functionality in Epic and built interface with Caris to allow tumor genetic data to be analyzed
- Recruiting a Precision Therapeutics Director (with Center for Clinical Research)
- Expanding interactions with UC Cancer Consortium



Cancer Imaging



- Imaging at 100x resolution, 1/100th dose
- Applications in cancer:
  - Imaging
  - Cancer screening
  - Radiotherapy, incl. FLASH
- Commercialized in Lumitron Technologies
- Prototype machine being completed for DARPA
- Current machine is producing a Very High Energy Electron (VHEE) beam (25 MeV) suitable for preclinical studies of FLASH radiotherapy (Dr. Charlie Limoli, **BIDD**)
- 500 keV x-ray beam production achieved, enabling imaging studies in mice

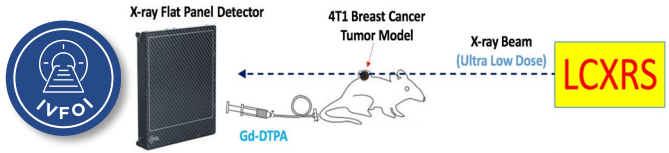
businesswire
A BERKSHIRE HATHAWAY COMPANY

Revolutionary X-Ray Innovation Set to Transform Cancer Treatment and Clinical Radiography

Lumitron Technologies advances the practical application of FLASH radiotherapy

February 20, 2023 12:45 PM Eastern Standard Time

IRVINE, Calif.--(BUSINESS WIRE)--Lumitron Technologies, Inc., a company pioneering the development of a unique x-ray system, HyperVIEW™ EBCS, today announced its underlying accelerator technology has successfully generated electron beams that, for the first time, enable electron FLASH radiotherapy for a variety of next generation cancer treatments.



- UCI Office of Research, Schools of Medicine and Engineering, CFCCC, and UCI Advancement negotiating agreement for purchase of second-generation machine for research/clinical applications

Integrative Oncology / Whole Person Cancer Care

Susan Samueli | Integrative Health Institute

Shaista Malik, MD, PhD, MPH
Director

- Susan Samueli Integrative Health Institute (SSIHI) provides inpatient and outpatient integrative medicine services for patients with cancer
  - Acupuncture, massage, mindfulness, yoga, Tai-Chi, biofeedback, nutrition

- Expanded outpatient locations in Newport Beach & Laguna Hills
- Recruited a clinician-scientist leader for integrative oncology program
  - With the Samueli Institute (endowed chair)
- Secured institutional commitments for supportive oncology services
  - dietary/nutrition, psychosocial, spiritual

Gary Deng, MD, PhD

- Launching interventional clinical research in integrative oncology
  - Develop evidence-based approaches to integrative health in cancer
  - ACC Pilot Project: UCI-21-33: Electroacupuncture for management of symptoms in AYA patients w/cancer
  - R01 CA276212 PIs Chan (**CC**)/Acharya (**BIDD**): Repurposing Riluzole for augmenting BDNF in chemobrain

UCI 趙 Chao Family Comprehensive Cancer Center

Clinical Research (*Outstanding*)

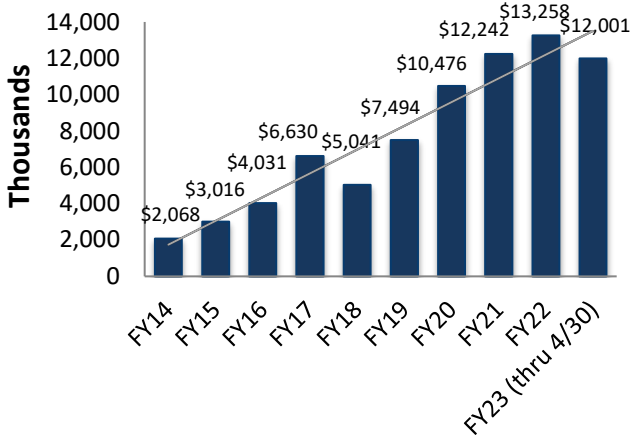
Stern Center for Cancer Clinical Trials & Research

Warren Chow, MD
Associate Director for
Clinical Science

Farshid Dayyani, MD, PhD
Medical Director, Stern Center

130 Staff
26 open positions

Clinical Trial Revenues



Source	$
Industry	8,212,439
Institutional Support	2,373,042
Gifts & Endowments	497,490
CCSG	349,166
National Cooperative Group	258,780
External	776,383
Total	**12,467,299**

CFCCC Clinical Research summary

Warren Chow, MD
Associate Director for Clinical Science

Farshid Dayyani, MD, PhD
Medical Director, Stern Center for Cancer Clinical Trials & Research

Arash Rezazadeh, MD
Co-Chair, Protocol Review & Monitoring Committee

John Fruehauf, MD, PhD
Chair, Data & Safety Monitoring Board

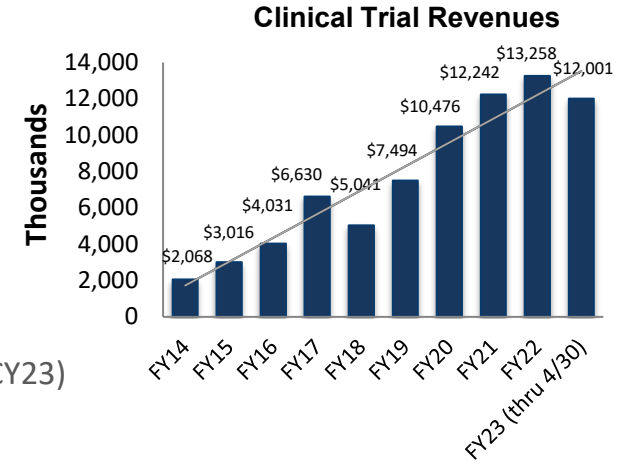
Christine Hui, MPH
Administrative Director for Clinical Research Operations

The GOOD:

- Joined NCI ETCTN (UPitt); UCI had the 3 top accruers for 2023
- eRegulatory binder system (Complion)
- Increased Stern Center efficiencies
- Decreased time to trial activation
- New ClinROC oversight committee
- Two clean not-for-cause FDA audits
- Excellent accrual of URMs and older adults
- Record number of IITs open to accrual (18)
- Robust accrual to interventional trials (670 in CY23)

ETCTN
Experimental Therapeutics Clinical Trials Network
Team Driven. Cancer Therapy Focused.
National Cancer Institute at the National Institutes of Health

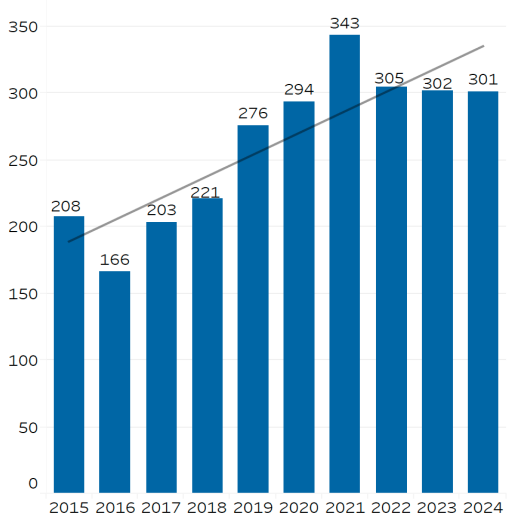
Complion
A RealTime Software Solutions Company

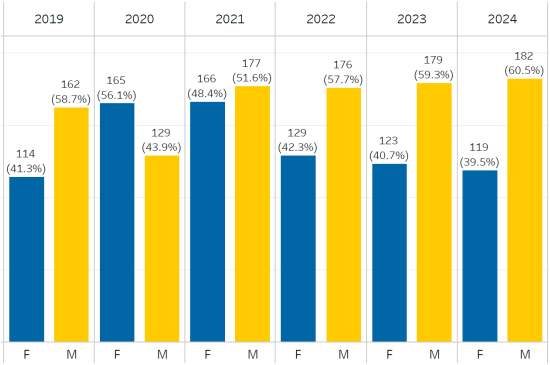


The BAD:

- Static accruals to interventional treatment trials (300 in CY23)
- Decrease in accrual of women to treatment trials (~40% in CY23)

Clinical Research: Corrective Action Plans





Treatment trial accruals:

- Increase referrals from outside groups: OPN Healthcare, Oncology Institute for Hope, VAH, Kaiser-Permanente
- Opening several IITs with potential for high accrual: HSCT, gastric cancer, prostate cancer
- Reform of DOT SOPs to better match trials with patient population
- Reorganization of Phase 1 infrastructure with recruitment of Director for early phase clinical trials
- Targeted recruitment of clinician-investigators in diseases with low accrual (H&N, melanoma, Gyn)

Accrual of women:

- Open more breast and Gyn trials targeting our patient population
- Recruit a medical oncologist specializing in Gyn cancers to oversee the Gyn DOT and clinical trials portfolio

UCI 趙 Chao Family Comprehensive Cancer Center

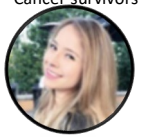
Community Outreach & Engagement (*Outstanding to Excellent)*

Community Outreach & Engagement

Community Equity Board

* Cancer survivors


Ellen Ahn


Karen Alvarez


Daniel Anderson


Isabel Becerra


Michelle Burroughs


Susan Choi


Charlene Kazner*


Maria Matza


Becky Nguyen


Steve Thronson


Robin Walker


Sora Park Tanjasiri, DrPH, MPH, AD COE

Office of COE


Daniel Rivas, MA
COE Director
(Spanish)


Vy Lê, CHE
(Vietnamese)


Jonathan Garzón, CHE
(Spanish)


Troy Tang, Navigator
(Vietnamese)


Iris Duran, CHE (Spanish)


Melenaite Fifita, CHE & Navigator
(Tongan)

CFCCC & UCI

- Associate Directors
- Program Leaders
- Center Members
- Disease-Oriented Teams (DOTs)
- Stern Center
- CRTEC

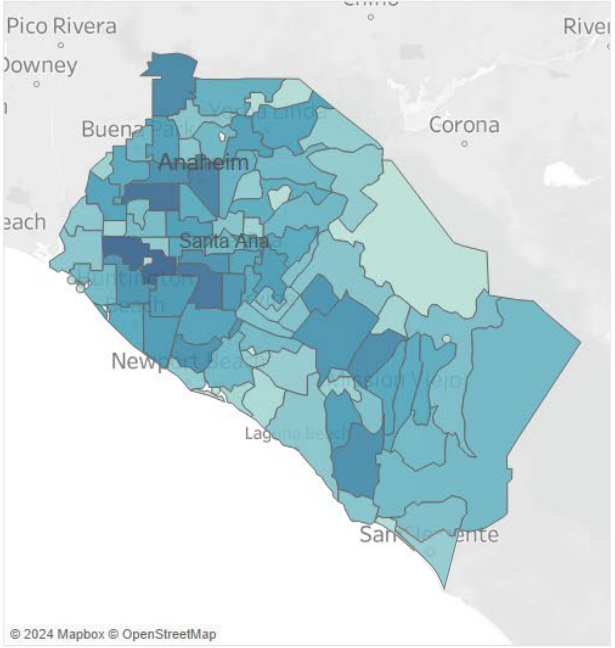
- UCI Health
- UCI FQHCs
- CoC Cancer Committee
- CTSA
- UC Cancer Consortium

Community Partners and Stakeholders

Understanding our Orange County community in detail

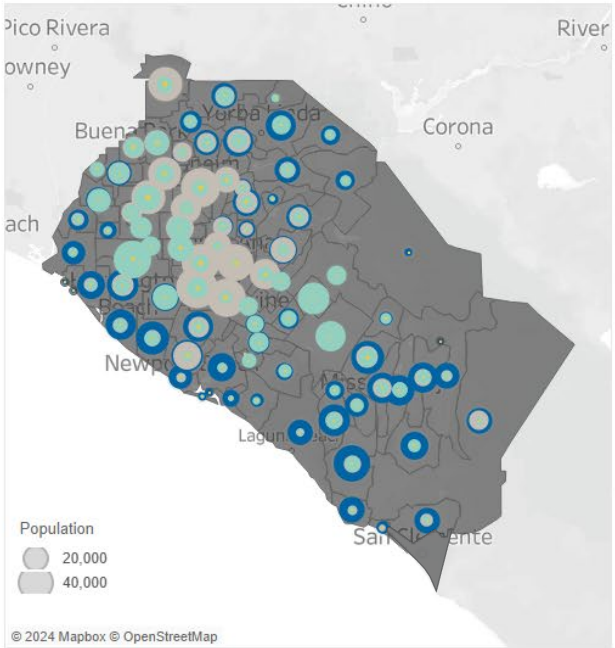
General — Specific

Standard OC-wide Analysis



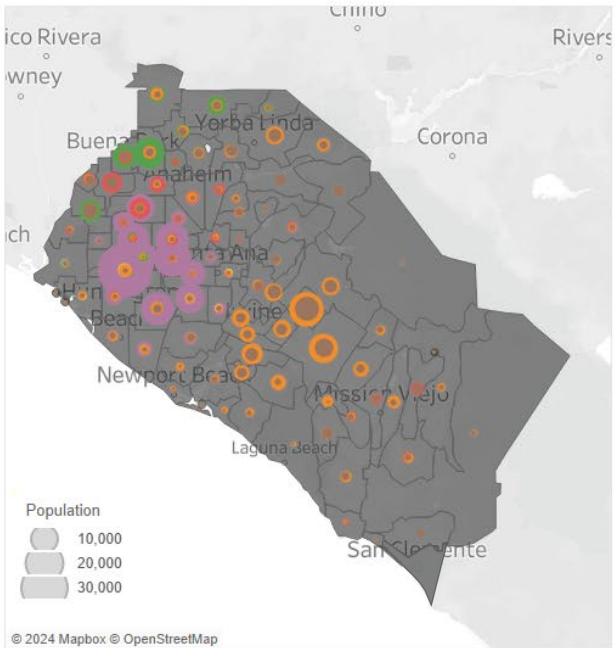
OC Residence
Low — High

Racial & Ethnic Diversity



- American Indian and Alaska Native
- Asian
- Black or African American
- Hispanic or Latino (of any race)
- Native Hawaiian/ Pacific Islander
- Two or More Races
- White

Asian Ethnic Diversity (23% of OC)

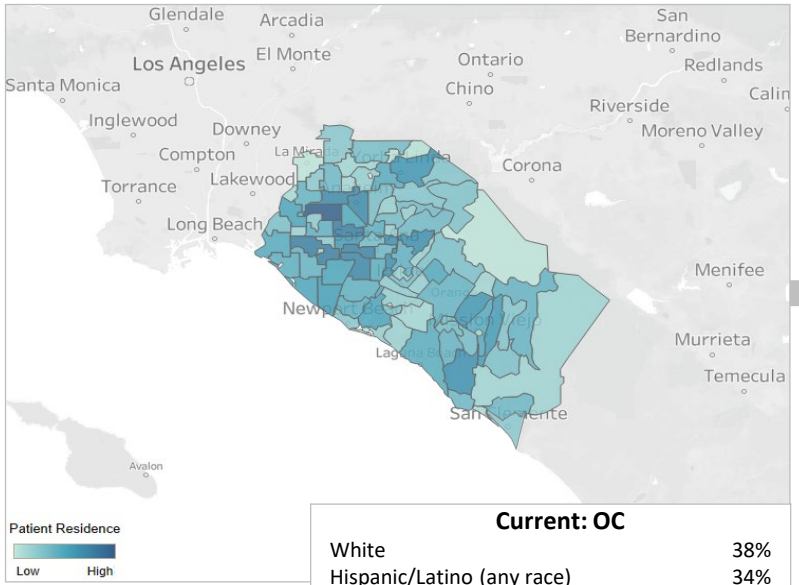


Vietnamese	31%	Asian Indian	9.%
Chinese	19%	Japanese	5%
Korean	15%	Other Asian	9%
Filipino	12%		

Proposed new Catchment Area

Orange County

Total # patients seen	4,869
# of analytic cases	3,649
% of analytic cases that reside in OC	**70%**

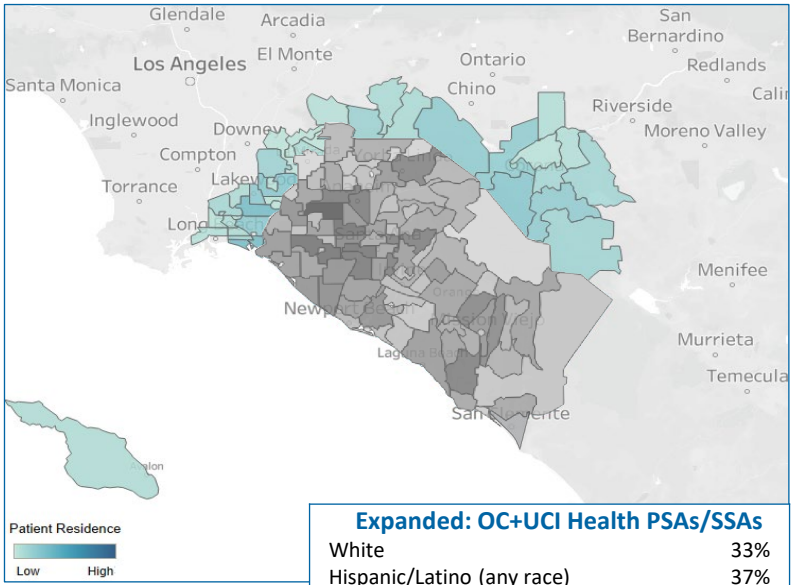


Current: OC

White	38%
Hispanic/Latino (any race)	34%
Asian	23%
Black/African American	2.3%
Native Hawaiian/Pacific Islander	0.4%
American Indian or Alaska Native	0.2%
Two or More Races	4%
TOTAL population	**3.2 million**

+UCI Health PSAs/SSAs

Total # patients seen	4,869
# of analytic cases	3,649
% of analytic cases that reside in OC+	**80%**



Adding OC-adjacent includes:

+5.4% Black/African American
+45% Hispanic/Latino

Expanded: OC+UCI Health PSAs/SSAs

White	33%
Hispanic/Latino (any race)	37%
Asian	22%
Black/African American	3%
Native Hawaiian/Pacific Islander	0.3%
American Indian or Alaska Native	0.2%
Two or More Races	4%
TOTAL population	**4.6 million**

Community Outreach & Engagement – Summary

- Active and engaged Community Equity Board
- Regular bilateral interactions with CFCCC Research Programs leading to new grants focused on Catchment Area
  - R37 CA266042 "*Defining Mechanisms of Genome Rearrangements in Ph-like ALL to Determine Predictive Markers in High-Risk Hispanic Populations*", PI Pannunzio (**SPT**)
- Multiple new extramural grants addressing Catchment Area cancer health disparities
- CFCCC/Cal State U Fullerton P20 Cancer Health Equity Research Partnership
- UCI Family Health Center awarded $500K from HRSA for *Accelerating Cancer Screening*
- Define Catchment Area priorities: cancer health disparities
- Expand the *Advancing Cancer Care Together* program with OC FQHCs ($5M CalOptima grant)
- Improve data collection and analysis of outcomes, starting with UCI FQHCs
- Potential collaborations with other NCI CCs in OC (e.g. City of Hope)
- Appointed COE Liaisons in the CFCCC Research Programs

COE Liaisons

Shawn Griffin, Pharm D
Systems, Pathways & Targets

Gelareh Sadigh, MD
Cancer Control

Darci Trader, PhD
Biotechnology, Imaging & Drug Development

UCI 趙 Chao Family Comprehensive Cancer Center

Cancer Research Training & Education (*Outstanding*)

Cancer Research Training & Education

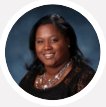
Edward Nelson, MD
Associate Director for Cancer
Research Training & Education

	PRE-BACCALAUREATE	UNDERGRADUATE	GRADUATE/MED STUDENTS	POST-DOCTORAL	FACULTY
CFCCC	ANTI-CANCER CHALLENGE				
CFCCC	HS YOUTH SCIENCE FELLOWSHIP	ANNUAL & PROGAM RETREATS | ANNUAL SYMPOSIA & CONFERENCES | DEI EDUCATION			
CFCCC		ANNUAL CHAO FAMILY LECTURESHIP			
CFCCC			R25s: BIG DATA SCIENCE & CANCER | INTERDISCIPLINARY CAREERS | CANCER SYSTEMS BIOLOGY		
CFCCC			SHARED RESOURCE TECH TALKS AND TRAININGS		
CFCCC			CANCER-RELATED UCI T32 AWARDS (8)		ACS IRG MINORITY SUPPLEMENT
CFCCC + Partners			ONCOLOGY SUMMER INTERNSHIP		CFCCC MET
CFCCC + Partners					CME>20 EVENTS W/CFCCC
CFCCC + Partners		P20 CSUF/UCI CANCER RESEARCH EXPERIENCE PROGRAM		CFCCC CLINICAL TRIALS BOOTCAMP	
CFCCC + Partners					UCI NSF CAREER INSTITUTE
CFCCC + Partners	COSMOS		MSTP		GRAND ROUNDS
CFCCC + Partners			ICTS: KL2 (2/4), TL1 NRSA (6/9), T35 SMART PROGRAM (2/8)		
CFCCC + Partners			CANCER-ASSOC.: 17 RESIDENCIES, 11 CLINICAL FELLOWSHIPS		NIH R01 BOOTCAMP
CFCCC + Partners	SUMMER SURGICAL FELLOWSHIPS: UROLOGY, SURG ONC, SURGERY		PRIME-LC	ICTS K CLUB	PHYSICIAN SCI. TRAINING PRG.
UCI	SCHOOL VISITS	BIO 199: UROP SURP	LEAD-ABC		NIH RESUBMISSION PROGRAM
UCI		CANCER CURR. 5 class>20 CC Members	QUARTERLY CAREER FAIR	NIH F AWARDS	VANGUARD GROUP (CCBS)
UCI		COLLEGES AGAINST CANCER	GPS STEM | RIPs | ANNUAL CAREER WORKSHOP		CAREER DEV. AWARDS 7 Fs, 2Ks
UCI			UCI BEALL APPLIED INNOVATION		
UCI		ASSOCIATION FOR WOMEN IN SCIENCE			

UCI 趙 Chao Family Comprehensive Cancer Center

Plan to Enhance Diversity

Equity, Diversity and Inclusion Steering Committee



CHAIR
Associate Director EDI
Ursula Worsham, PhD

UNIVERSITY

Vice Chancellor for Diversity Equity & Inclusion and UCI Chief Diversity Officer
Dyonne Bergeron, EdD

Assistant Vice Chancellor
Equity, Diversity & Inclusion
Marguerite Bonous-Hammarth, PhD

COHS SCHOOLS

School of Medicine
Assistant Dean DEI
Ursula Worsham, EdD

School of Nursing
DEI Officer
TBD

School of Pharmacy
DEI Officer
Mahtab Jafari, Pharm D

Program in Pop. Science & Public Health
DEI Officer
Sora Tanjasiri, DrPH, MPH (CC)

TRAINING & EDUCATION

Associate Director CRTEC
Edward L. Nelson, MD (BIDD)

Co-Director, LEAD ABC
Carrol Major, MD
OB/Gyn

Co-Director, LEAD ABC
Candace Taylor Lucas, MD
Pediatrics

Director, PRIME-LC
Charles P. Vega, MD

COMMUNITY OUTREACH

Associate Director COE
Sora Tanjasiri, DrPH, MPH (CC)

CATCHMENT AREA

Associate Professor of Pharmaceutical Sciences
Claudia Benavente, PhD (SPT Program)

School of Medicine
Office of Belonging, Equity & Empowerment
Xavier Hernandez, PhD

Professor Epidemiology & Biostatistics
Karen Edwards, PhD (CC Program)

Professor of Family Medicine
Juliet McMullin, PhD

Professor Epidemiology & Biostatistics
Sunmin Lee, PhD (CC)

CFCCC Plan to Enhance Diversity

- CFCCC CAO with extensive experience in DEI administration and operational leadership
- CFCCC Director of Admin Programs supporting DEI efforts
- EDI Steering Committee formed Sept 2022
- Leveraging numerous ongoing SOM and UCI Diversity programs
- Anti-Cancer Challenge 2023-24 Pilot Project categories for Underrepresented Investigators, Re-entry after family care
- Pilot Pulse Survey (Jan 2023) on Diversity, Inclusion & Belonging
- CFCCC LEAD program for leadership development
- Creation of CFCCC Plan and Metrics

Melanie Funes, PhD
CAO & Associate Director
Administration & Finance

April Bagaporo, MBA
Director for Administrative Programs

UCI Office of Inclusive Excellence

UCI Anti-Cancer Challenge

UCI Public Health

UCI 趙 Chao Family Comprehensive Cancer Center

Philanthropy

www.cancer.uci.edu

CFCCC Philanthropy - summary

Dedicated Cancer Advancement Team (6 FTE)

- Jenn Sarrail, Denice Lanuti, Jared Bigman, Tim Preletz, Joy Kliewer, Freddy Vega
- Last 7 yrs: >$50M raised, endowment increased from $5M to $32M, 6 new endowed chairs

Executive Director of Development (Cancer)
Angelique Andrulaitis

UCI Brilliant Future Campaign

- UCIMC Irvine and FLF-MIB: Raised $26M towards cancer building and associated space
- Research Endowments: Raised ~$25M to support cancer research

BRILLIANT FUTURE
THE CAMPAIGN FOR UCI

UCI Anti-Cancer Challenge

- Eight-year fundraising total ~$6.3M
- 100% dedicated to cancer research
- Overall ROI on pilot projects is ~17:1
- Collaborative agreement with CHOC
- Aldrich Park event October 5, 2024
- 2024 ACC fundraising: >$1,500,000
- RFP will be released in December
- Gina Lee award

CHOC

11th Annual Chao Lecturer in Cancer: Feb. 27th, 2025

Karen M. Winkfield, MD, PhD
Ingram Professor of Cancer Research
Professor of Radiation Oncology
Vanderbilt University

Executive Director, Meharry-Vanderbilt Alliance
Member, National Cancer Advisory Board

Research: Design & implementation of programs to reduce socioeconomic barriers contributing to disparate health outcomes in cancer

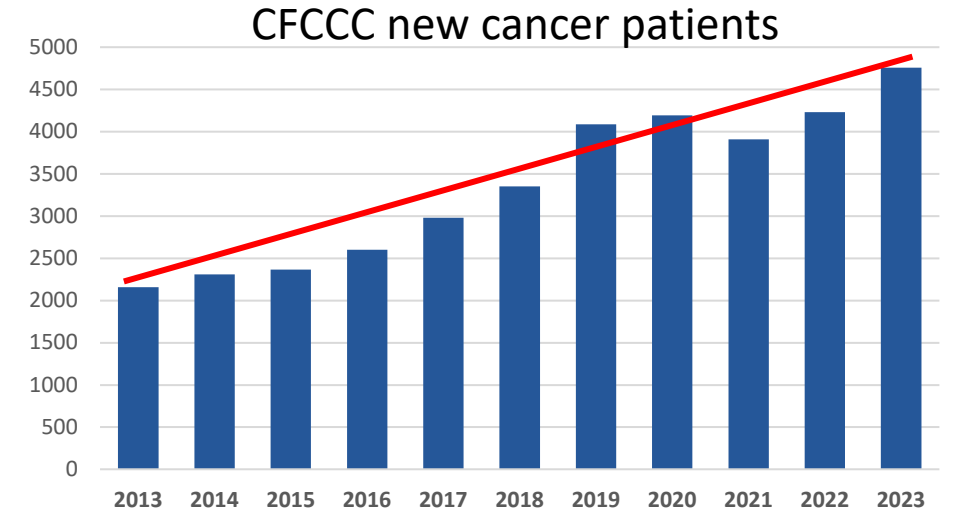
UCI 趙 Chao Family Comprehensive Cancer Center

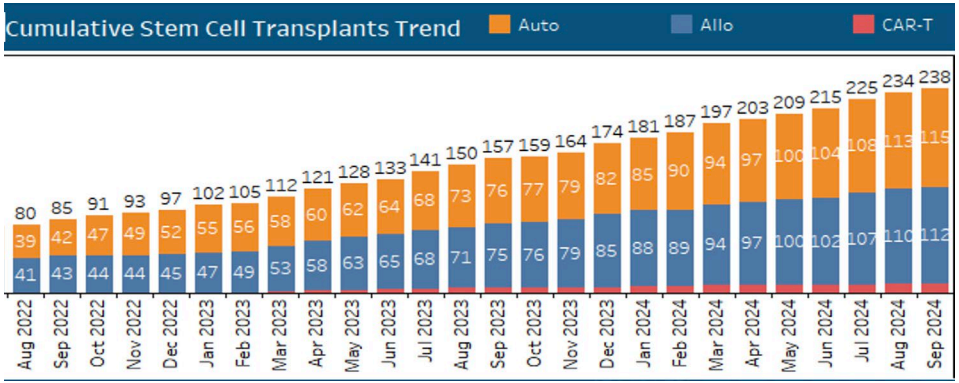
Questions?

UCI 趙 Chao Family Comprehensive Cancer Center

Recognition: Edward L. Nelson, MD

We would not be where are today without Ed Nelson…





UC Irvine
Joe C. Wen School of
Population & Public Health

UCI 趙 Chao Family
Comprehensive Cancer Center

Advancing Tobacco Policy Research to Reduce Disparities

Denise D. Payán, PhD, MPP
Associate Professor | UC Irvine Dept. of Health, Society & Behavior

2024 CFCCC Scientific Retreat
Friday, Nov. 8, 2024

Background

- Globally, tobacco use continues to be a leading modifiable risk factor for cancer-related deaths

- In California, cigarette smoking was associated with ~21.6% of cancer deaths among adults (25-79 yrs) and $1.6B in lost earnings in 2019 (Islami, Marlow, Zhao, et al., 2022)

- **Health Disparities Exist**
  - While some ethnic/racial groups have lower tobacco use prevalence rates (e.g., Latinos), they are *less* likely to be screened for smoking &/or cancer **and** are at *higher risk* of receiving a late-stage diagnosis for tobacco-related cancers compared to white smokers (Unger & Falcon, 2022)

Flavored Tobacco Products & Policy

- **Regulating flavored tobacco/e-cigarette products is critical for tobacco prevention efforts**
  - Products are easier to initiate, more appealing, particularly among youth, and seen as less harmful (Meernik et al., 2019; Leventhal et al., 2019)
  - Menthol cigarette use rates are higher among Black and Latino young adults and adolescents (Cullen et al., 2019; Watkins et al., 2022)
- **Flavored Tobacco Sales Restrictions (FTSRs)** can ↓ access and use
  - CA residents with a comprehensive FTSR vs. no ban had 30% lower odds of using any flavored tobacco (Timberlake, Aviles, & Payán, 2023)
- By 06/2024, 8 states, 395 local jurisdictions, and 3 Native American tribes had enacted FTSRs (some partial)

2009 Tobacco Control Act (Federal)

- Restricted flavored tobacco product sales
  - Exemption: menthol

2020 Senate Bill or SB 793 (California)

- Prohibits retailers from selling or possessing flavored tobacco products, including menthol cigarettes & flavored e-cigarettes
  - Exemptions: hookah, pipe tobacco, premium cigars
- No preemption, which allows for more comprehensive local FTSRs
- Effective Dec 2022 post-referendum vote

Limited research exists on state and local FTSR implementation

Brief report

OPEN ACCESS

Public support for policies to regulate flavoured tobacco and e-cigarette products in rural California

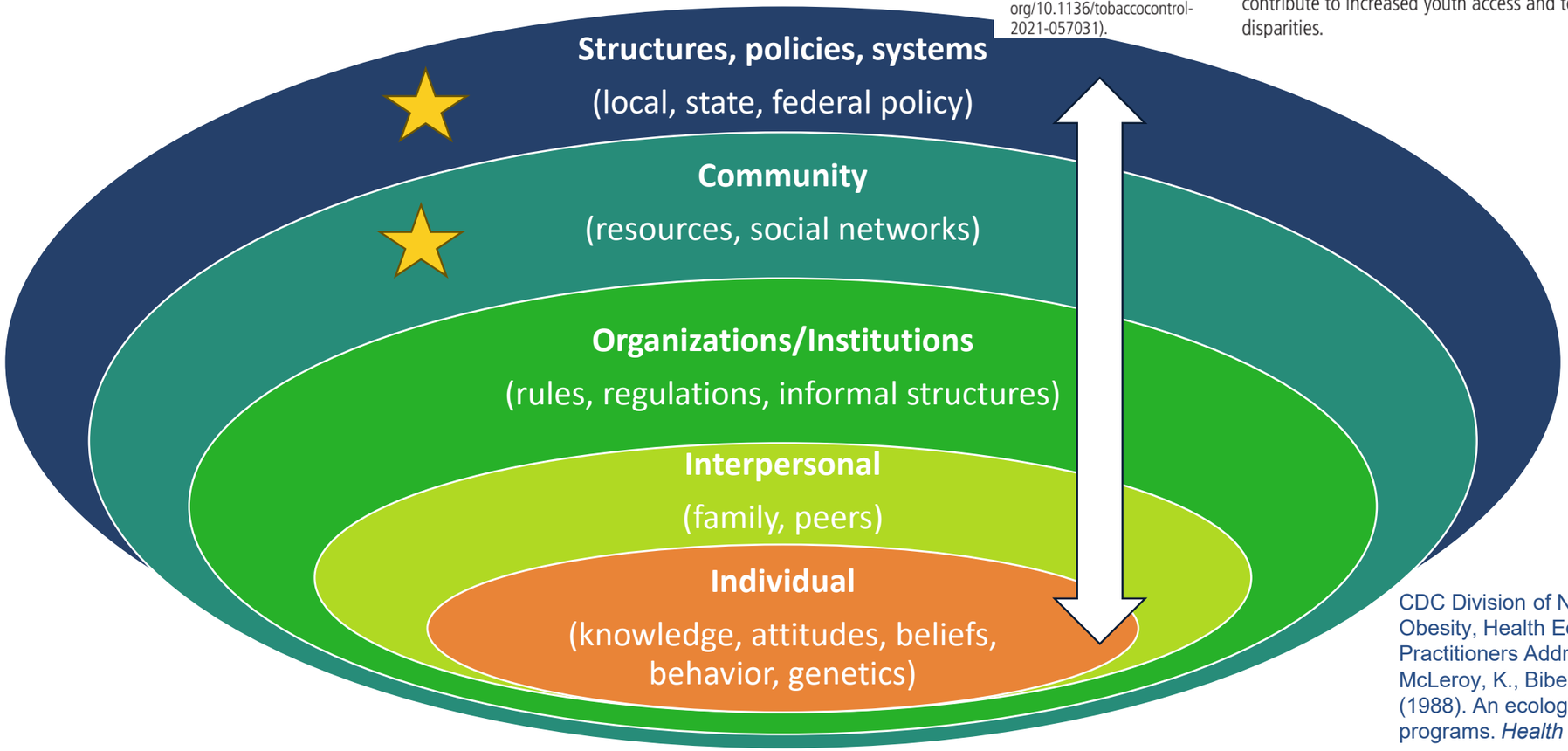
Denise Diaz Payán ,[1,2] Nancy J Burke,[1,2] Jamie Persinger,[3] Juliette Martinez,[3] Lisa Jones Barker,[3] Anna V Song [4,2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/tobaccocontrol-2021-057031).

ABSTRACT

Introduction Flavoured tobacco control policy exemptions and electronic cigarette products may contribute to increased youth access and tobacco use disparities.

e-cigarette use was a notable public health concern,[7] with popular flavours like fruit, mint, menthol and candy/desserts.[8] While pandemic shelter-in-place orders disrupted youth access and reduced utilisation,[9] 11% of high school students reported current



CDC Division of Nutrition, Physical Activity, and Obesity, Health Equity Resource Toolkit for State Practitioners Addressing Obesity Disparities. McLeroy, K., Bibeau, D., Steckler, A., & Glanz, K. (1988). An ecologic perspective on health promotion programs. *Health Education Quarterly, 15:351-377.*

Policy surveillance & local implementation of flavored tobacco product sales ban

1. **To conduct a systematic literature review to assess the policy implementation of state and local FTSRs in the U.S.**

2. **To compare implementation of the state's law (SB 793) vs. local comprehensive FTSR in California**
   - Mixed methods study design
   - Two case study sites
     - City of Santa Ana (policy conditions: comprehensive local FTSR)
     - 1 County in the San Joaquin Valley (policy conditions: SB 793)

Study Site 1: Santa Ana, CA

Santa Ana chooses to ban sale of flavored tobacco products

A researcher holds vape pens in a laboratory. (Associated Press)

By Ben Brazil
Staff Writer

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Oct. 16, 2024

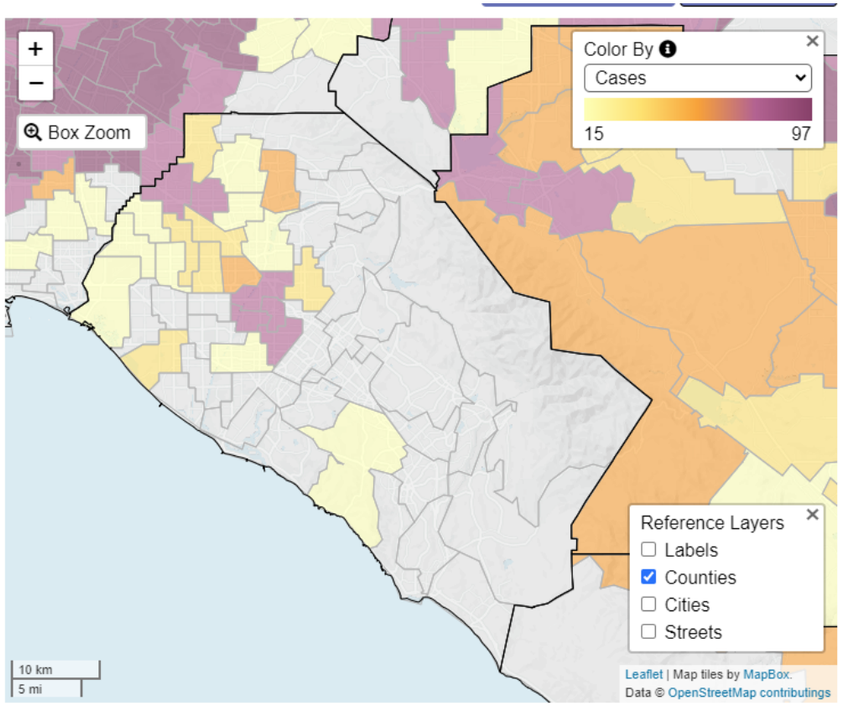
San Clemente's 'sand czar' looks to

Date Range
5-Year: 2017-2021

Cancer Site/Type
Lung Cancer

Sex
Male and Female

Race and Ethnicity
Hispanic



Source: https://www.californiahealthmaps.org/
Data source: Cancer incidence rates calculated from CA Cancer Registry data. Selected population sociodemographic data based on ACS 2015-2019 & 2018-2022, Census 2010 & 2020, and SEER census tract estimates by race/origin

Policy surveillance & local implementation of flavored tobacco product sales ban (2)

- Mixed methods study design
- Data Collection (*in progress*)

  Policy Scan ✓ *Tobacco retailer survey* *Key Informant Interviews*

  (cross-sectional)

- Implementation Measures & Outcomes

Outcome	Measure	Description
Implementation	Acceptability	How acceptable is the flavored tobacco product sales ban?
	Appropriateness	How appropriate and compatible is the policy with the scope of the problem?
	Feasibility	How feasible is implementation given the availability of resources and supports?
	Penetration or Reach	What is the tobacco retailer compliance rate post-implementation?
Service	Equity	How equitable is enforcement within local jurisdictions?
Recipient	Stakeholder satisfaction	Are key stakeholders (retailers, health departments, enforcement agents, advocates) satisfied with implementation processes and outcomes?

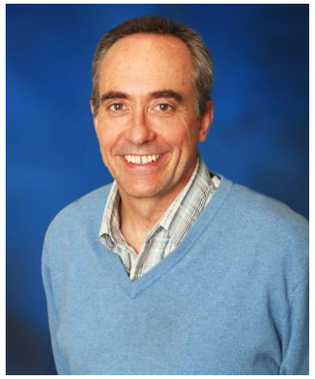
Significance & Future Work

- Patchwork of state and local tobacco policy exists in the U.S.
- Results may reveal important gaps and opportunities from the perspective of various policy stakeholders to improve implementation and compliance
- Planned community-engaged dissemination efforts to prioritize local action
  - Tobacco and Vape Free OC Coalition
  - UC Merced Nicotine & Cannabis Policy Center

Acknowledgments

Funding provided by the California Tobacco-Related Disease Research Program of the University of California, Grant Number [T32KT4713]

UC Irvine UCMERCED



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Thank you

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UCI 趙 Chao Family Comprehensive Cancer Center

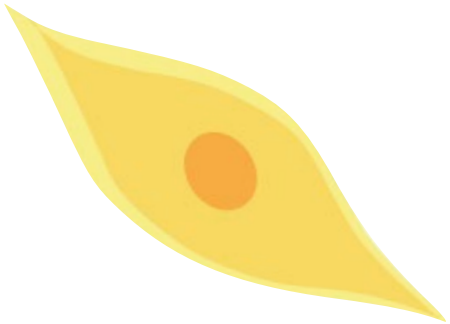
3D Spheroid DNA-Encoded Library Screening Technology:
Hit Finding on the STING Pathway

Brian Paegel, PhD
Associate Dean of Research, School of Pharmacy & Pharmaceutical Sciences
BIDD Program Leader, CFCCC

+

= ?

TARGET-BASED



CELL-BASED

Journal of Medicinal Chemistry

pubs.acs.org/jmc

Perspective

Is Target-Based Drug Discovery Efficient? Discovery and "Off-Target" Mechanisms of All Drugs

Arash Sadri*

Cite This: https://doi.org/10.1021/acs.jmedchem.2c01737

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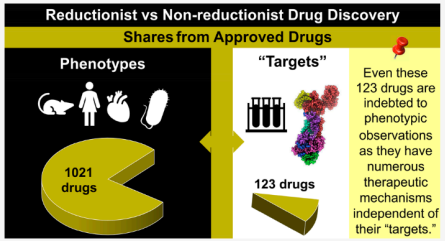
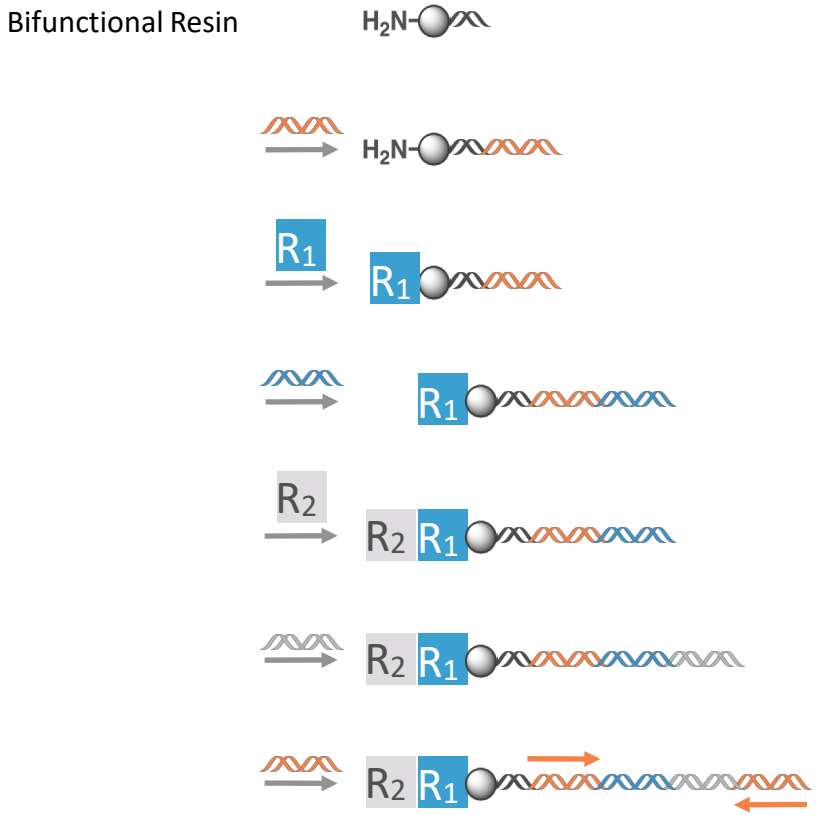
IRVINE on September 24, 2023 at 03:28:08 (UTC).
options on how to legitimately share published articles.

ABSTRACT: Target-based drug discovery is the dominant paradigm of drug discovery; however, a comprehensive evaluation of its real-world efficiency is lacking. Here, a manual systematic review of about 32000 articles and patents dating back to 150 years ago demonstrates its apparent inefficiency. Analyzing the origins of all approved drugs reveals that, despite several decades of dominance, only 9.4% of small-molecule drugs have been discovered through "target-based" assays. Moreover, the therapeutic effects of even this minimal share cannot be solely attributed and reduced to their purported targets, as they depend on numerous off-target mechanisms unconsciously incorporated by phenotypic observations. The data suggest that reductionist target-based drug discovery may be a cause of the productivity crisis in drug discovery. An evidence-based approach to enhance efficiency seems to be prioritizing, in selecting and optimizing molecules, higher-level phenotypic observations that are closer to the sought-after therapeutic effects using tools like artificial intelligence and machine learning.

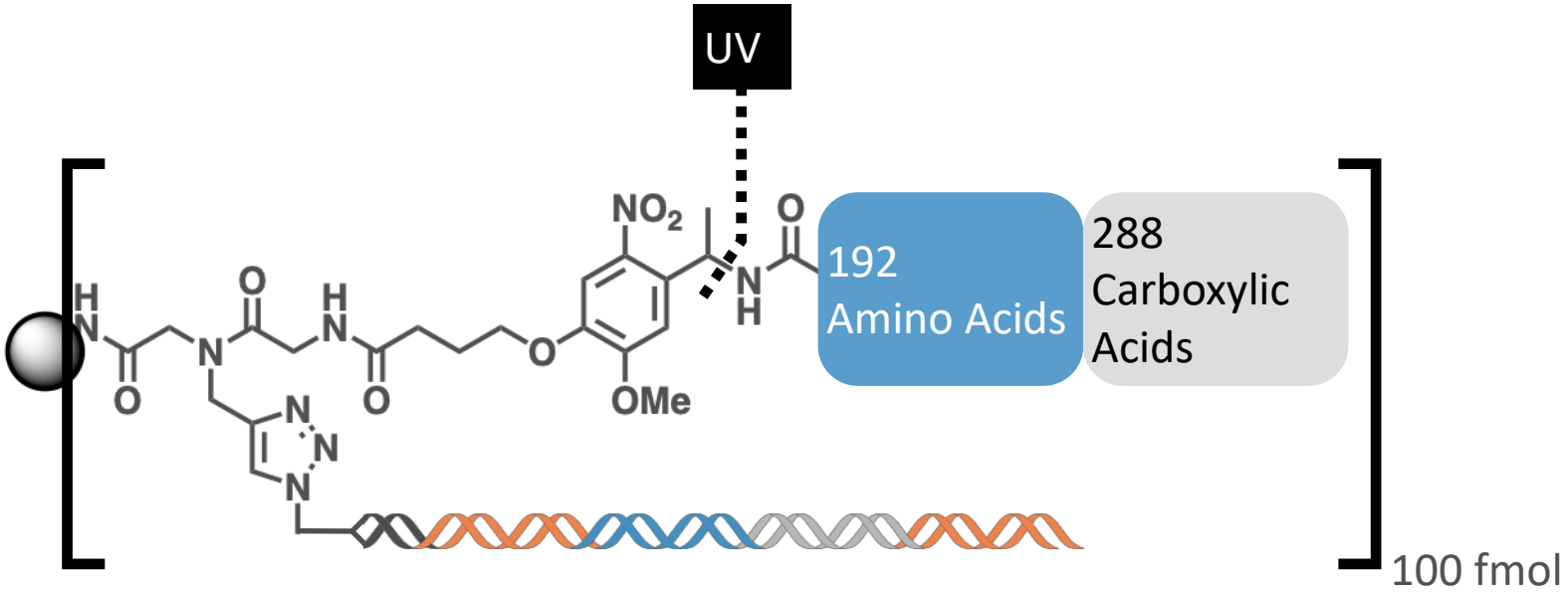


Sadri, J. Med. Chem. (2023)

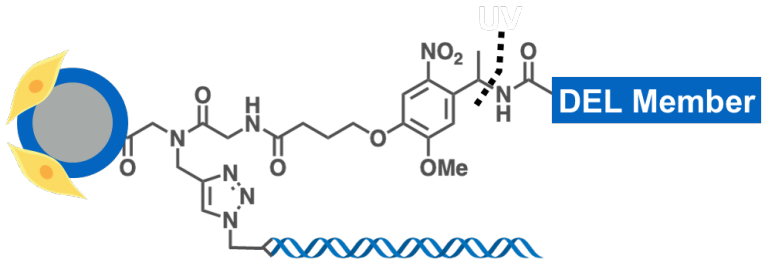
Solid-Phase DNA-Encoded Synthesis



MacConnell et al., ACS Comb Sci. (2015)



Cochrane et al., ACS Comb Sci. (2019)
Fitzgerald et al., ACS Med Chem Lett. (2023)


UV
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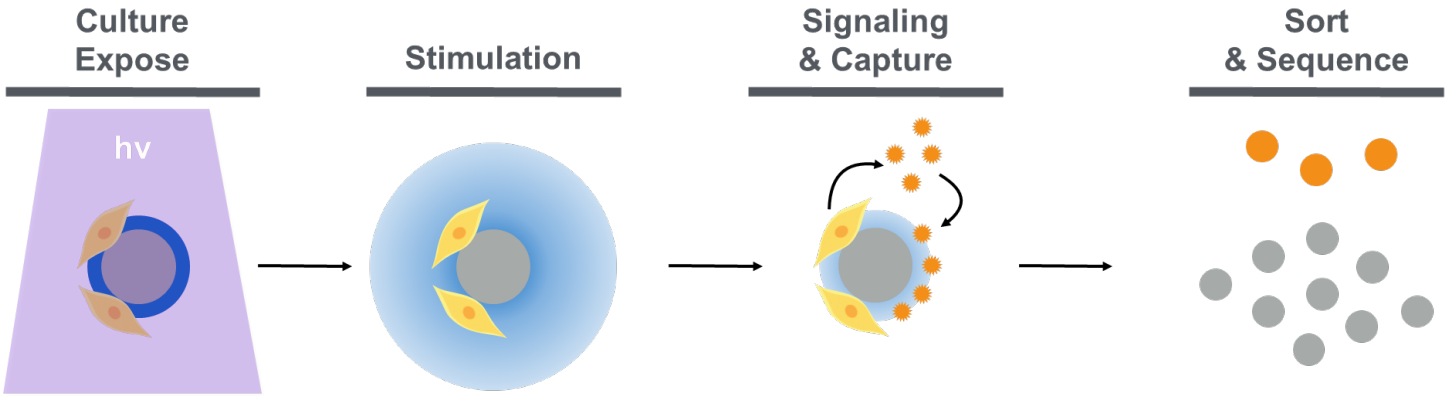
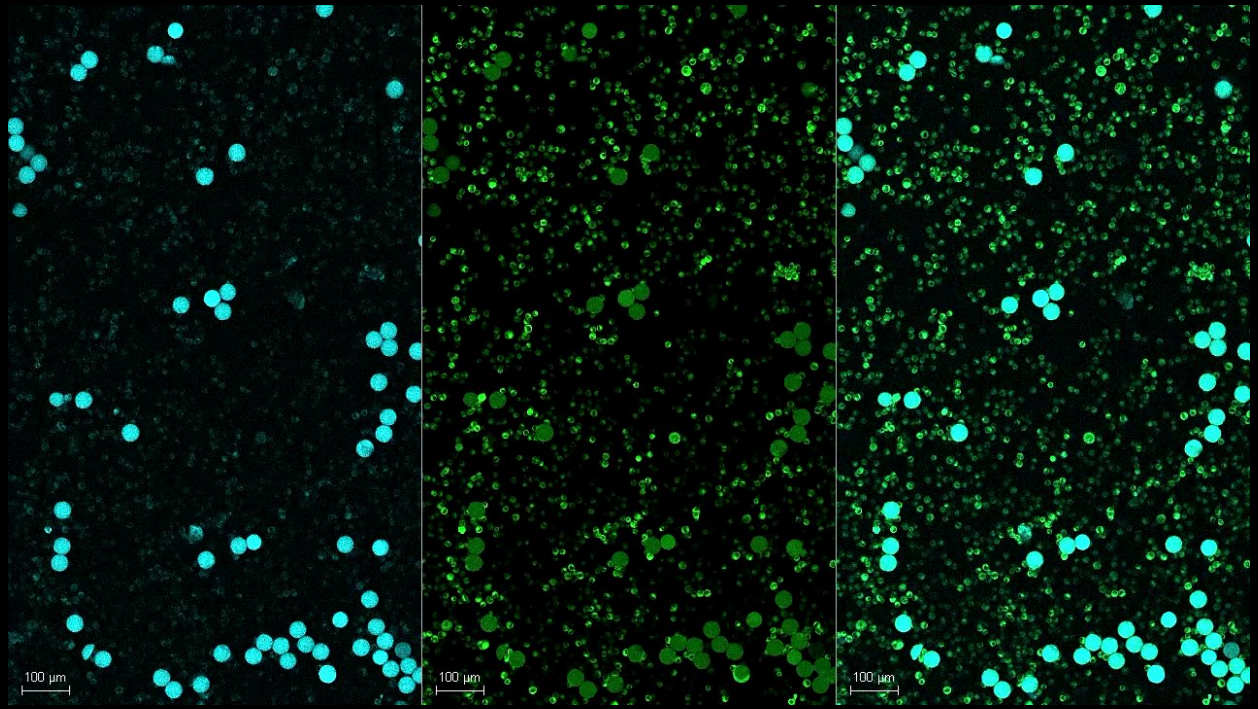
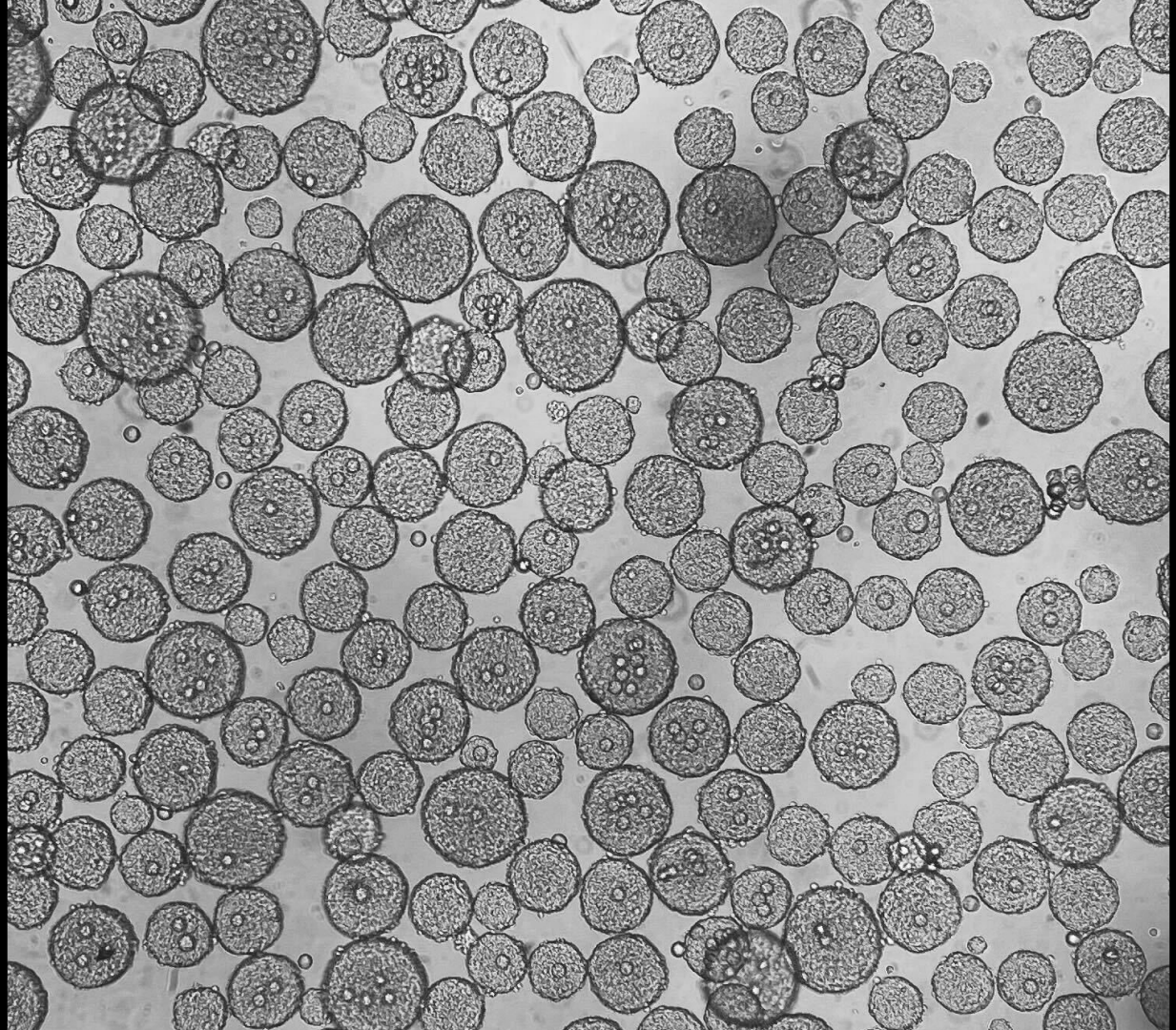

Culture
Expose
Stimulation
Signaling
& Capture
Sort
& Sequence
hv

HEK293T Bead Seeding Occurs Rapidly

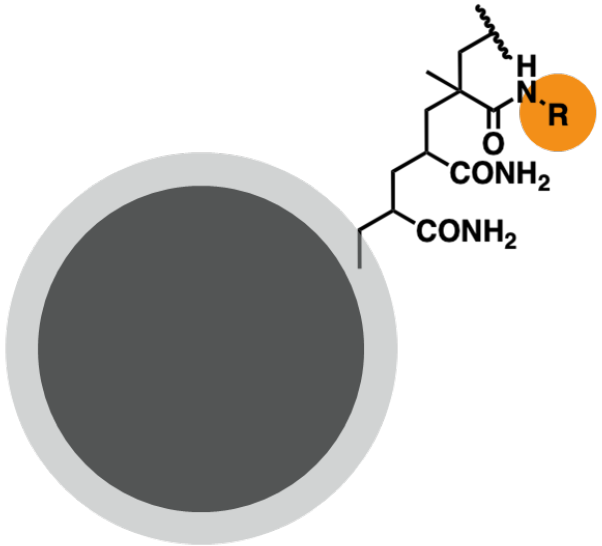


- Seeding over 17 h, 20 min / frame
- DEL beads in cyan (left), cells in green (cente), merged (right)

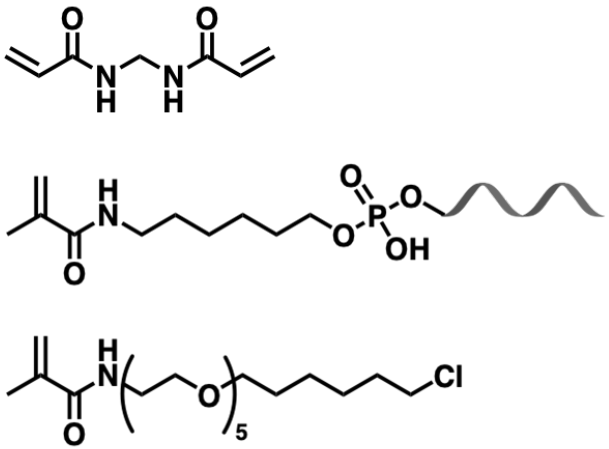
Callie Fredlender (unpublished)



Hydrogel Coat is a Multifunctional Signal Detection Scaffold



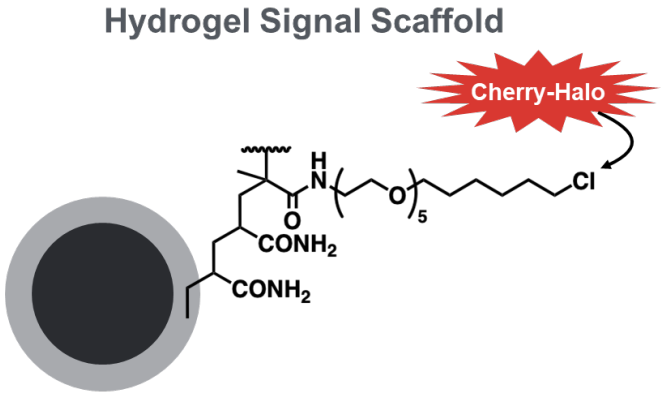
Hydrogel Shell
Signaling Scaffold

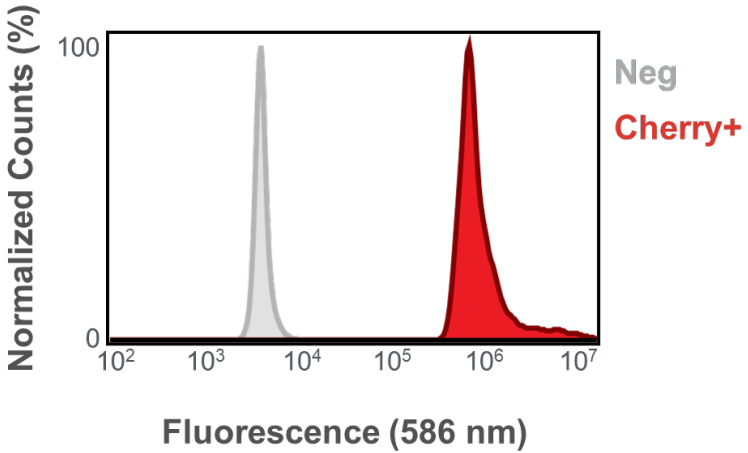


PLL, FN, other ECM

Fryer et al., ACS Cent Sci. (2022)
Cavett et al., ACS Cent Sci. (2023)

Co-polymerized Affinity Tag Ligands Capture Tagged Proteins

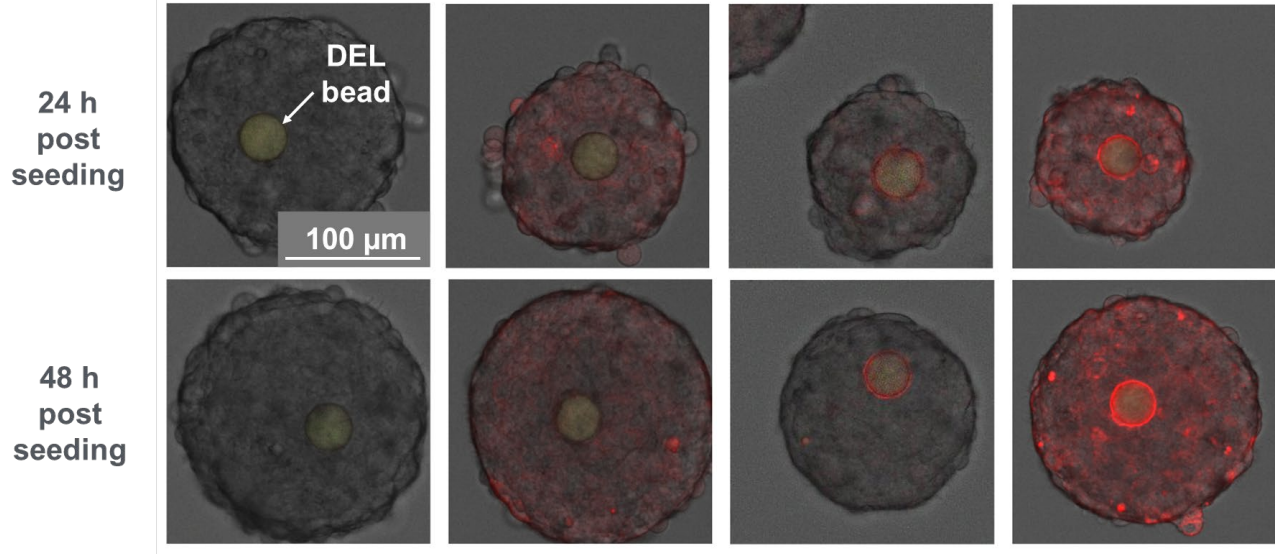




Callie Fredlender (unpublished)

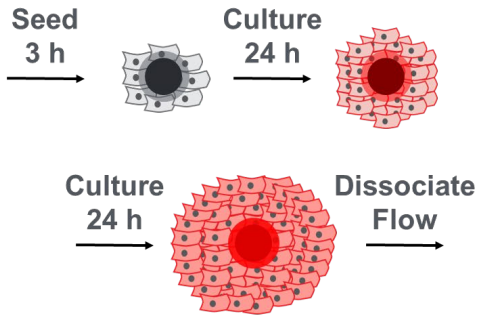
Fluorescent Protein Capture from HEK293T Spheroids (Constitutive Reporters)

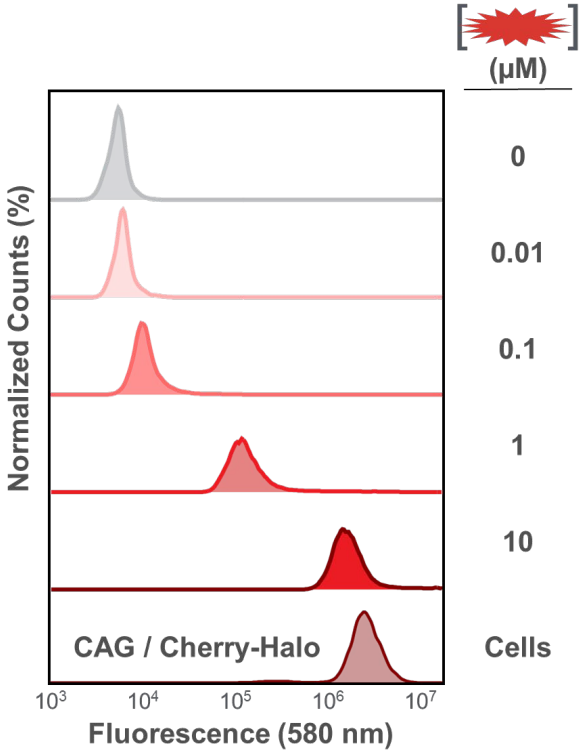
Reporter	—	mCherry-Halo	mCherry-Halo	mCherry-Halo
Secretion Tag	—	—	+	+
Promoter	—	PGK (low)	PGK (low)	CAG (high)



Callie Fredlender (unpublished)

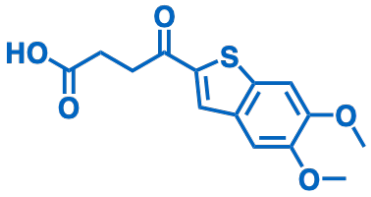
Constitutive Reporter Labels DEL Beads @ ~10 µM Equivalent Labeling Rxn



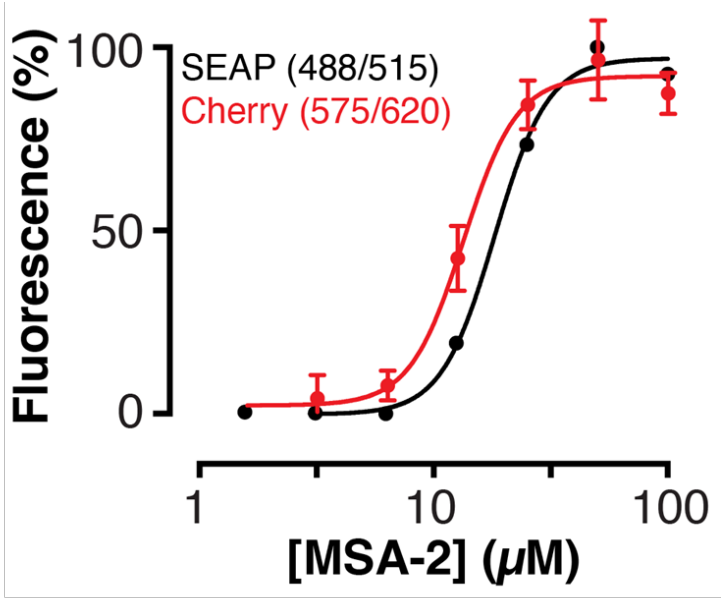


Callie Fredlender (unpublished)

Cherry-HaloTag STING Reporter Line Responds Similarly to Commercial Line

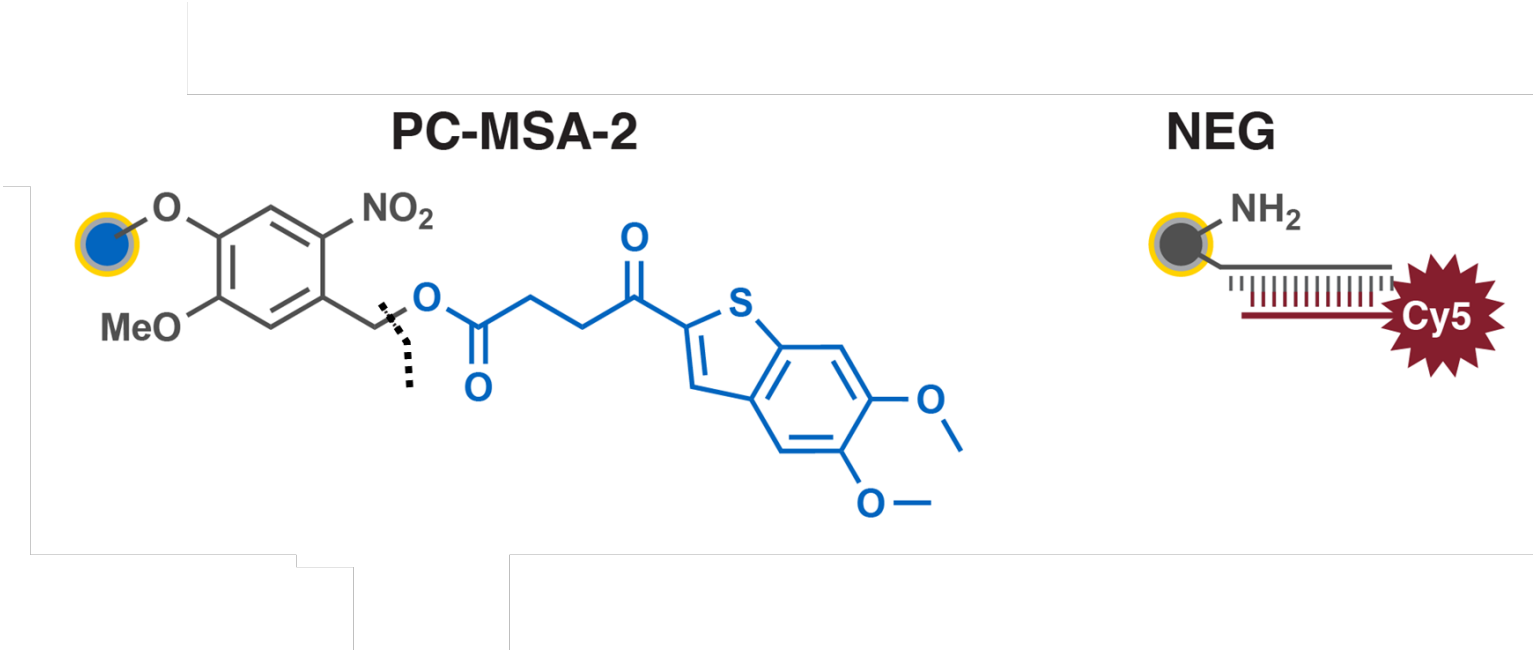


MSA-2



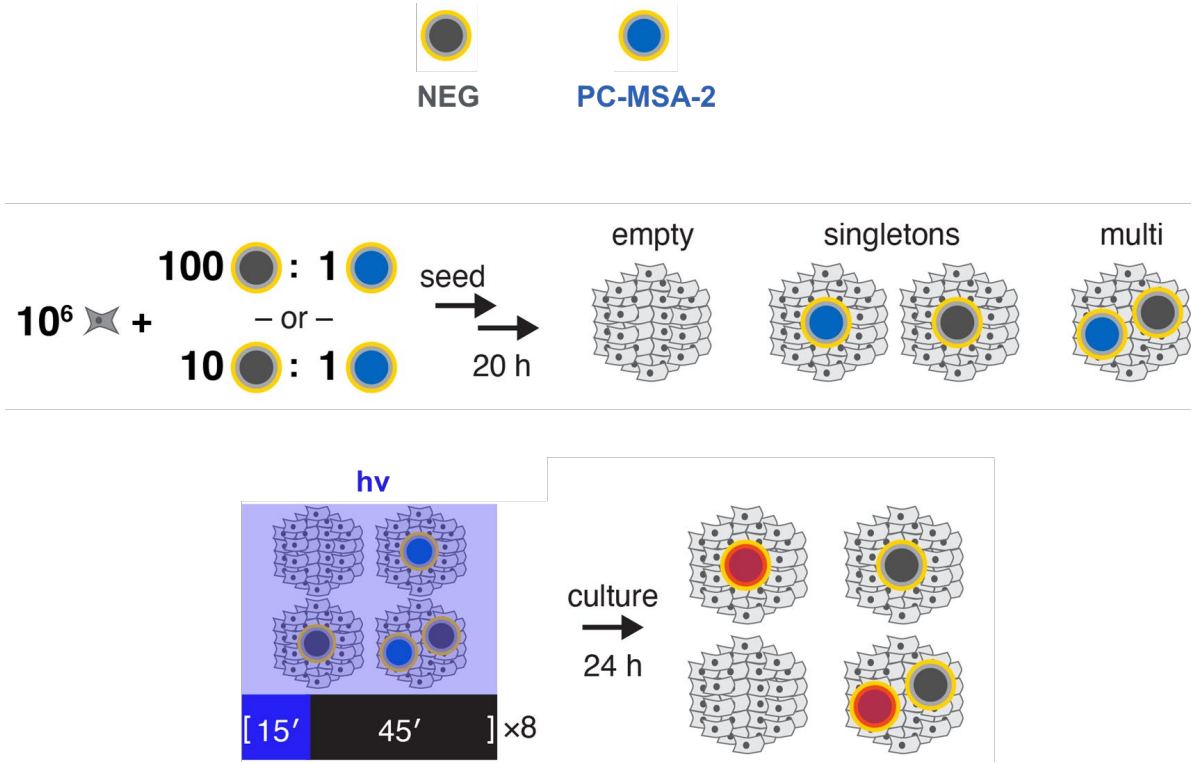
Pan et al. Science (2020)
Callie Fredlender (unpublished)

Control Bead Structure

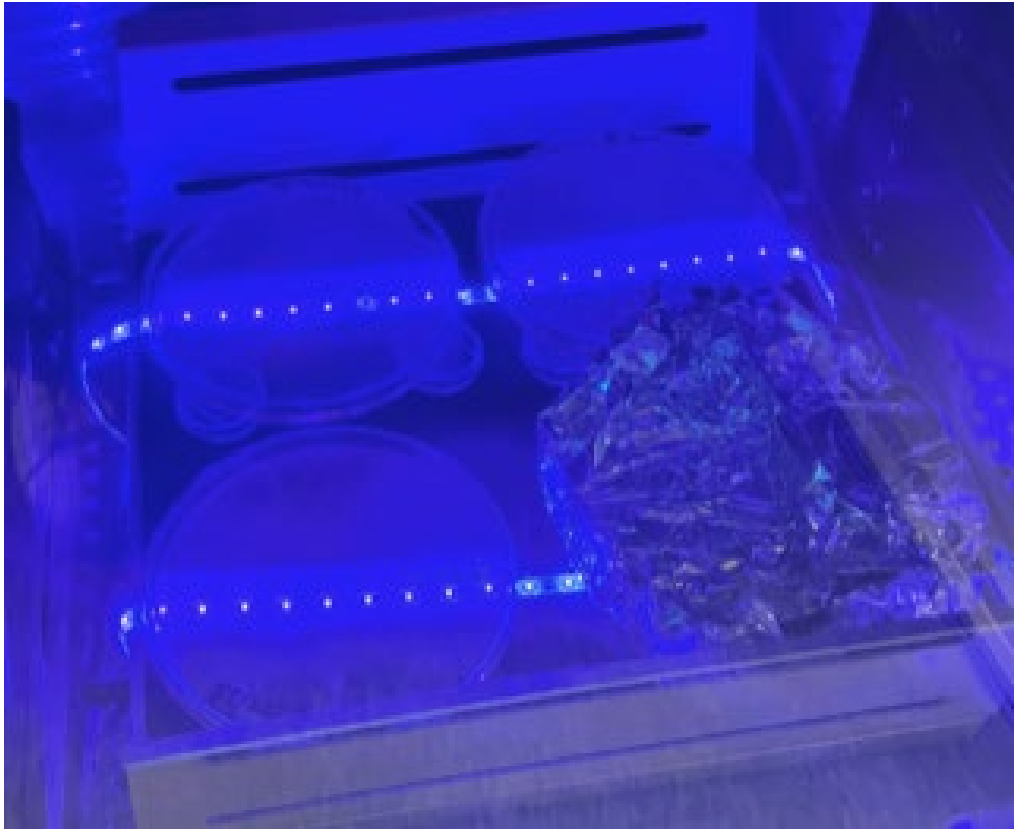


Pan et al. Science (2020)

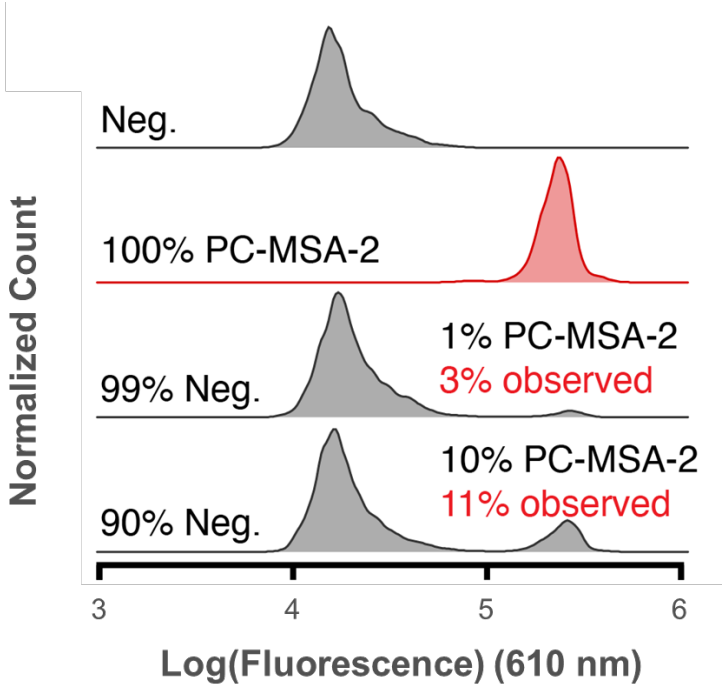
Control PC-MSA-2 Beads Used to Generate Mock Libraries (1 & 10% Hit Rates)



Party Light Photocleavage of Spheroid DEL Culture



Robust Separation Observed in Flow Cytometry of PC-MSA-2 Beads

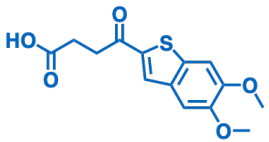


Callie Fredlender (unpublished)

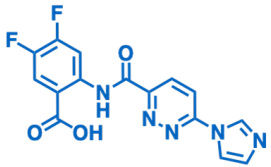
Mini-DEL Explores Structural Themes of Known STING Agonists

48 Amino Acids	72 Carboxylic Acids

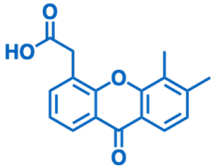
Diversity = 3,456 Compounds



MSA-2



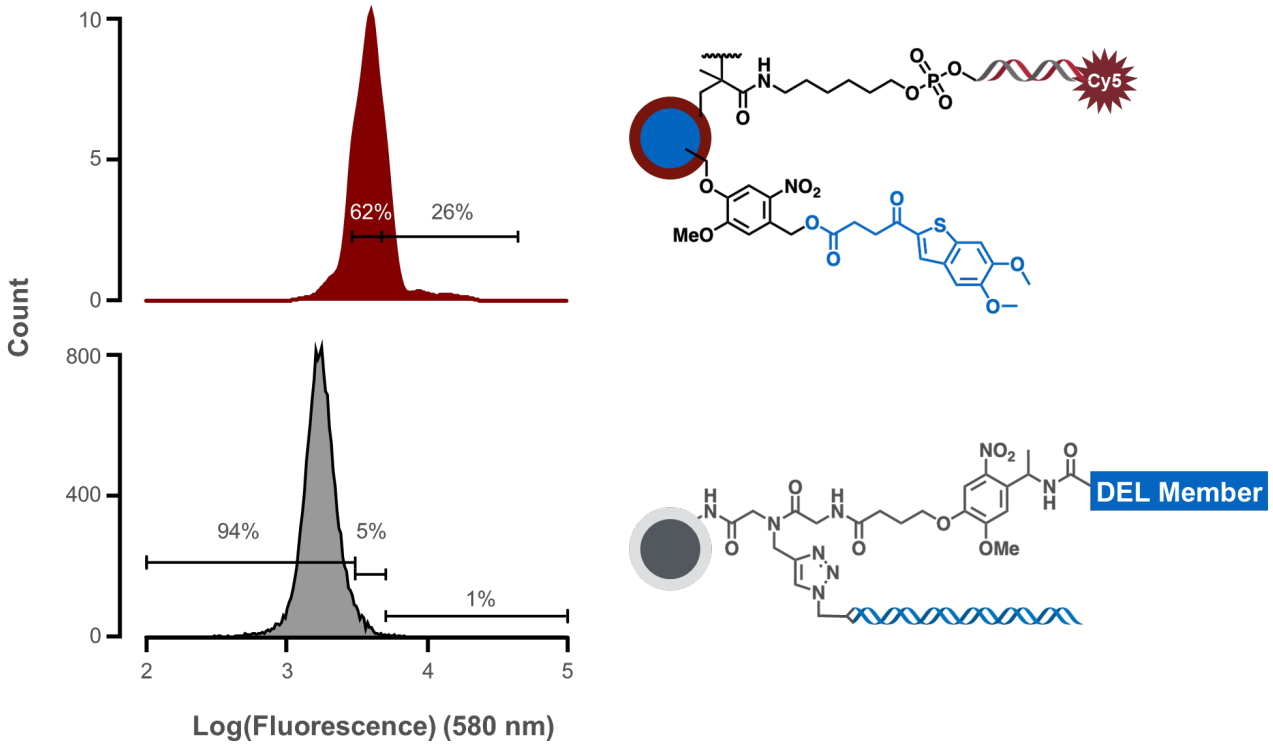
SR-717



DMXAA

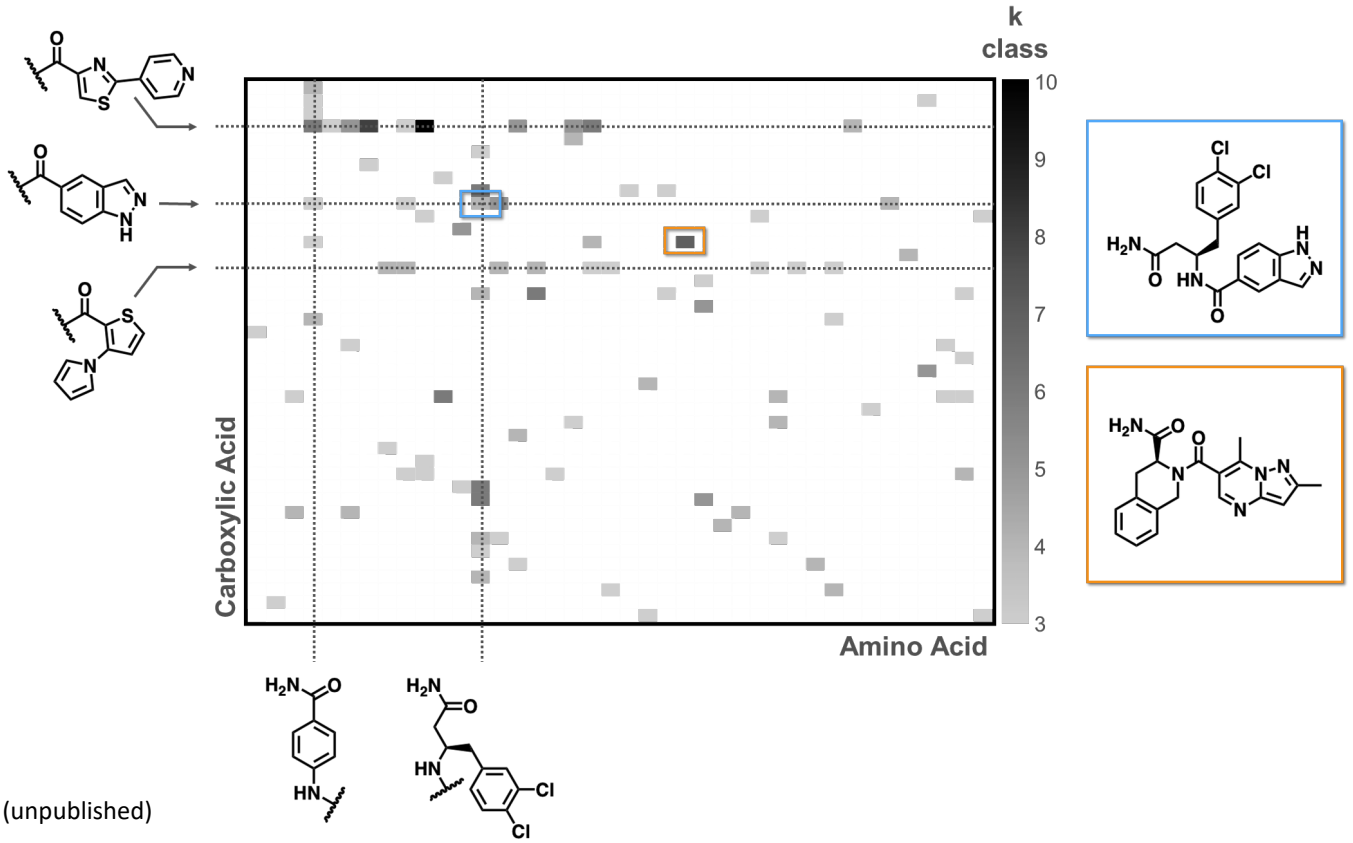
Pan et al. Science (2020)
Chin et al. Science (2020)

Cellular DEL Screens Isolate High Cherry Fluorescence Beads as Hits



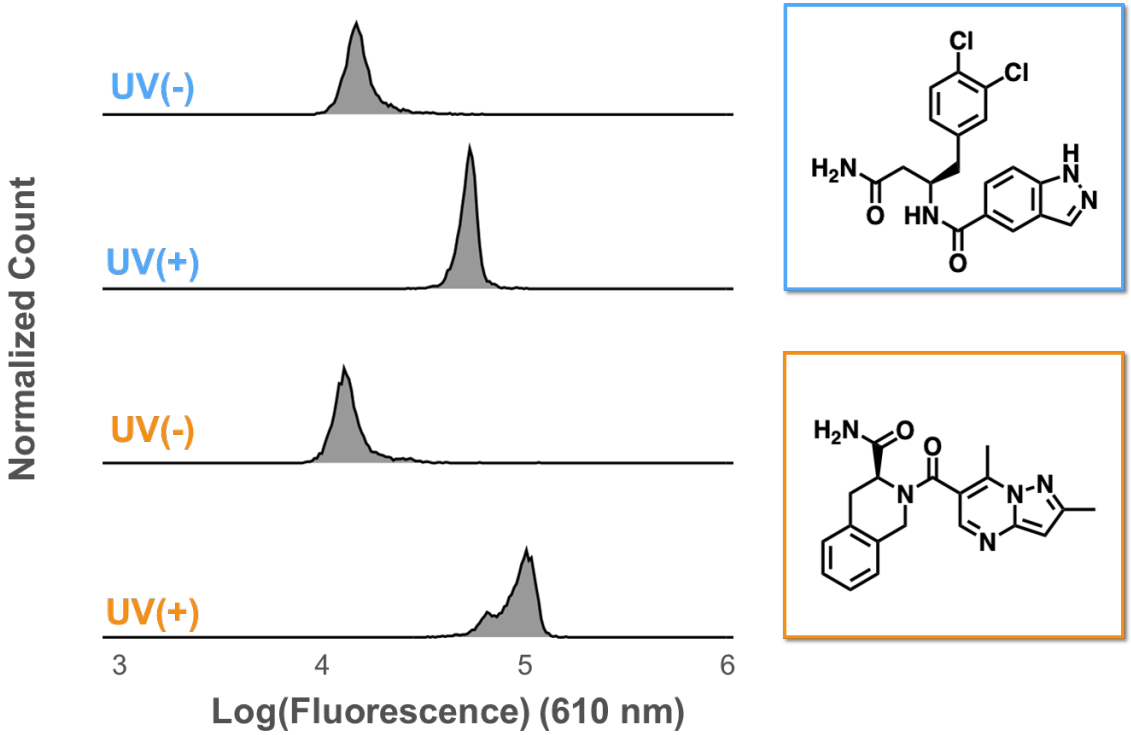
Callie Fredlender (unpublished)

Cellular DEL Screening: Hit Structure Deconvolution



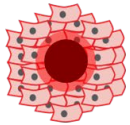
Callie Fredlender (unpublished)

Two Selected Cellular DEL Screening Hits Validate in Spheroid Culture

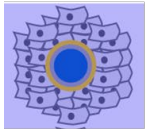


Callie Fredlender (unpublished)

Cells form spheroids around DEL beads



On-bead secreted reporter capture is proximity-driven



Photocleavage liberates sufficient ligand to stimulate signaling

Labeled beads can be sorted and sequenced to find hits

pL Trainees & Staff (UCI)

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Valerie Cavett
Anjali Dixit
Patrick Fitzgerald
Callie Fredlender
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Sherry Huang
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Margot Paulick (Initial)
Jennifer Prescher (UCI)
Alex Satz (WuXi)
Robert Spitale (UCI)

UCI 趙 Chao Family Comprehensive Cancer Center

Thank You

www.cancer.uci.edu

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Madhuri Paul

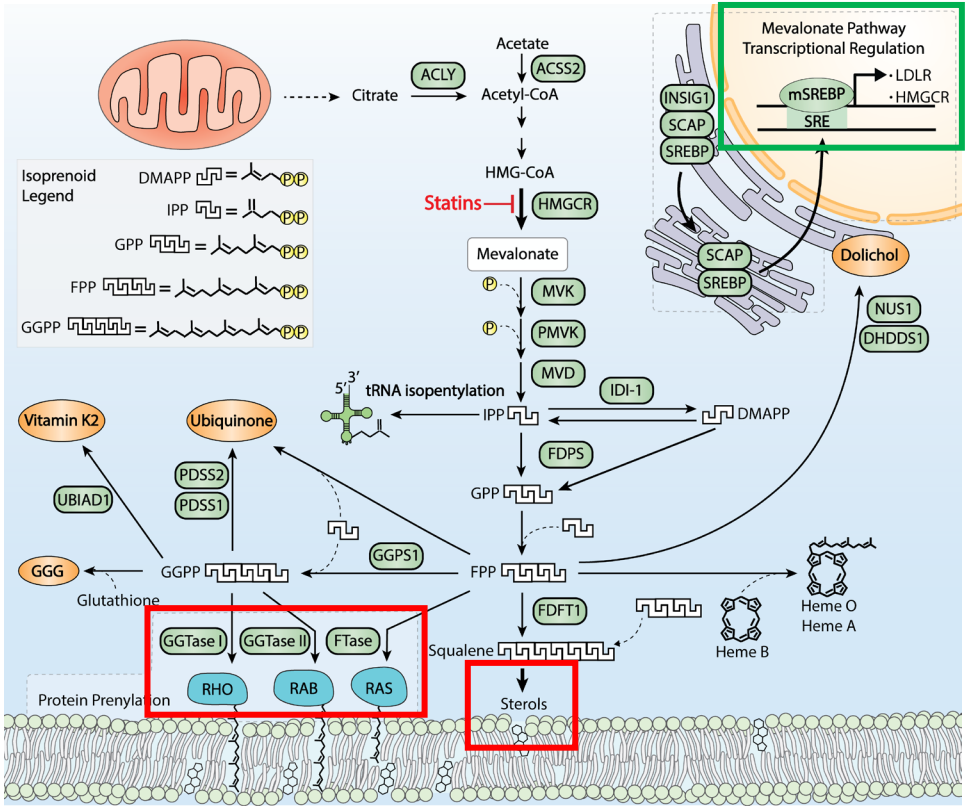

Roberta Buono


Ian Wong

How do statins trigger AML cell death?

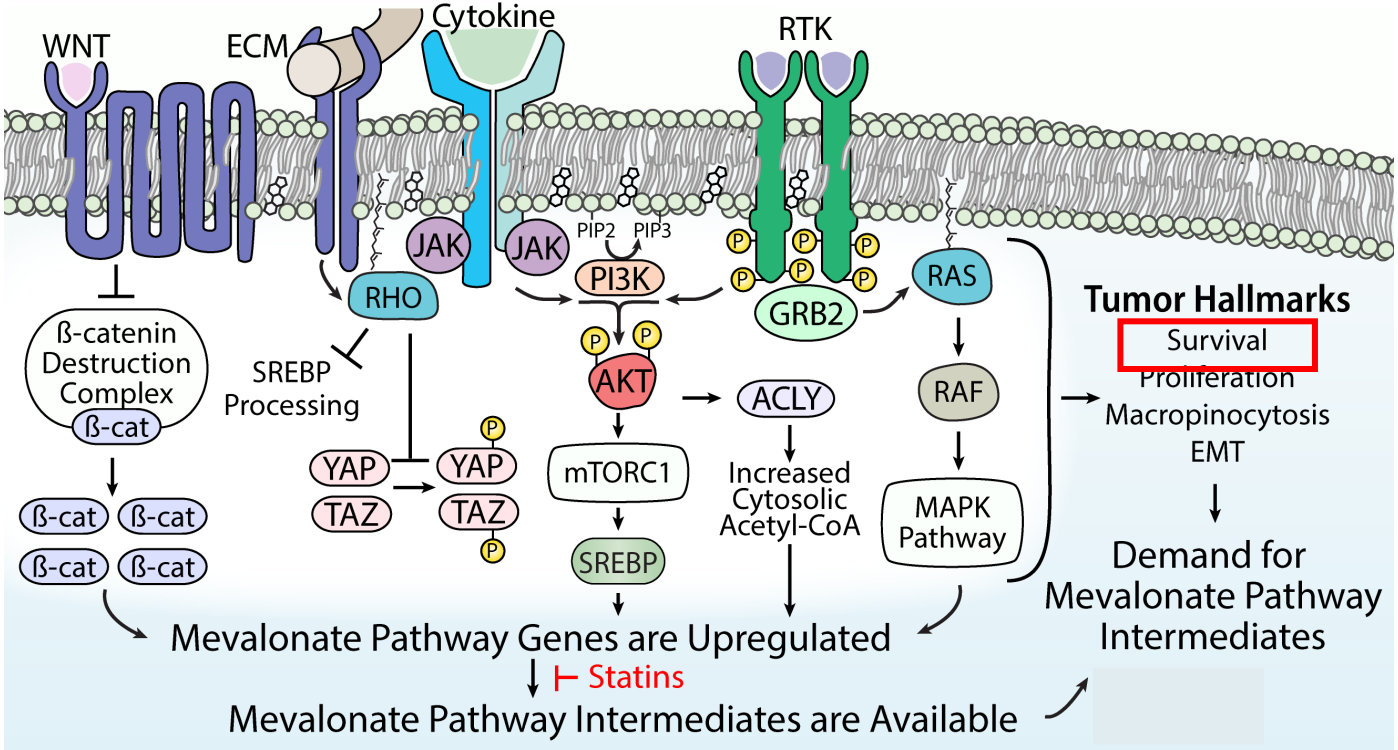
David Fruman, PhD
Professor and Chair, Department of Molecular Biology & Biochemistry
Associate Director for Basic Science, CFCCC

Mevalonate pathway is a targetable cancer dependency



D Juarez and DA Fruman, *Trends in Cancer* 2021

Oncogene pathways increase mevalonate demand and supply



D Juarez and DA Fruman, *Trends in Cancer* 2021

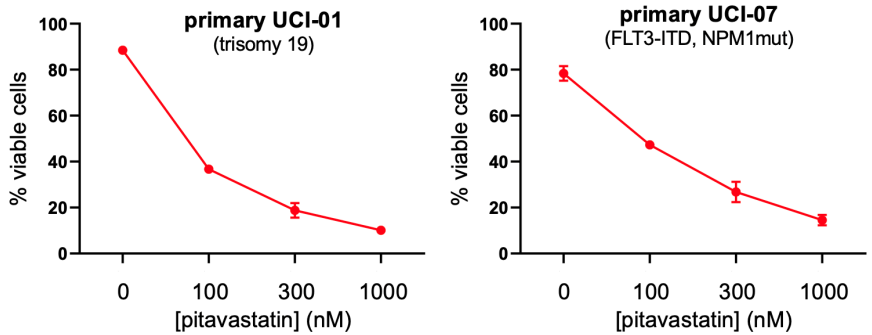
Statins in oncology: untapped potential

- Well-tolerated, cost-effective
- Statins can cause apoptosis in cancer cell lines (esp. blood cancers: AML, myeloma)

› Leukemia. 1994 Feb;8(2):274-80.

Selective inhibition of primary acute myeloid leukaemia cell growth by lovastatin

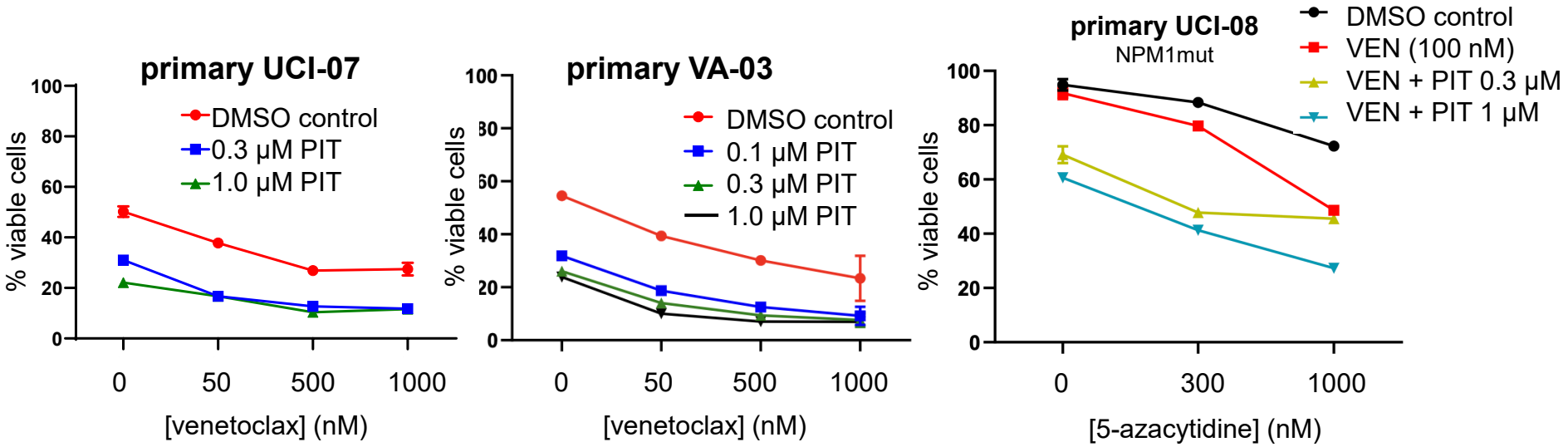
A Newman [1], R D Clutterbuck, R L Powles, J L Millar



Roberta Buono

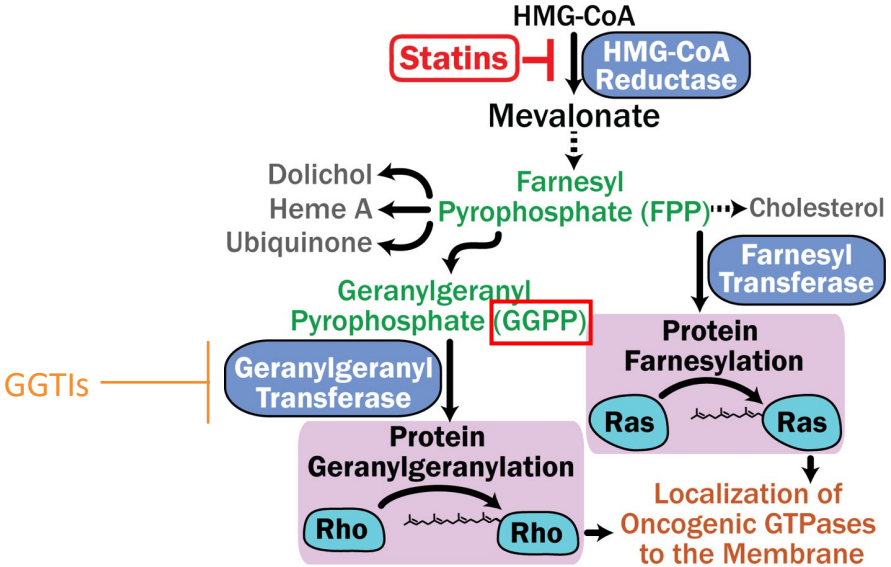
Angela Fleischman (Heme Biobank)

Pitavastatin enhances cytotoxicity of AML standard-of-care agents



What is the mechanism for statin-mediated apoptosis?

Statins suppress prenylation of signaling proteins



Prenylation → growth and survival signaling

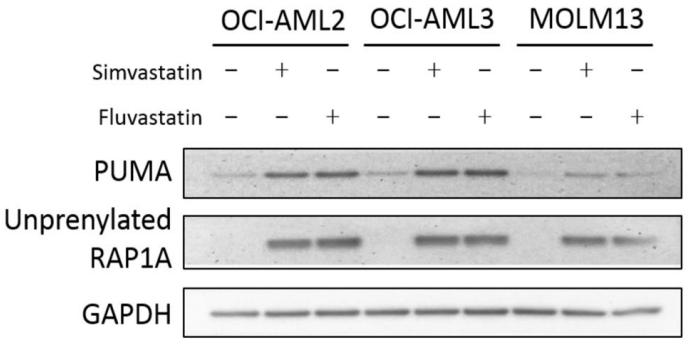
Leukemia (2001) 15, 1398–1407
© 2001 Nature Publishing Group All rights reserved 0887-6924/01 $15.00
www.nature.com/leu

Blocking protein geranylgeranylation is essential for lovastatin-induced apoptosis of human acute myeloid leukemia cells

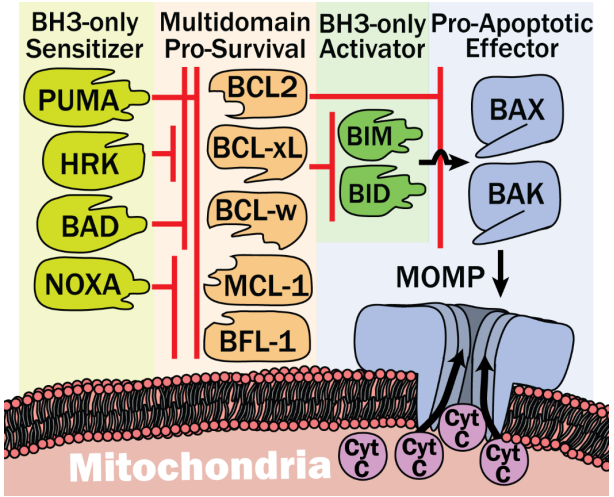
Z Xia[1,3], MM Tan[1], W Wei-Lynn Wong[1,2], J Dimitroulakos[1,4], MD Minden[1,2] and LZ Penn[1,2]

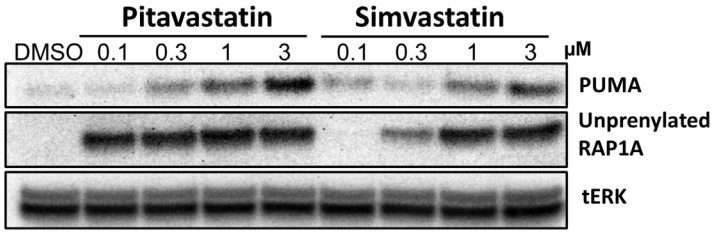
[1]*Department of Cellular and Molecular Biology, Ontario Cancer Institute, University Health Network, Toronto; and* [2]*Department of Medical Biophysics, University of Toronto, Toronto, Canada*

Statins increase PUMA expression in blood cancer cell lines



J. Scott Lee et al., Sci. Transl. Med. 2018; 10(445)

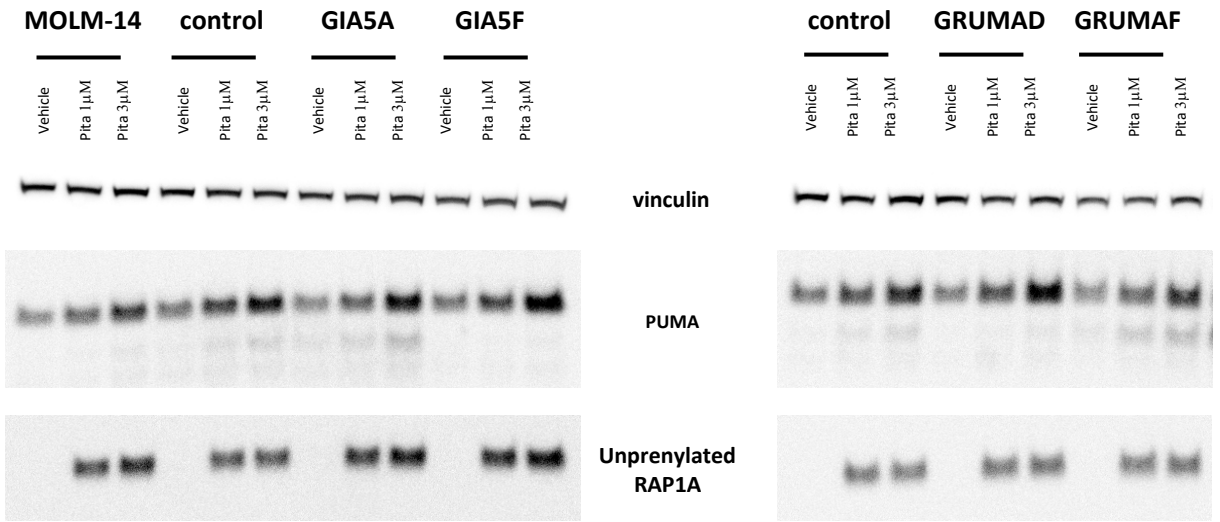




D. Juarez et al., *Cancer Res. Comm.* 2023, 3: 2497

PUMA upregulation is p53-independent

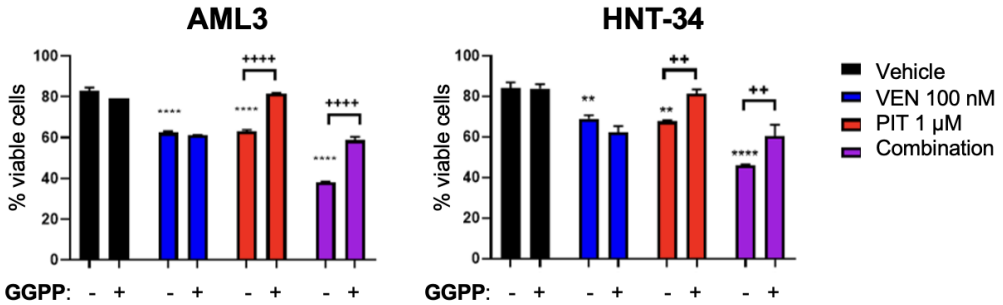
MOLM-14 cell lines and TP53-mutant derivatives

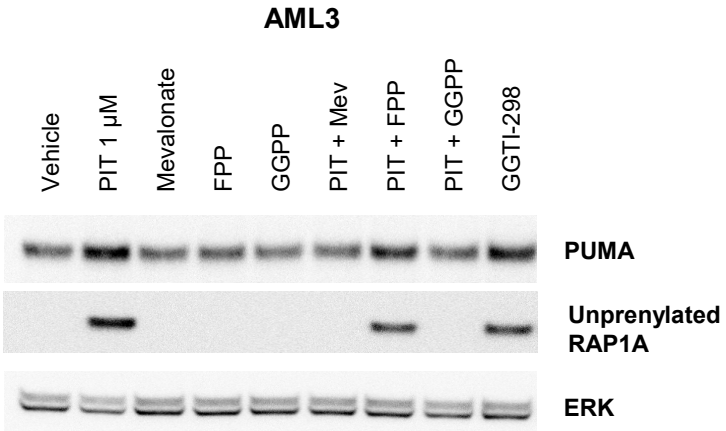


Roberta Buono

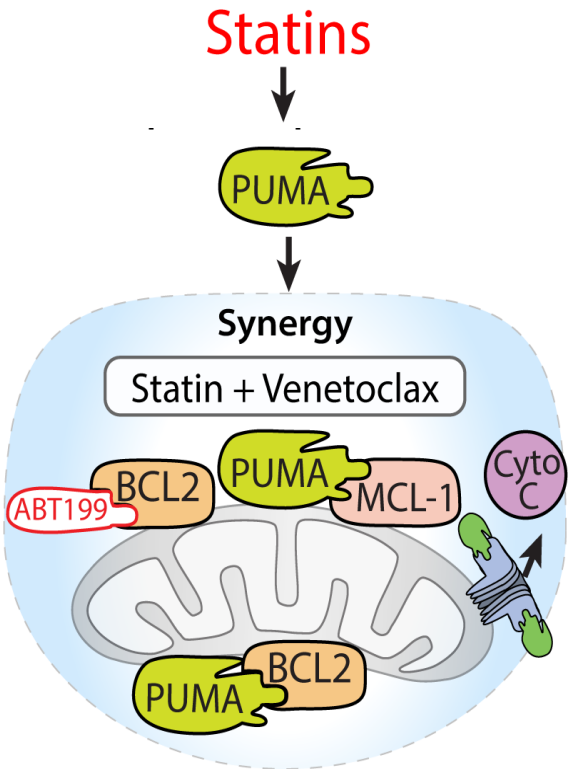
MOLM-14 cells and derivatives
provided by Sarah Skuli and Martin Carroll (U-Penn)

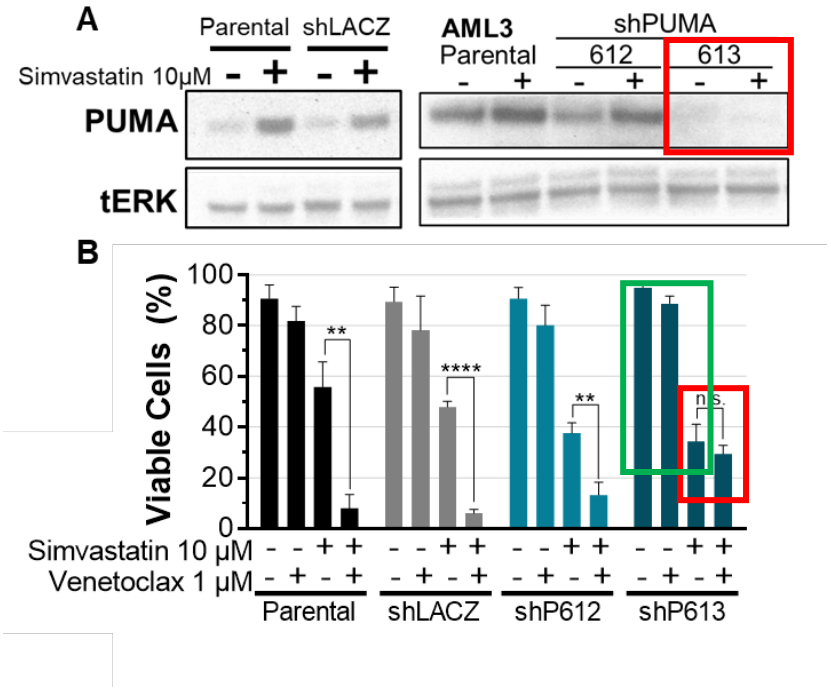
GGPP rescues cytotoxicity and PUMA upregulation





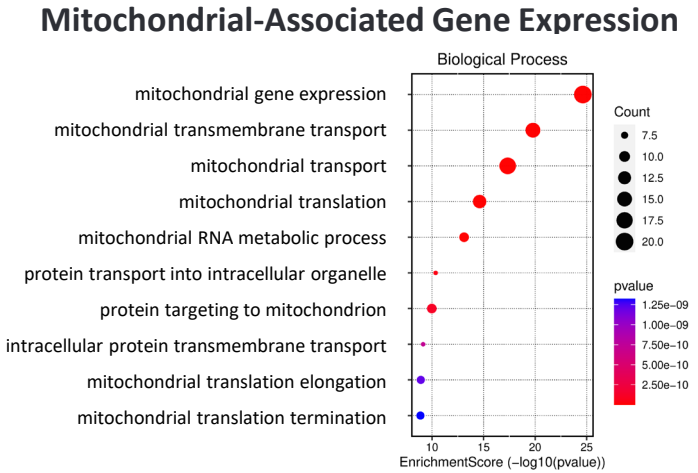
PUMA contributes to cytotoxicity but is not the whole story

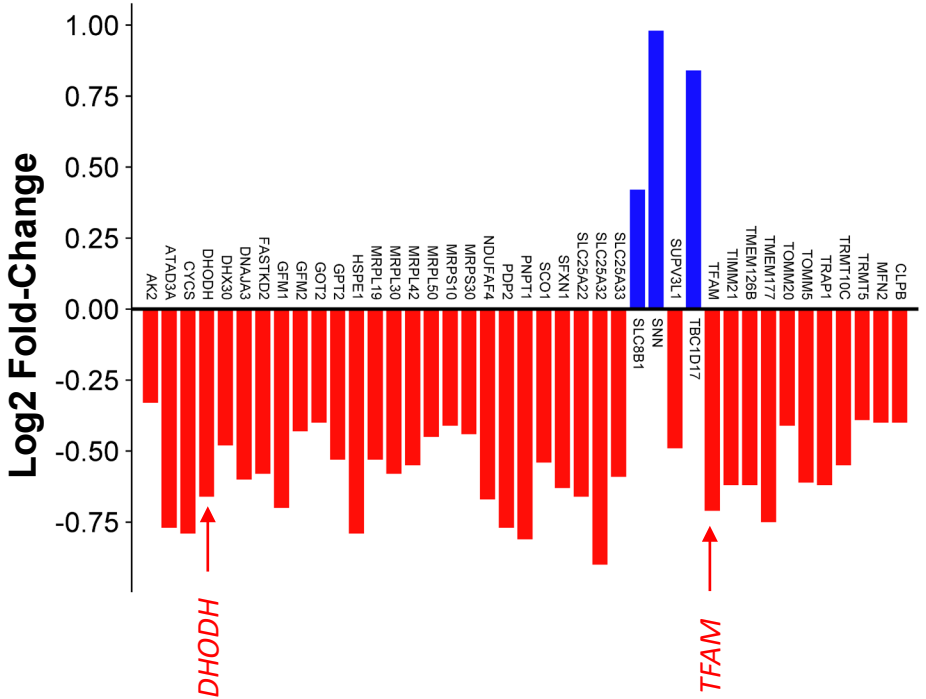




J. Scott Lee et al., Sci. Transl. Med. 2018; 10(445)

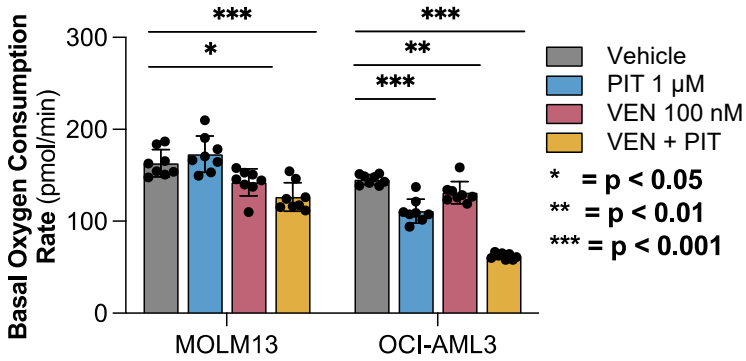
GGPP depletion downregulates mitochondrial gene expression



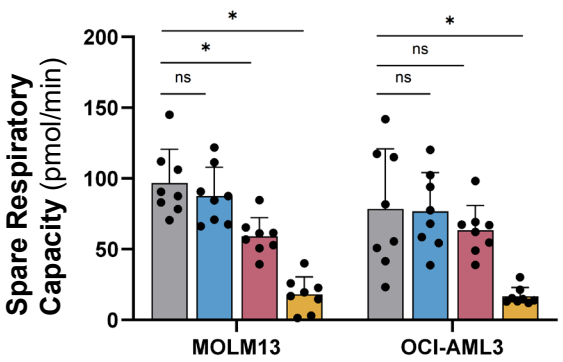


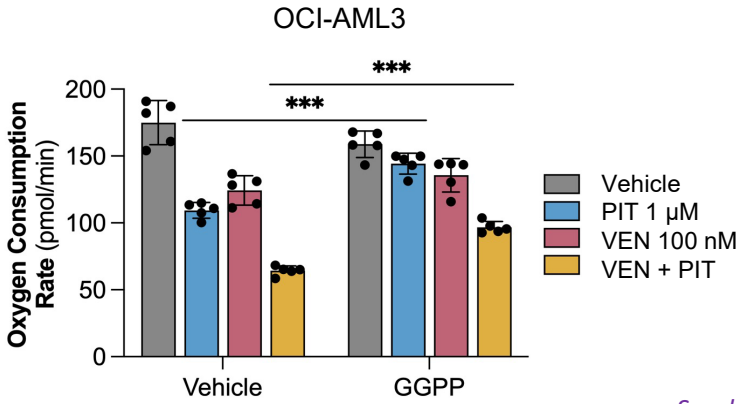
Bulk RNAseq, 16hr treatment
Pitavastatin vs. PIT+GGPP

Pitavastatin and venetoclax suppress mitochondrial metabolism



Seahorse metabolic flux analysis

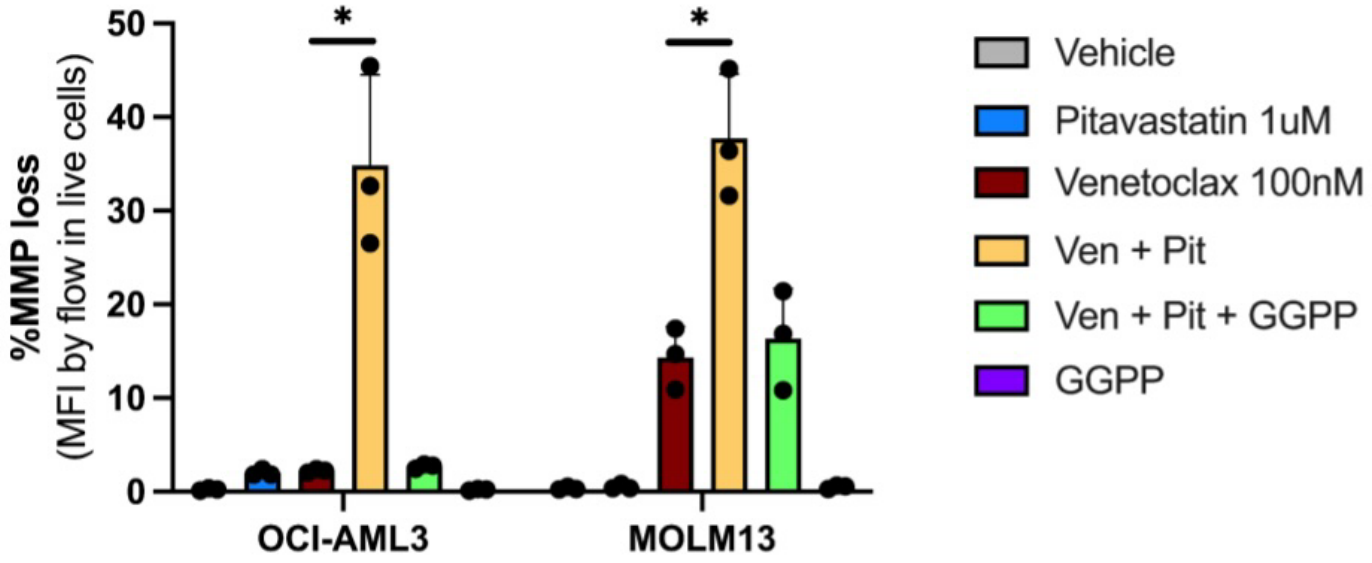




Sarah Skuli
Martin Carroll
U-Penn

Pitavastatin and venetoclax cause loss of membrane potential

16hr treatment: MMP loss measured by TMRE staining

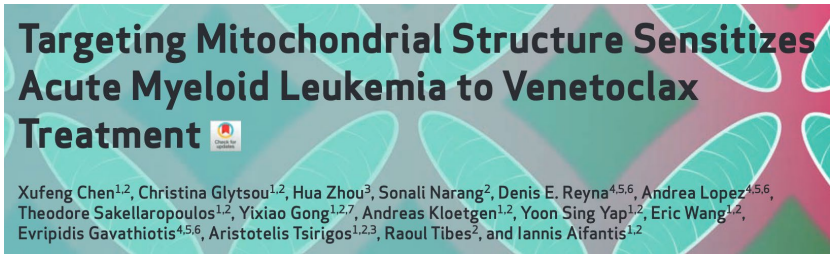


Ian Wong

Mitochondrial Mechanisms of Venetoclax Resistance in AML

Mitochondrial inhibitors circumvent adaptive resistance to venetoclax and cytarabine combination therapy in acute myeloid leukemia

Claudie Bosc[1,2,3], Estelle Saland[1,2,3], Aurélie Bousard[4], Noémie Gadaud[1,2,3,5,6], Marie Sabatier[1,2,3], Guillaume Cognet[1,2,3], Thomas Farge[1,2,3], Emeline Boet[1,2,3], Mathilde Gotanègre[1,2,3], Nesrine Aroua[1,2,3], Pierre-Luc Mouchel[1,2,3,5,6], Nathaniel Polley[1,2,3], Clément Larrue[1,2,3], Eléonore Kaphan[1,2,3], Muriel Picard[7], Ambrine Sahal[1,2,3], Latifa Jarrou[1,2,3], Marie Tosolini[1], Florian Rambow[4], Florence Cabon[1,2,3], Nathalie Nicot[8], Laura Poillet-Perez[1,2,3], Yujue Wang[9], Xiaoyang Su[9], Quentin Fovez[10], Jérôme Kluza[10], Rafael José Argüello[11], Céline Mazzotti[1,12], Hervé Avet-Loiseau[1,12], François Vergez[1,2,3,5,6], Jérôme Tamburini[13], Jean-Jacques Fournié[1,2], Ing S. Tiong[14], Andrew H. Wei[14], Tony Kaoma[15], Jean-Christophe Marine[4], Christian Récher[1,2,3,5,6], Lucille Stuani[1,2,3,16], Carine Joffre[1,2,3,16] and Jean-Emmanuel Sarry[1,2,3] ✉

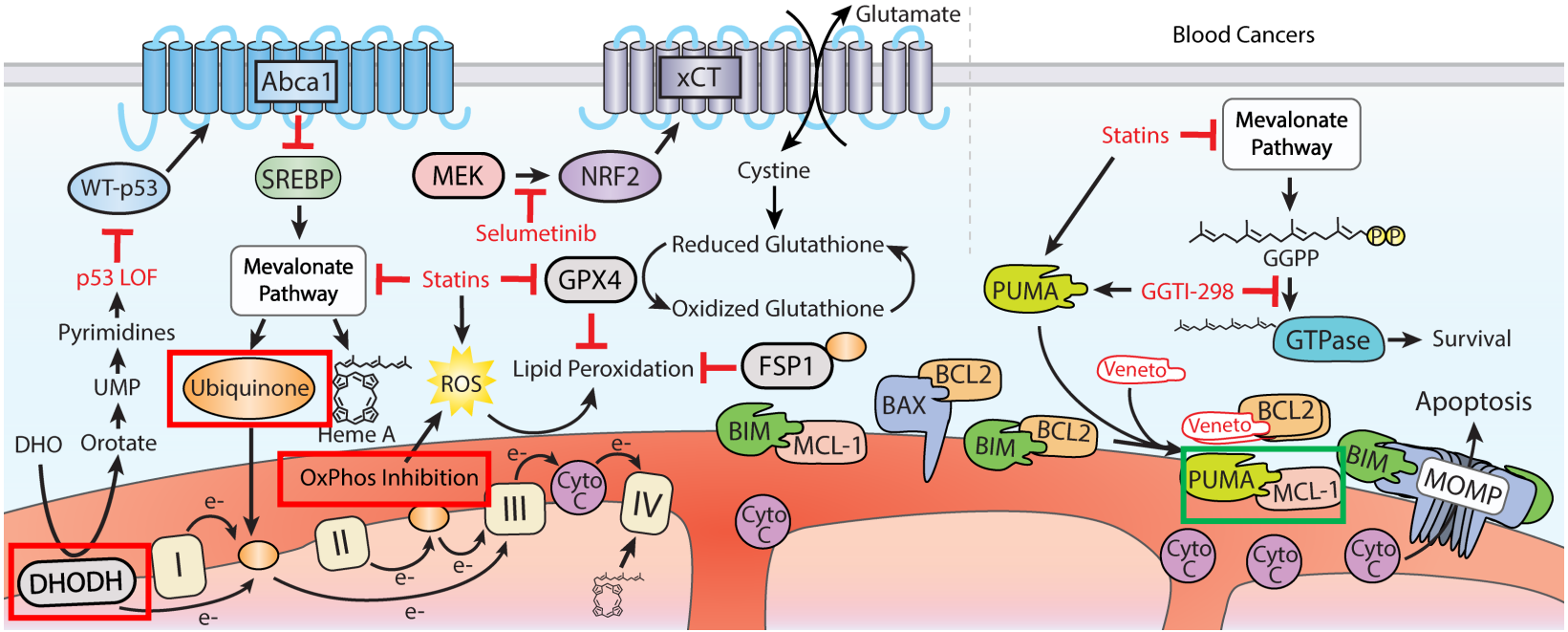


Article

Cotargeting of Mitochondrial Complex I and Bcl-2 Shows Antileukemic Activity against Acute Myeloid Leukemia Cells Reliant on Oxidative Phosphorylation

Fangbing Liu [1], Hasini A. Kalpage [2], Deying Wang [3], Holly Edwards [4,5], Maik Hüttemann [2], Jun Ma [1], Yongwei Su [1,4,5], Jenna Carter [6], Xinyu Li [1], Lisa Polin [4,5], Juiwanna Kushner [4,5], Sijana H. Dzinic [4,5], Kathryn White [4,5], Guan Wang [1,*], Jeffrey W. Taub [7,8] and Yubin Ge [4,5,6,*]

Working Model: statins disrupt mitochondrial physiology



D Juarez and DA Fruman, *Trends in Cancer* 2021

Next questions

- Can statin cytotoxicity be rescued by restoring mitochondrial function? (Ubiquinone, αketo-butyrate, aspartate)
- Metabolomics, mito structure, mito mass
- Which GTPases are critical for maintaining mitochondrial health and suppressing PUMA?
  - CRISPR screen for small GTPases, GEFs, GAPs

Next questions

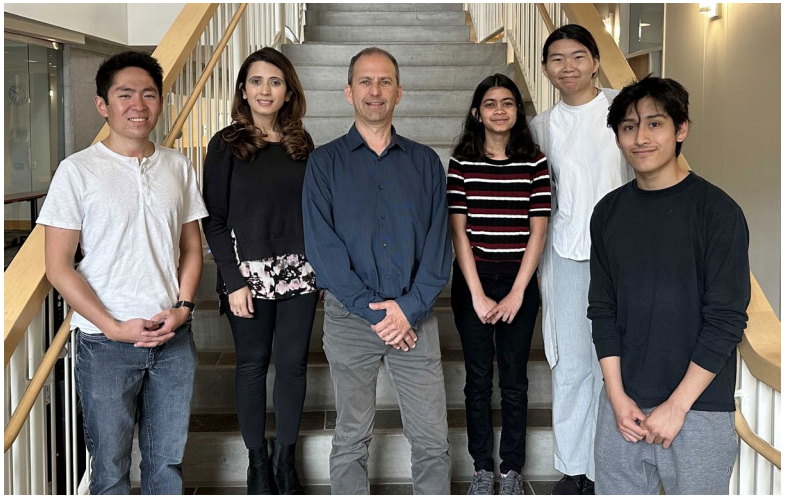
- Can statin cytotoxicity be rescued by restoring mitochondrial function? (Ubiquinone, αketo-butyrate, aspartate)
- Metabolomics, mito structure, mito mass
- Which GTPases are critical for maintaining mitochondrial health and suppressing PUMA?
  - CRISPR screen for small GTPases, GEFs, GAPs
- Does addition of pitavastatin to VEN regimens prolong survival in *TP53*-mutant AML? Phase 2 in planning stage…

Dr. Elizabeth Brèm

Acknowledgements

Fruman Lab

Roberta Buono, PhD
Madhuri Paul
Ian Wong
Scott Lee, PhD
Dennis Juarez, MD-PhD
Many Bio 199 students



Collaborators

Andy Roberts
Orlando Bueno
Joel Leverson, **AbbVie**

Sarah Skuli
Martin Carroll, **UPENN**

LEUKEMIA & LYMPHOMA SOCIETY®

CDMRP Department of Defense PRCRP Peer Reviewed Cancer Research Program

American Cancer Society®

UCI Collaborators

Elizabeth Brèm
Susan O'Brien
Angela Fleischman

Cholsoon Jang

UCI 趙 Chao Family Comprehensive Cancer Center

Thank You

UCI 趙 Chao Family Comprehensive Cancer Center

Adding pitavastatin to venetoclax-based therapies for leukemias:
An experience in drug re-purposing

Elizabeth Brem, MD
Associate Clinical Professor

Heme Malignancies: Major Concepts

- Aggressive = chance of cure
  - Indolent = incurable (but manageable!)

- Staging is different than solid tumors
  - Prognosis is typically driven by cytogenetics
    - -17p (p53 deletion) = bad

How to Categorize Lymphomas/Leukemias

- Myeloid vs lymphoid
  - Lymphoid: B vs T
- Indolent (slow growing) vs aggressive (fast growing)

- Mostly in blood (high white blood cell count) = leukemia
- Mostly in lymph nodes (or other places you might find white blood cells): lymphoma

A phase 1 study of adding PIT to VEN-based therapies in AML and CLL/SLL

Eligibility Criteria

- Patients with diagnosed AML otherwise eligible for induction therapy with azacitidine (AZA) and venetoclax (VEN) per SOC
- Patients with CLL/SLL could receive VEN with either obinatuzumab or rituximab
- Patients already on a statin were eligible if their other statin was stopped for 72 hours before starting PIT
- For DL1 (2mg) — CrCl > 30ml/min
  - For DL2 (4mg) cohort — CrCl > 60ml/min

Study Design

- Phase 1
- Single center
- 3+3 design
- 2 dose levels: 2mg, 4mg
  - DL -1 if needed: 1mg
  - Planned sample size 6-12
- Primary endpoint: safety, RP2D

Patient Enrollment

- 14 patients signed informed consent
  - 6 were ineligible
  - 2 withdrew consent before starting PIT
- 6 patients were treated
  - 2 had AML
  - 2 CLL, 2 SLL — all 4 received ven + obinatuzumab
- 1 subject was on rosuvastatin prior to enrollment
  - The other 5 were statin-naive

All pts achieved CR!

Clinical characteristics and outcomes of treated patients

Treated patient	PIT dose	Disease with relevant mutations	Best response	Outcome	Grade 3-5 adverse events•
1	2 mg	AML (+9; ASXL1, TET2, ETV6; progression from MDS)	CR	Achieved CR after 1 cycle but was MRD-positive on flow cytometry. Passed away shortly thereafter due to infection.	Leukopenia (grade 3), neutropenia (4), thrombocytopenia (4), lung infection (5)
2	2 mg	CLL (11q-, 13q-, unmutated IgVH)	CR	Treatment discontinued early due to neutropenia but was MRD-negative by clonoSEQ negative at the end of therapy. Had a history of cirrhosis and passed away during admission for acute encephalopathy; CLL was in remission when passed.†	Neutropenia (grade 4), pancreatitis (3)
3	2 mg	SLL (11q-; IgVH unknown)	CR	Was in remission at the last follow-up.†	
4	4 mg	AML (del 20q, +8; progression from MDS)	CR	Treatment discontinued due to recurrent pericardial effusion, unclear if related. Resumed AZA for treatment of MDS, but AML remained in remission at the last follow-up.	Febrile neutropenia (grade 3), vasovagal reaction (3)
5	4 mg	CLL (IgVH-negative, FISH unable to be done)	CR	Clinically remains in remission. MRD positive by peripheral blood flow (0.01%).†	Leukopenia (grade 3), neutropenia (4), thrombocytopenia (4), anemia (3)
6	4 mg	SLL (trisomy 12; IgVH status unknown)	CR	In CR based on CT scans. MRD-negative by peripheral blood flow.	

Brem et al, Blood Neoplasia, 2024

In Vivo response to VEN and PIT via flow

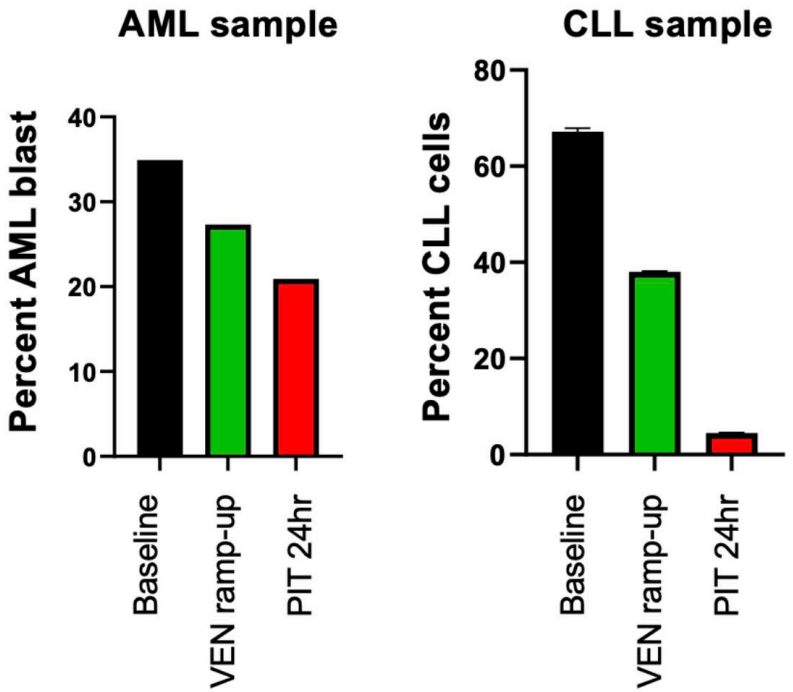


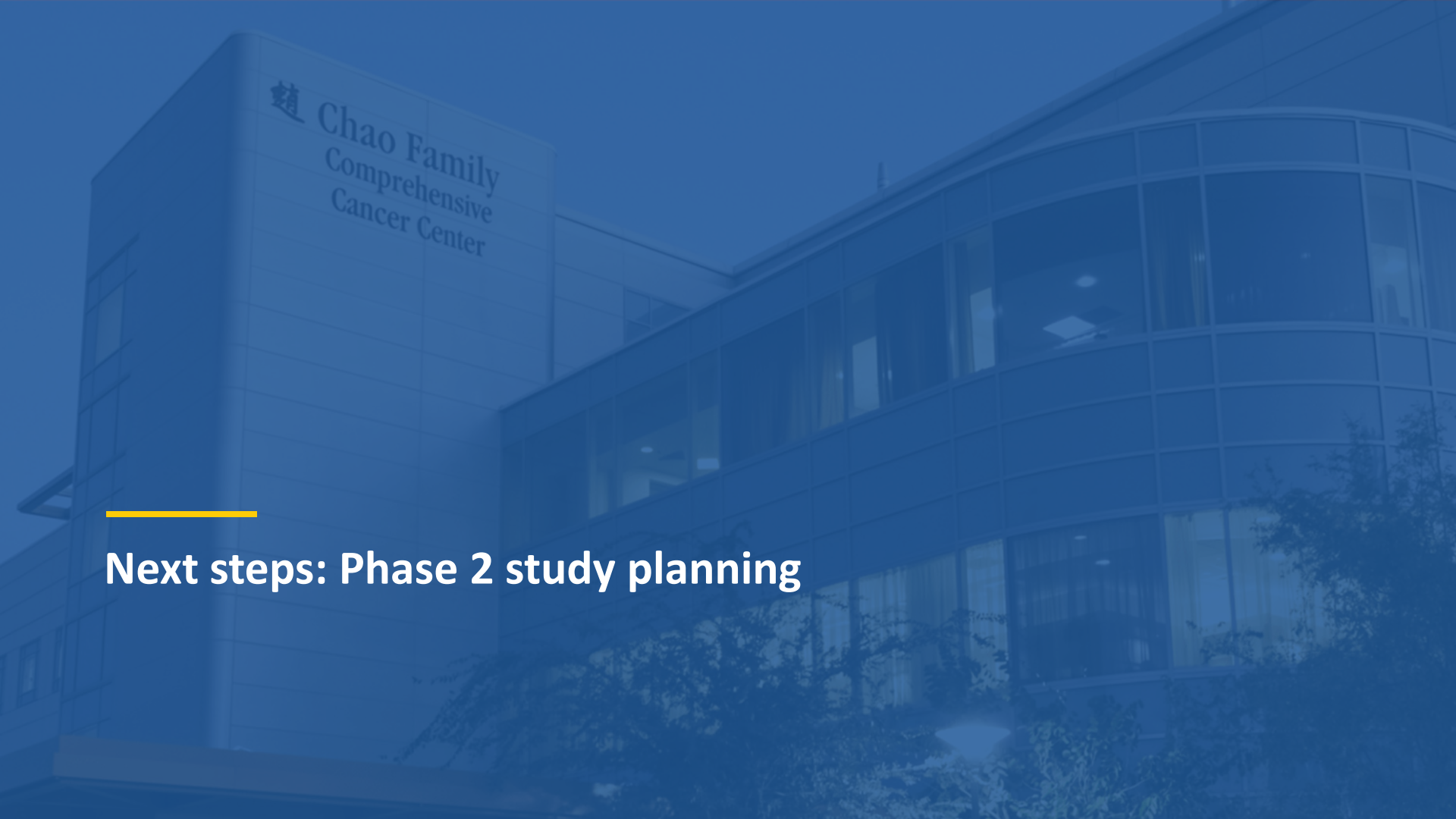
Figure 4: % AML blasts ($CD45^{lo}CD33+$) or CLL cells (CD19+CD5+) was assessed by flow cytometry using PBMCs from trial subjects. Blood samples were collected at **diagnosis** (baseline), after **venetoclax** ramp-up, and 24hr after the first dose of **pitavastatin** at dose level 1 (2 mg).

Study Take Aways

- RP2D: 2mg
- Toxicities were not worse or different than what would be expected with SOC therapies alone

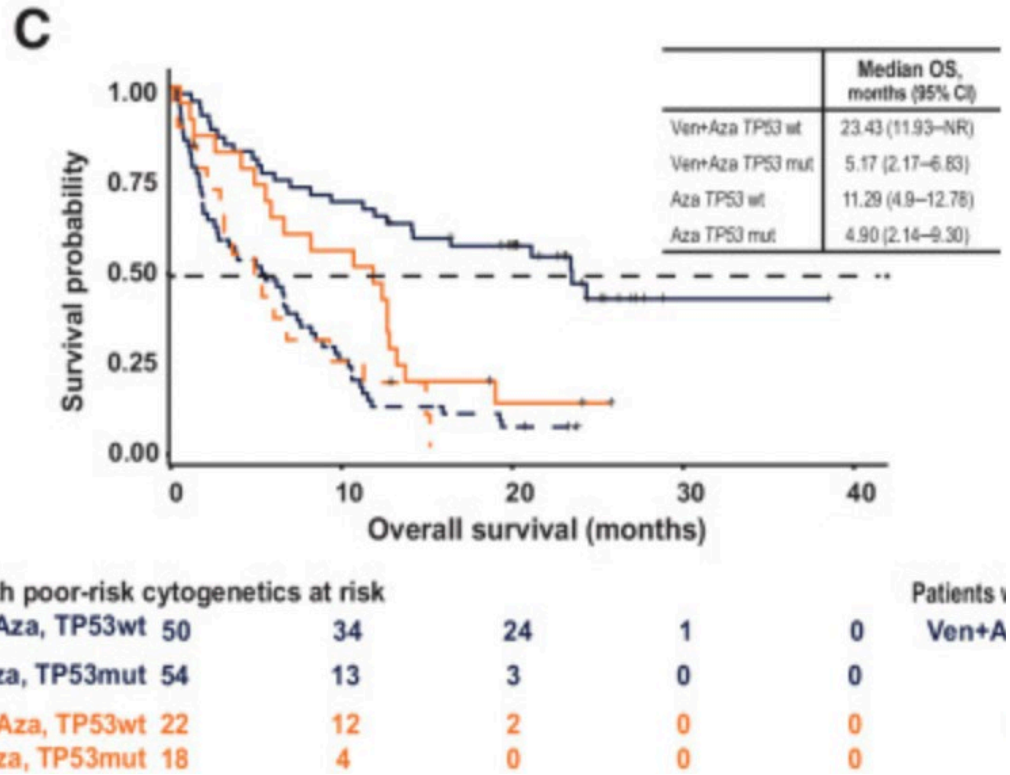
What have we learned?

- Most patients with AML receiving aza/ven do not have a CrCl of > 60
- There's a lot of room for improvement for our AML therapies
  - Patients with CLL/SLL on ven-based therapies do very well, and it's hard to make this better with out a very big or very long study
- Funding studies like this is hard!



Next steps: Phase 2 study planning

AML with TP53 aberrations have worse outcomes



Pollyea DA et al, 2022

AML with TP53 aberrations may particularly benefit from statins

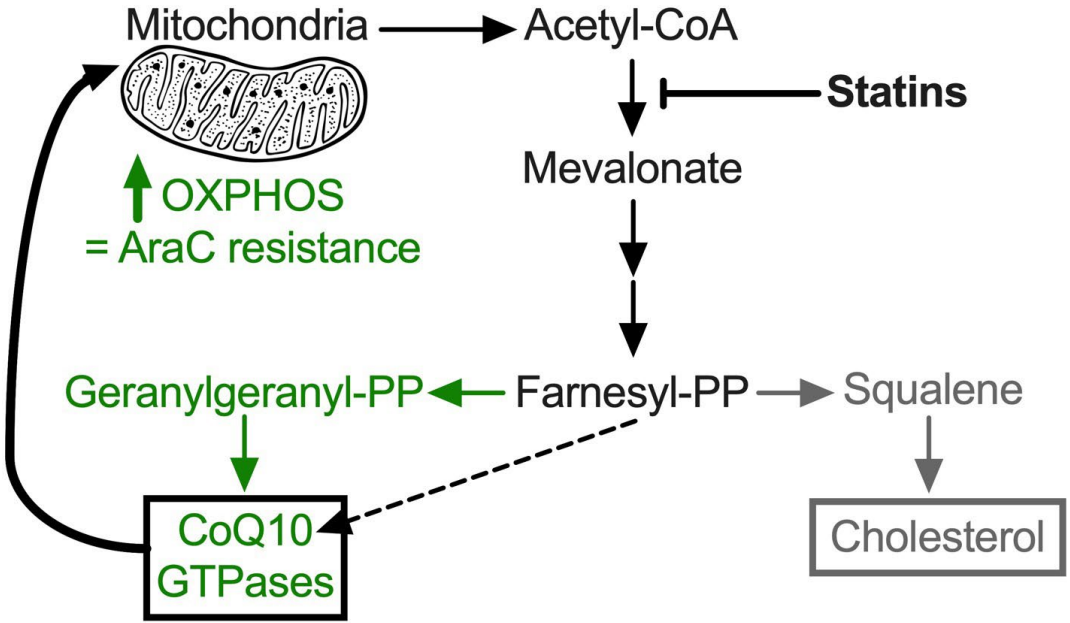


Figure 1. Proposed mevalonate pathway dependencies in chemoresistant *TP53* MT AML.

Next steps: Phase 2

- AML patients whose disease has a 17p deletion or other TP53 aberration
- Primary endpoint: OS
  - Secondary endpoints: rates of MRD undetectability, CR/CRi rate
  - Correlative endpoints — both looking at both modulation of the BCL2 pathway and cardiac outcomes
- N = 70
- Multiple sites: UC Heme Consortium (Davis and SF), U Penn, Roswell Park
- DoD grant submitted 

Many thanks needed!

- David Fruman
- UCI Heme/Onc: Susan O'Brien, Deepa Jeyakumar, Kiran Naqvi
- UCI Chao Family Comprehensive Cancer Center: Christine Hui, Rick Van Etten, Claudine Soriano and the budget team, Blake Johnson and the CRC team, Anti-Cancer Challenge
- UCHMC: Jesika Reiner, Brian Jonas, Rebecca Oil
- UPenn: Sarah Skuli, Catherine Lai, Martin Carroll
- RPCI: Pamela Sung

UCI 趙 Chao Family Comprehensive Cancer Center

Questions?

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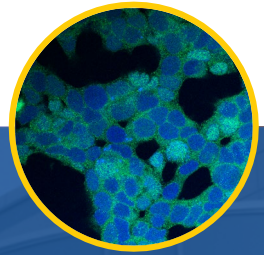
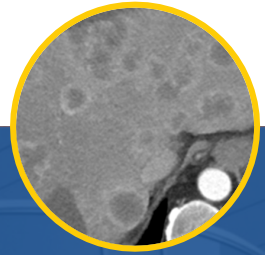
𝕏 @DrLizBrem

UCI 趙 Chao Family Comprehensive Cancer Center

Exportin 7-Laden Exosomes Unveil Ste-20-like Kinase as a Translatable Therapeutic Target in Cholangiocarcinoma

Reed L. Ayabe, MD
Assistant Professor of Surgery
Division of Hepatobiliary and Pancreas Surgery
University of California, Irvine

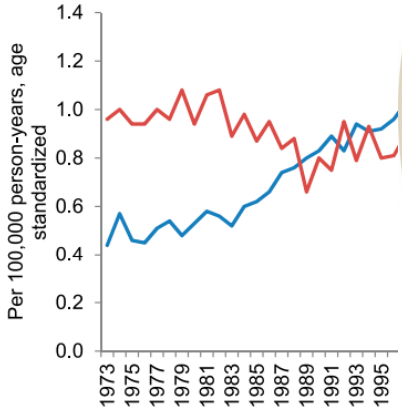
Disclosures

Aveo Pharmaceuticals – Cooperative Research And Development Agreement (CRADA)

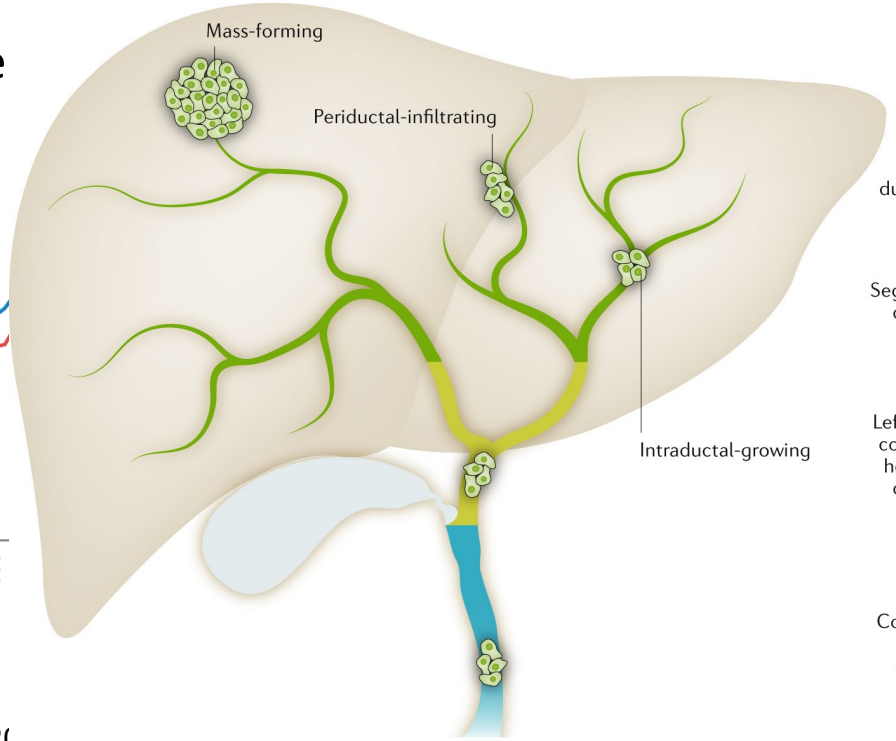
US Patent US2021/060902 Methods for treating bile duct cancers with Tivozanib

Cholangiocarcinoma is a Challenging Malignancy

↑ Incide

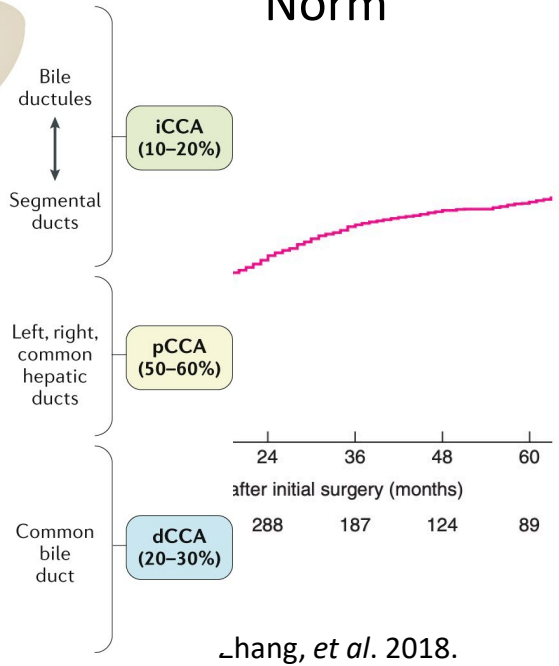


Saha, *et al*. 2018.



Kosmol, et al. 2022.

ırrence is the Norm

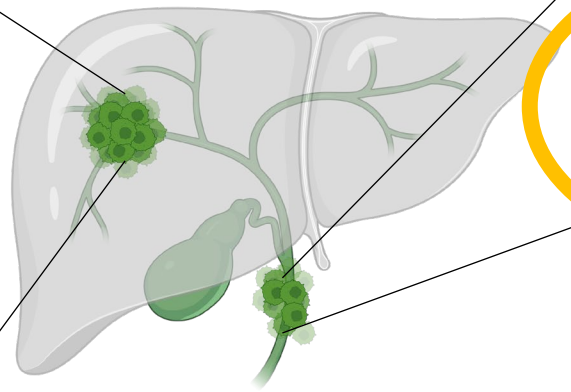


Zhang, *et al*. 2018.

Banales, et al. 2020.

Accelerated Progress in Cholangiocarcinoma

iCCA
FGFR1-3: 18-45%
IDH1/2 mutation: 23-36%
TP53: 21%
KRAS: 16%
RNF43 mutation: 9%
PIK3CA mutation: 3%
BRAF mutation: 3-7%%
ERBB3 amplification: 7%
MET amplification: 2-7%
EGFR mutation: 1-2%



eCCA
ERBB2/3 amplification: 7-11%
BRAF mutation: 3%
MET amplification: 2-7%
MET mutation: 4%
PIK3CA mutation: 7%

ABC-02
Gem/Cis

BILCAP
Adjuvant
Capecitabine

Pemigatinib
for FGRF F/R
2020

Larotrectinib
and
Entrectinib for
NTRK

Ivosidenib
for IDH1

Infigratinib
FGRF F/R

TOPAZ-1
Gem/Cis/Durva

Keynote-966
Gem/Cis
Pembro

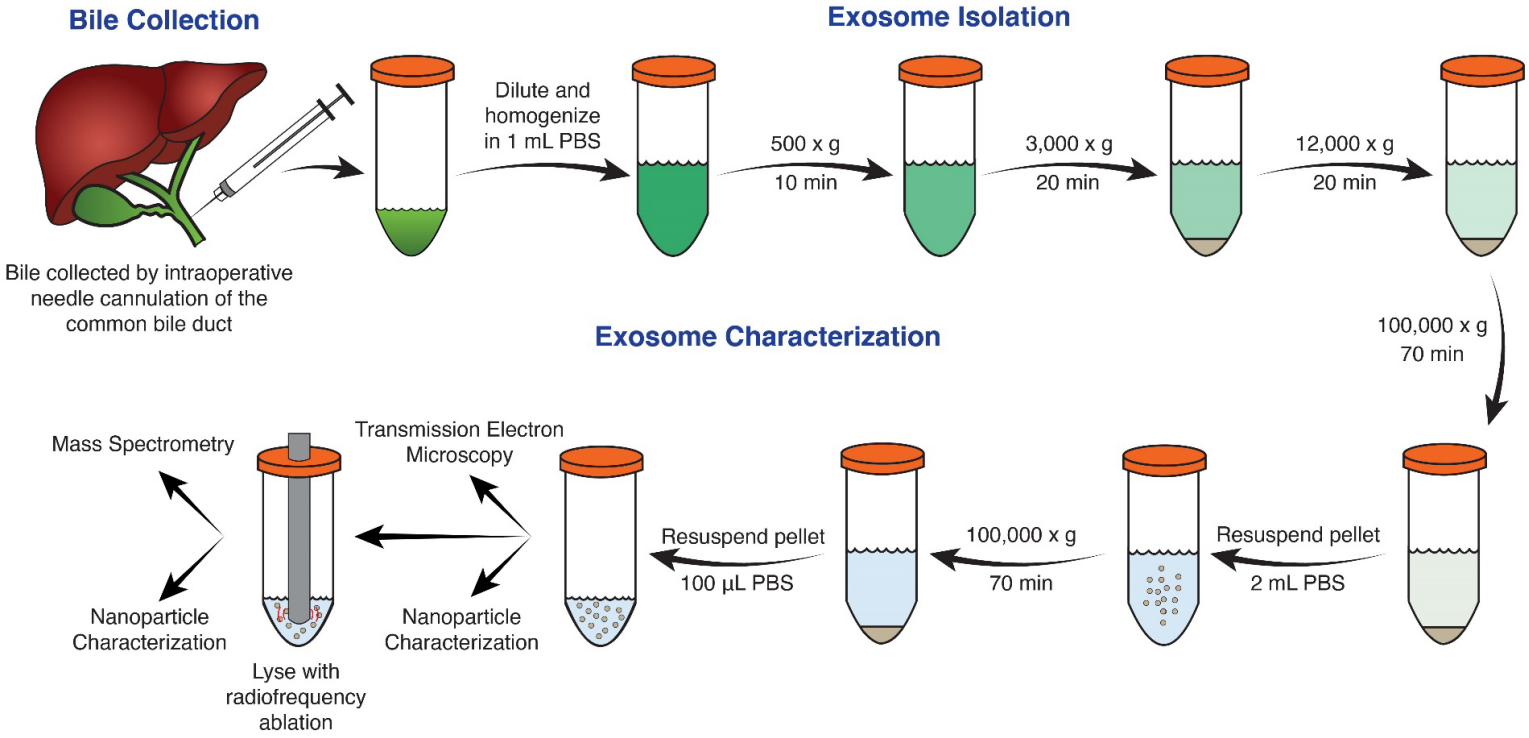
Futibatinib
for FGFR F/R

Trametinib/
Dabrafenib
for BRAF

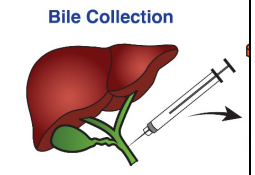
2010 2011 2018 2019 2020 2021 2022

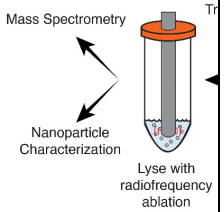
Next Generation Sequencing

XPO7 is Present in the Biliary Exosomes of Patients with eCCA

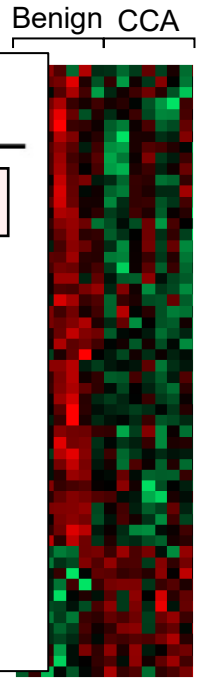


XPO7 is Present in the Biliary Exosomes of Patients with eCCA





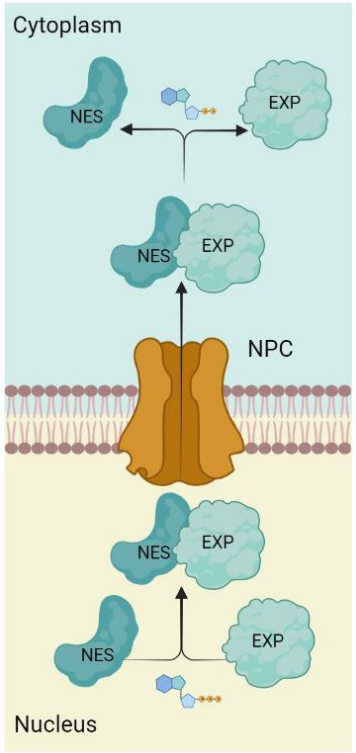
Protein	Gene	Fold Change	P Value
Exportin-7	*XPO7*	16.46	0.002
Olfactomedin-4	*OLFM4*	6.95	0.01
Integrin alpha-M	*ITGAM*	3.73	0.04
Myeloid cell nuclear differentiation antigen	*MNDA*	3.40	0.06
Fibronectin	*FNI*	2.65	0.09



Ayabe, *et al*. In revision. Please do not copy.

XPO7 is Present in the Biliary Exosomes of Patients with eCCA

- RAN-GTP dependent nuclear export protein.
- Increased expression associated with poor survival in ovarian cancer.
- Necessary for nuclear extrusion during erythropoiesis.



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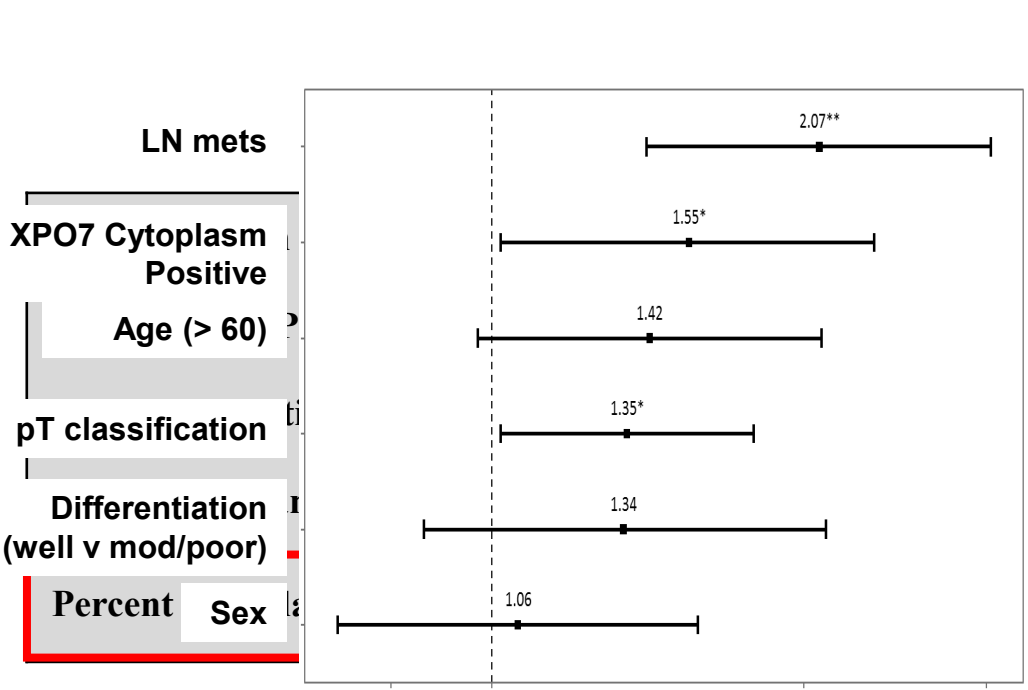
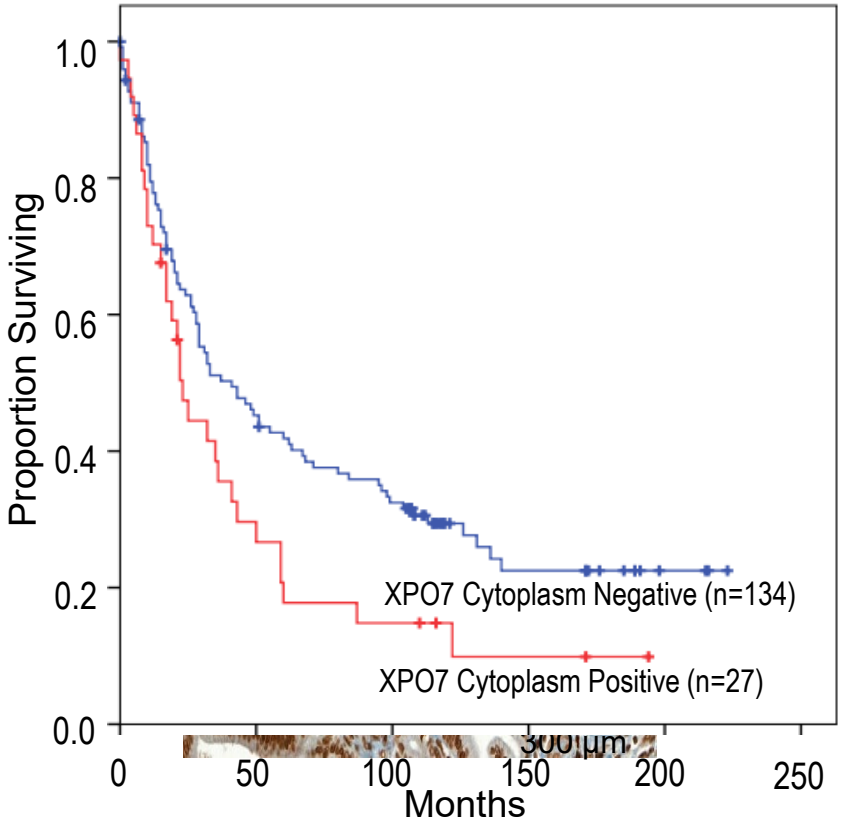
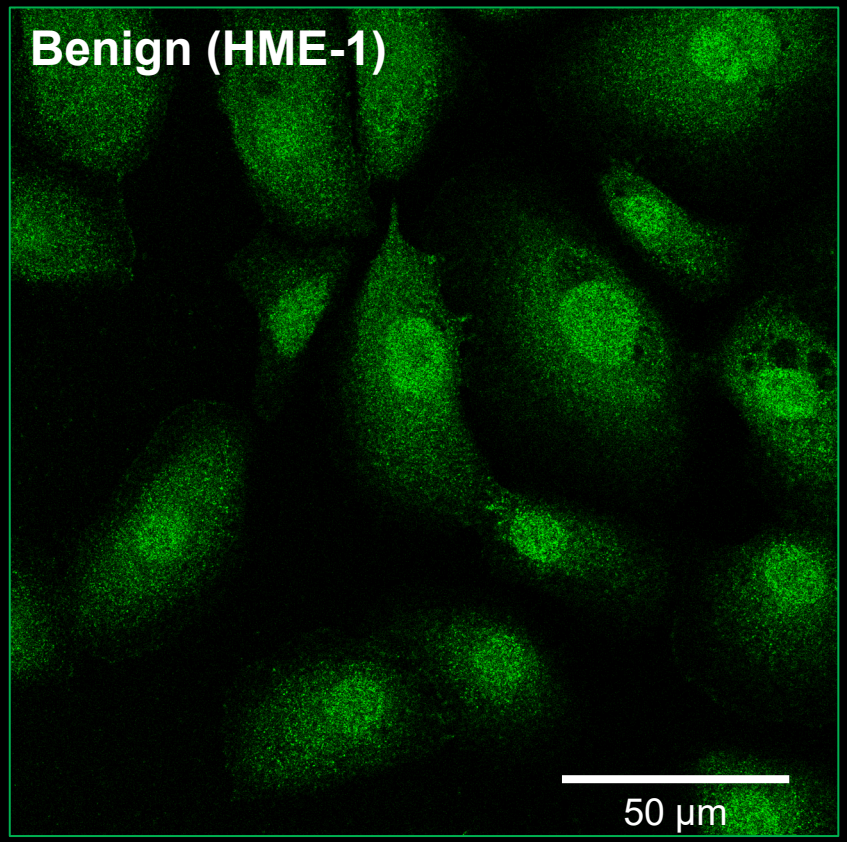
Cytoplasmic XPO7 is Associated with a Poor Prognosis

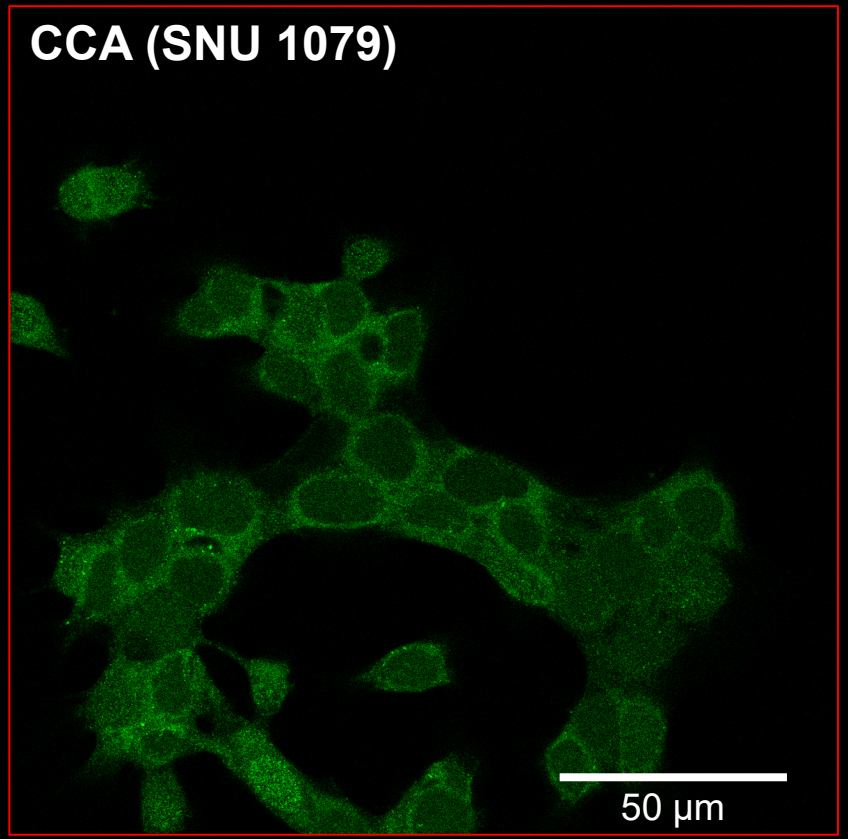




Ayabe, *et al*. In revision. Please do not copy.

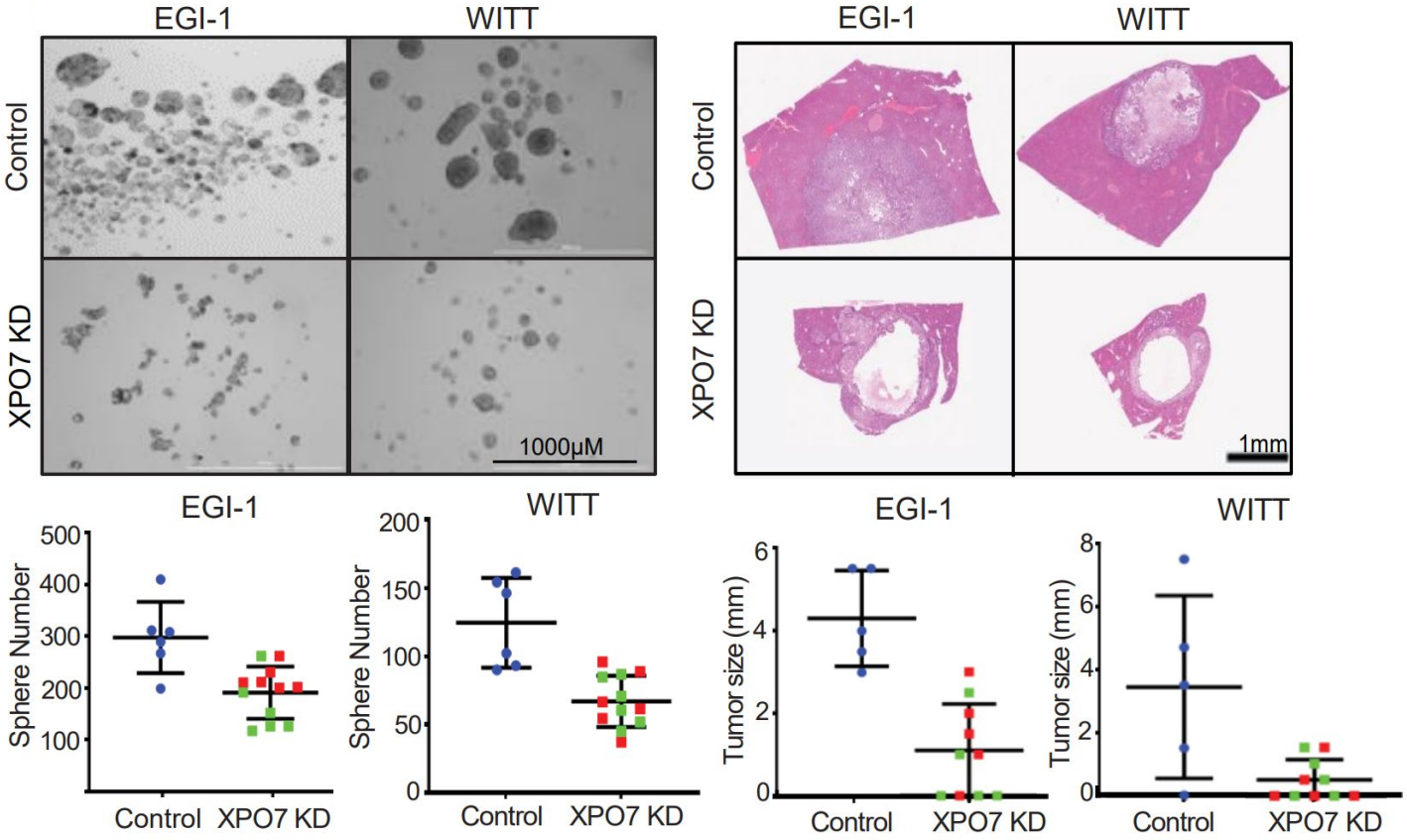
XPO7 Localizes to the Cytoplasm in CCA Cell Lines





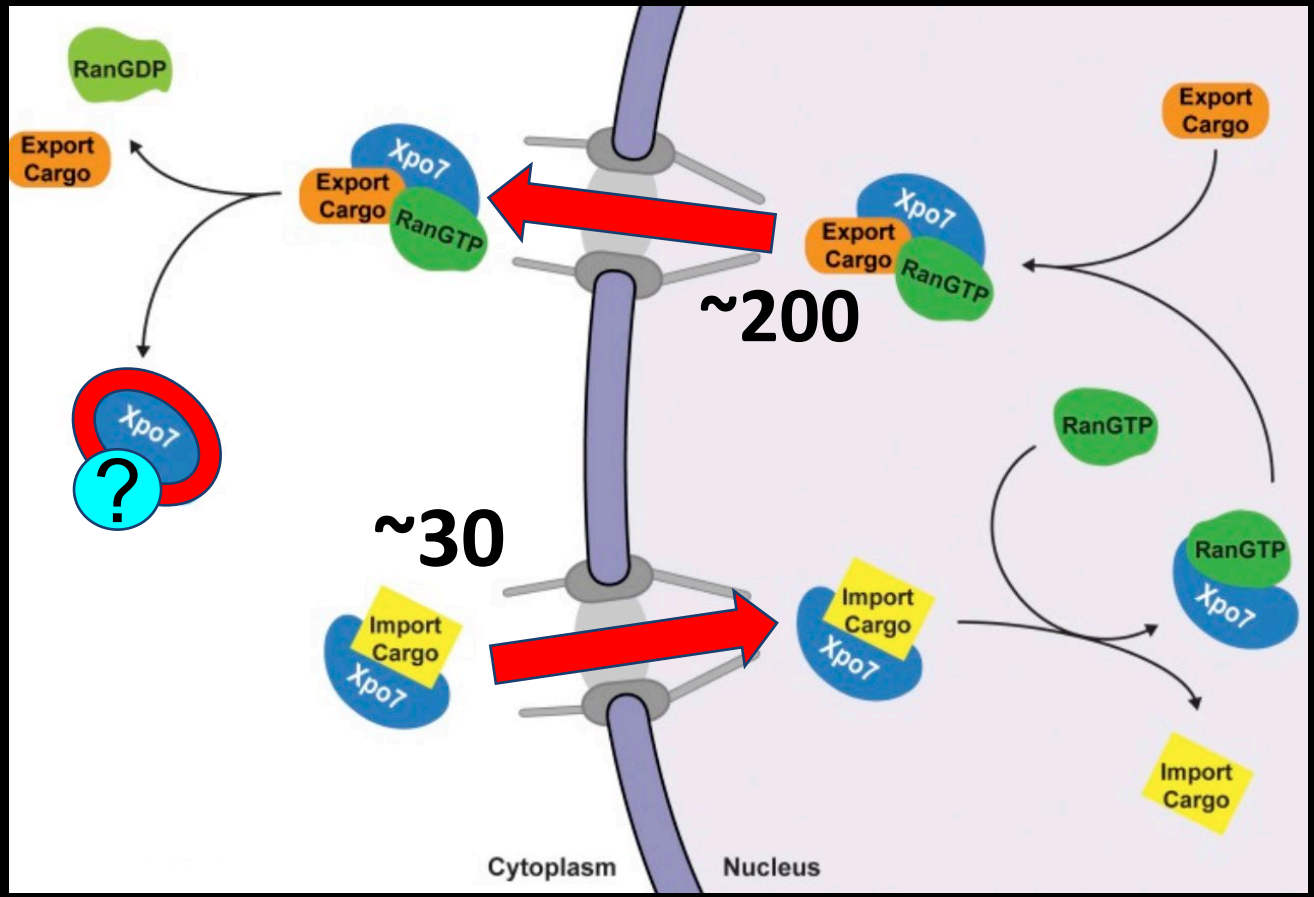
XPO7

XPO7 Knockdown Alters Cell Phenotype

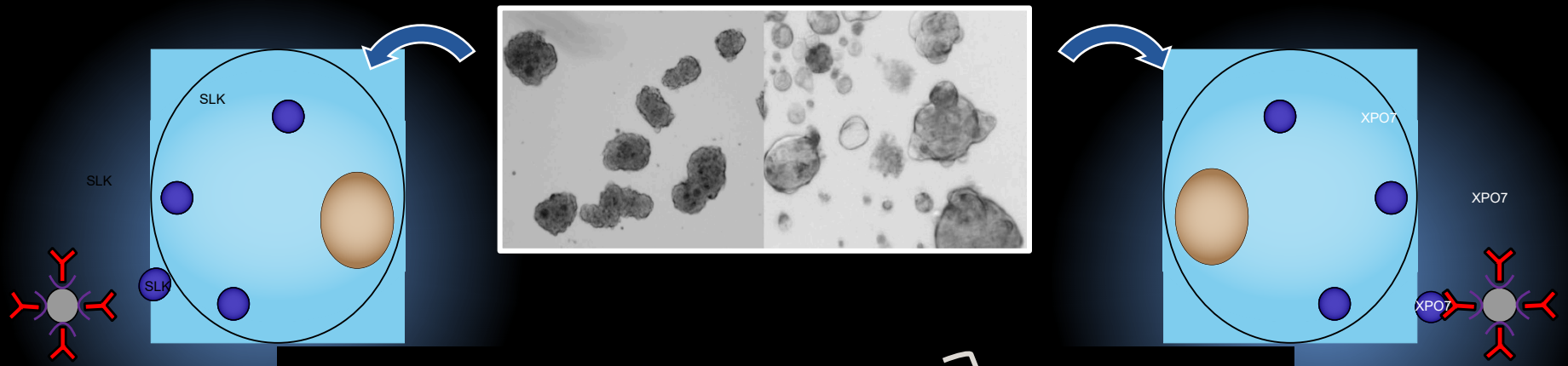


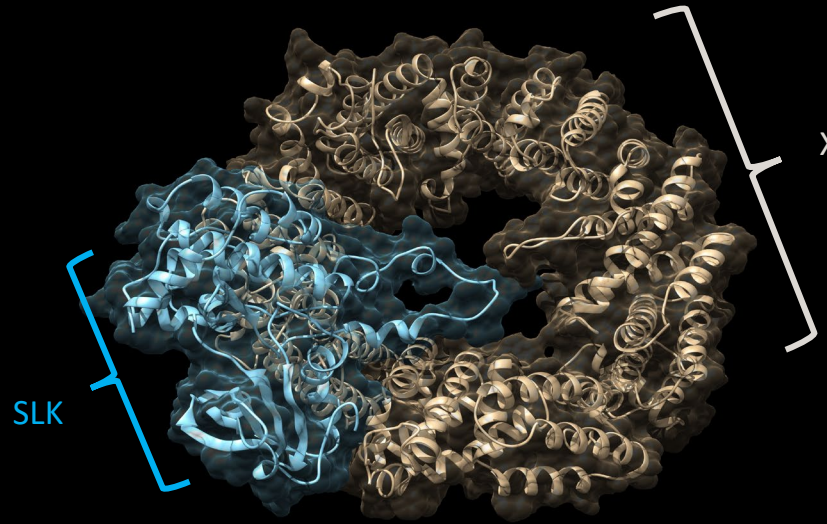
Ayabe, *et al*. In revision. Please do not copy.

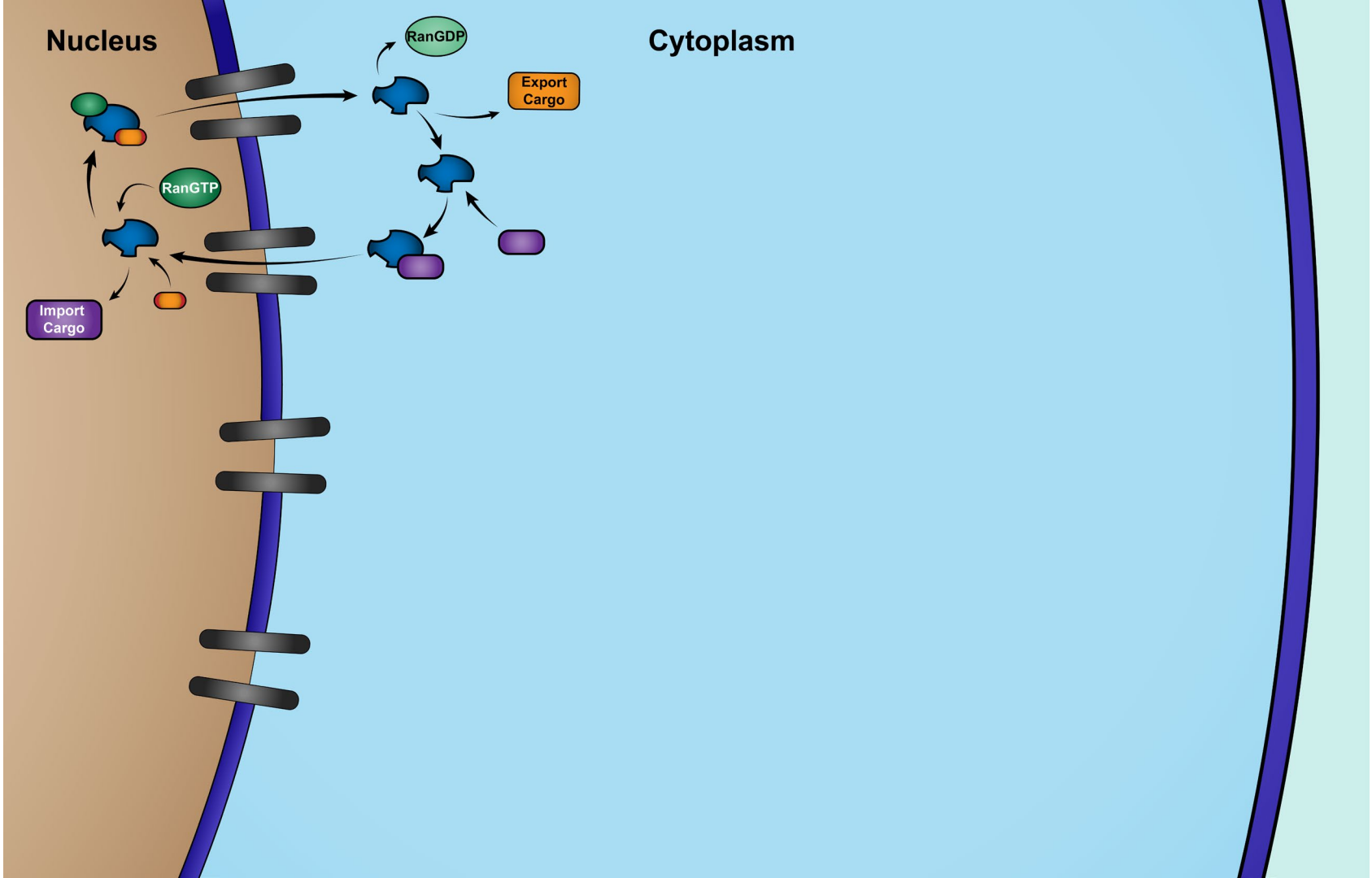
Exportin-7 (XPO7)

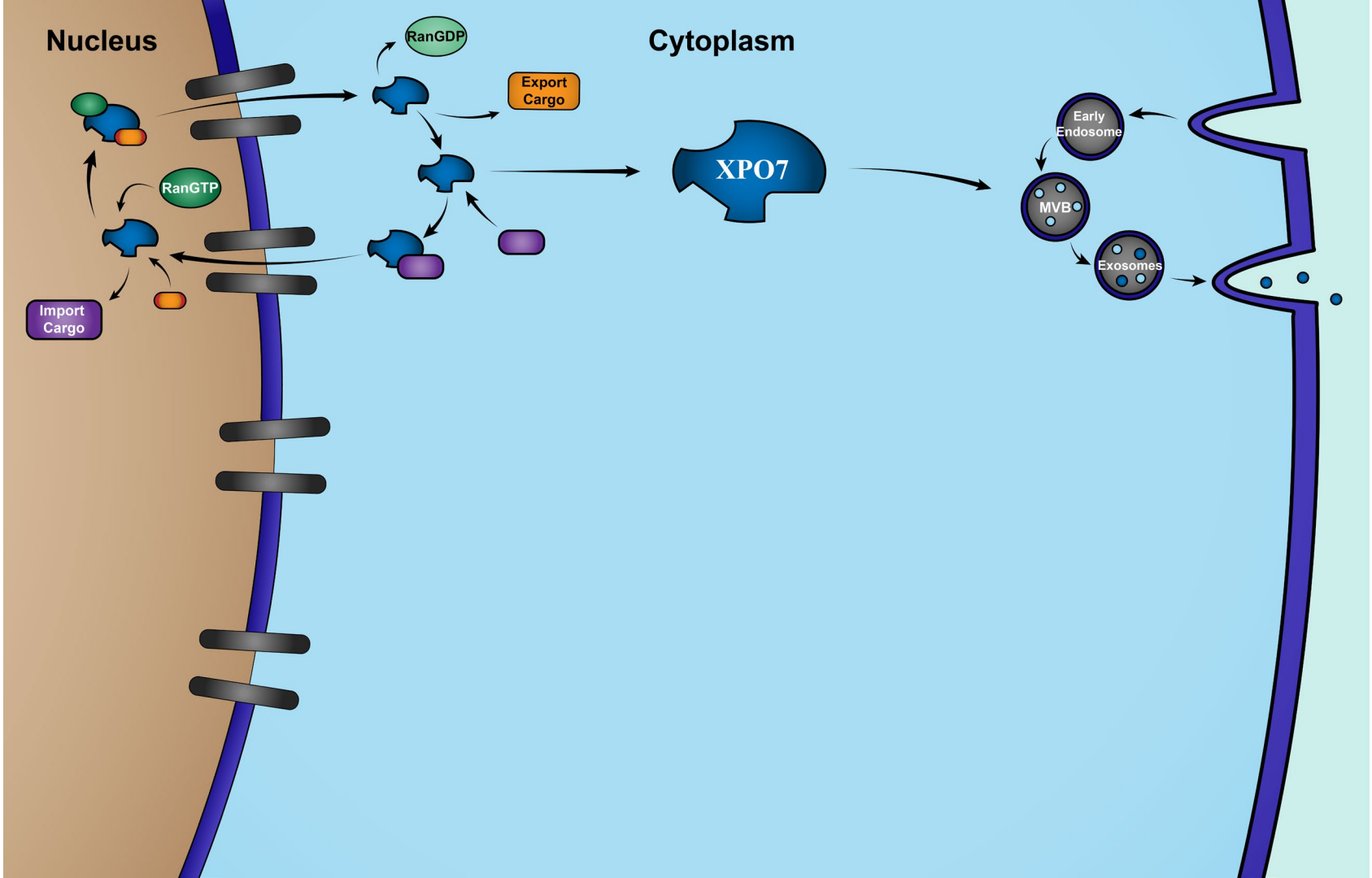


Cytoplasmic XPO7 binds SLK






Nucleus
Cytoplasm
RanGDP
Export Cargo
RanGTP
Import Cargo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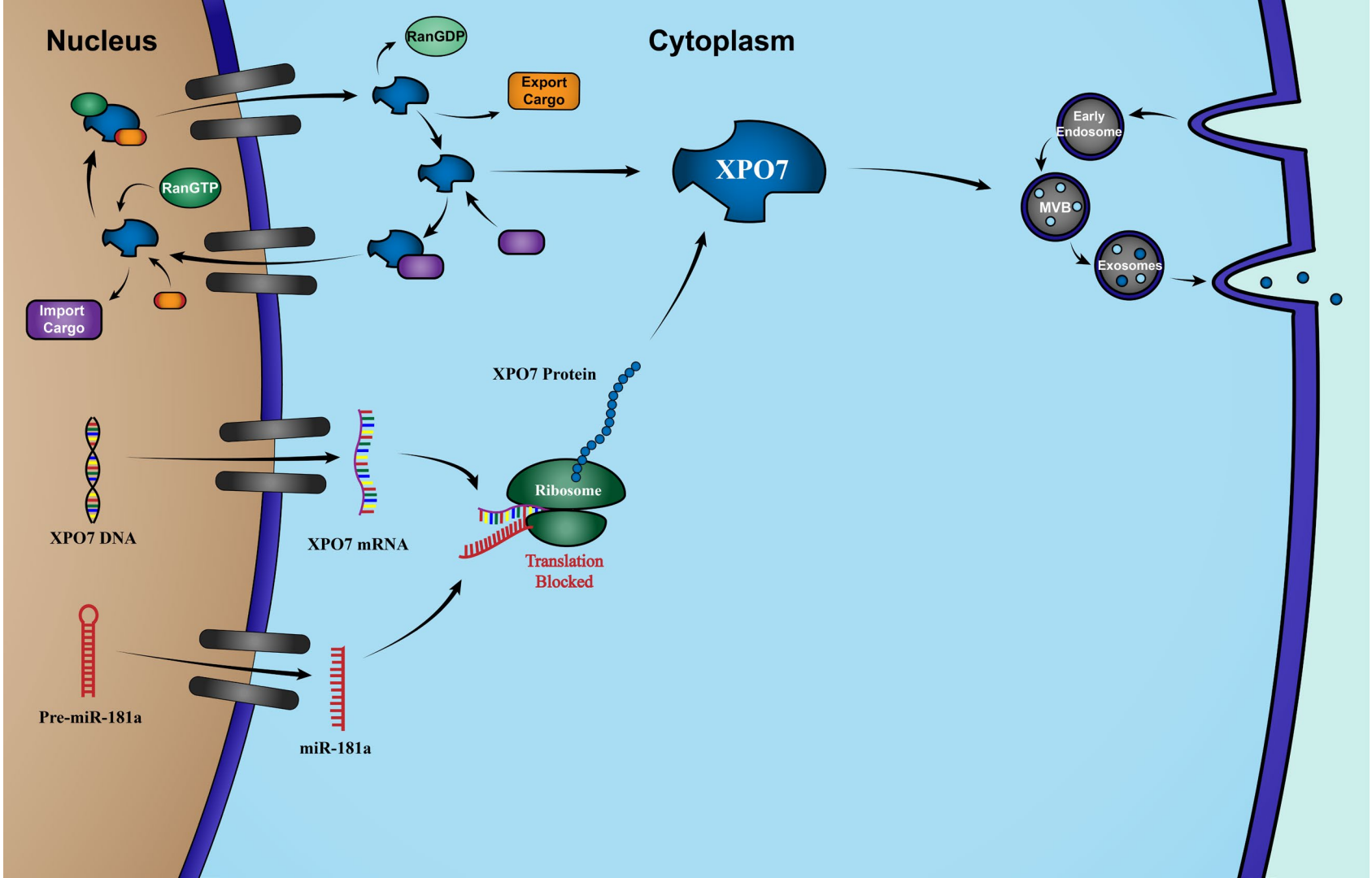
Import Cargo
XPO7
Early Endosome
MVB
Exosomes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MVB
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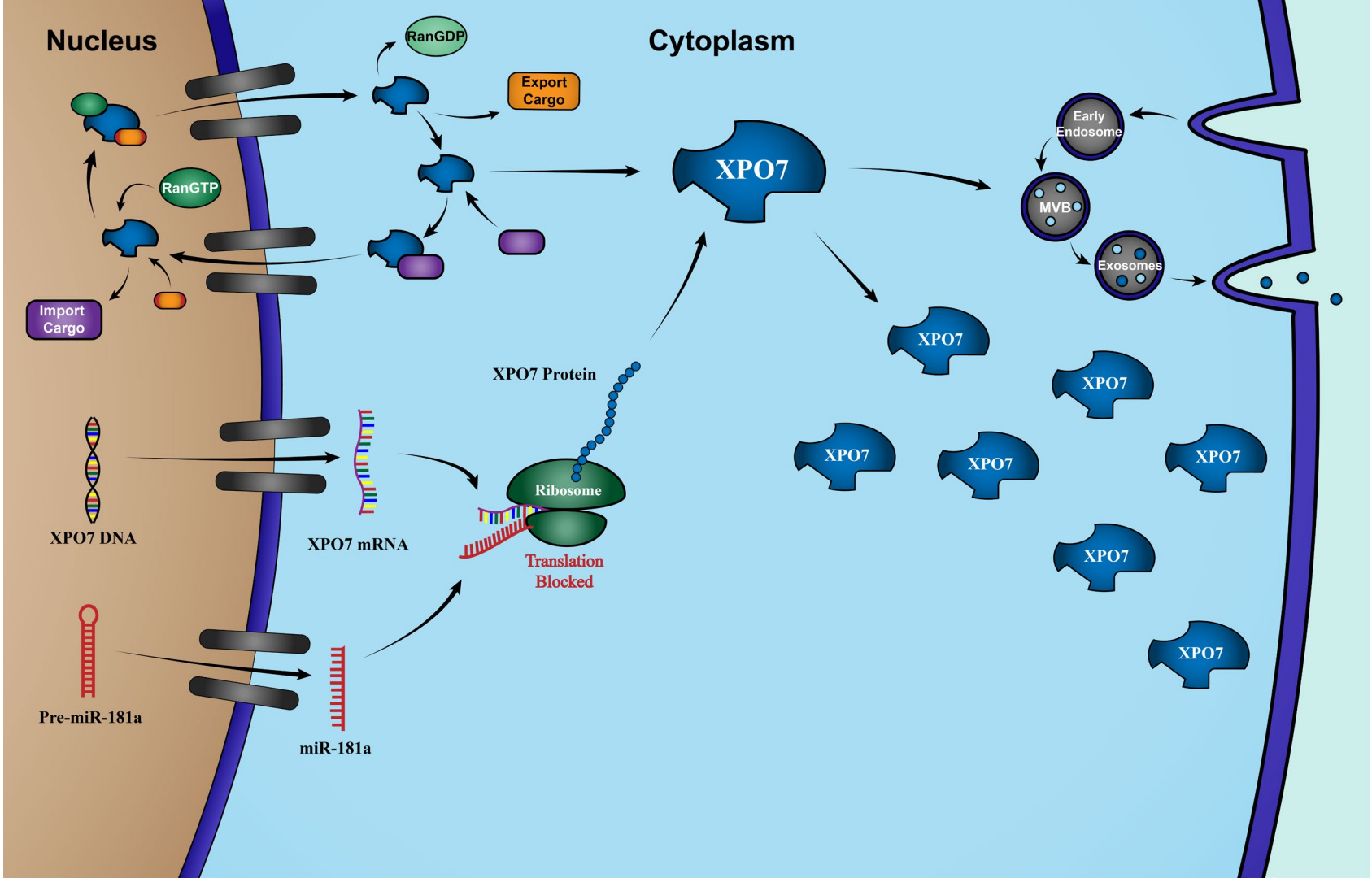
Ribosome
XPO7 DNA
XPO7 mRNA
Translation Blocked
Pre-miR-181a
miR-181a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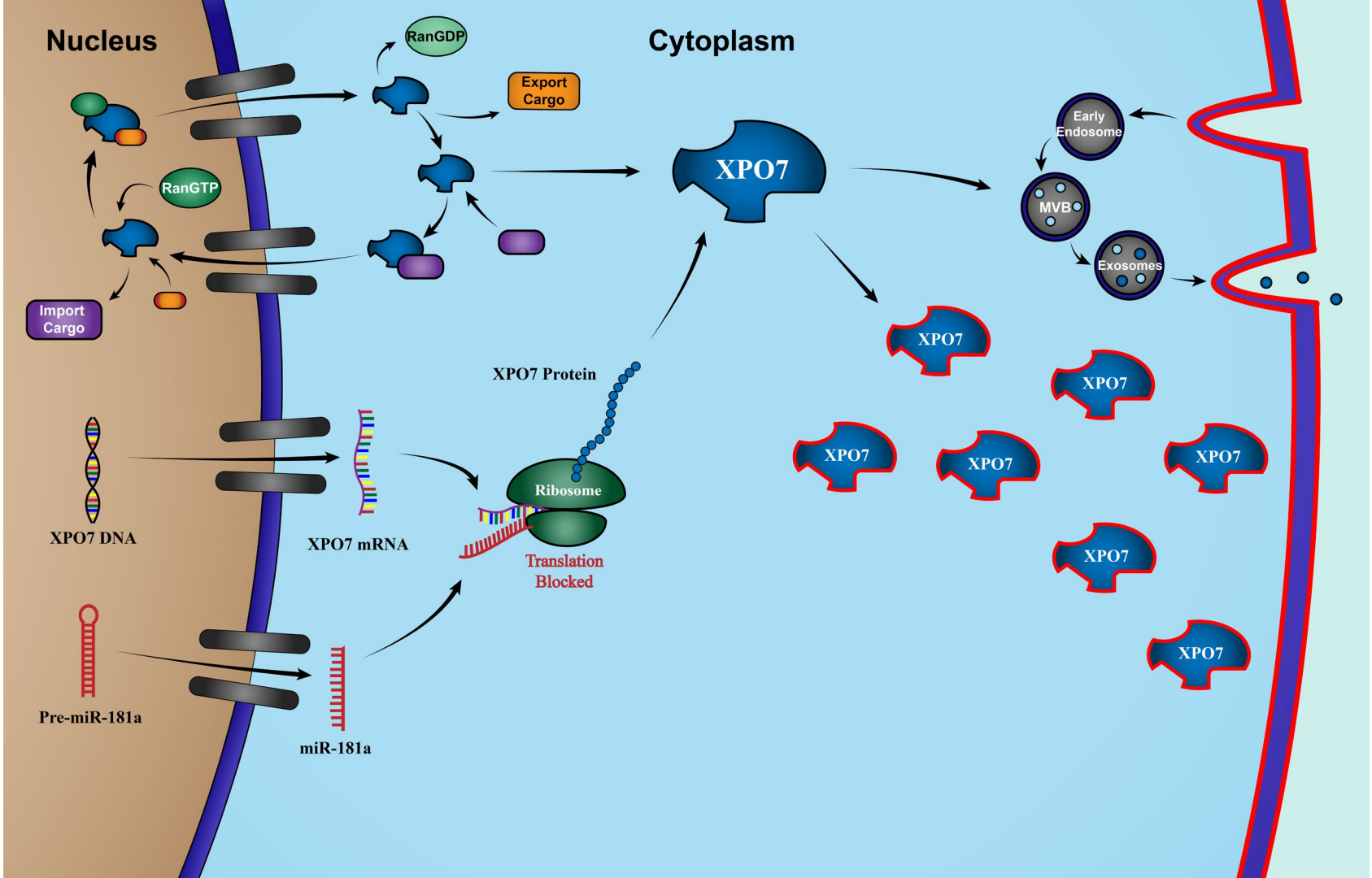
miR-181a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Export Cargo
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Early Endosome
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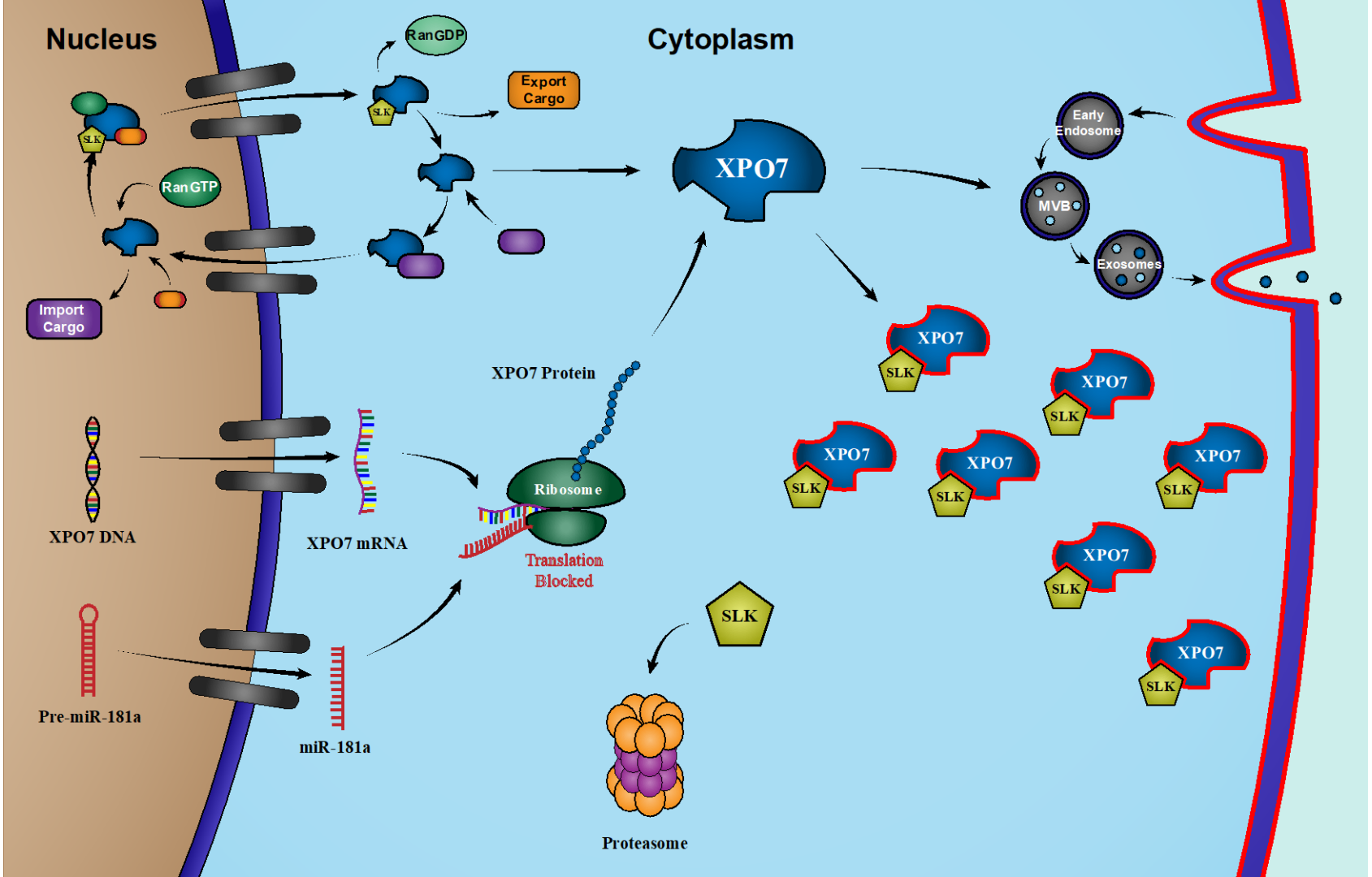
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SLK
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XPO7
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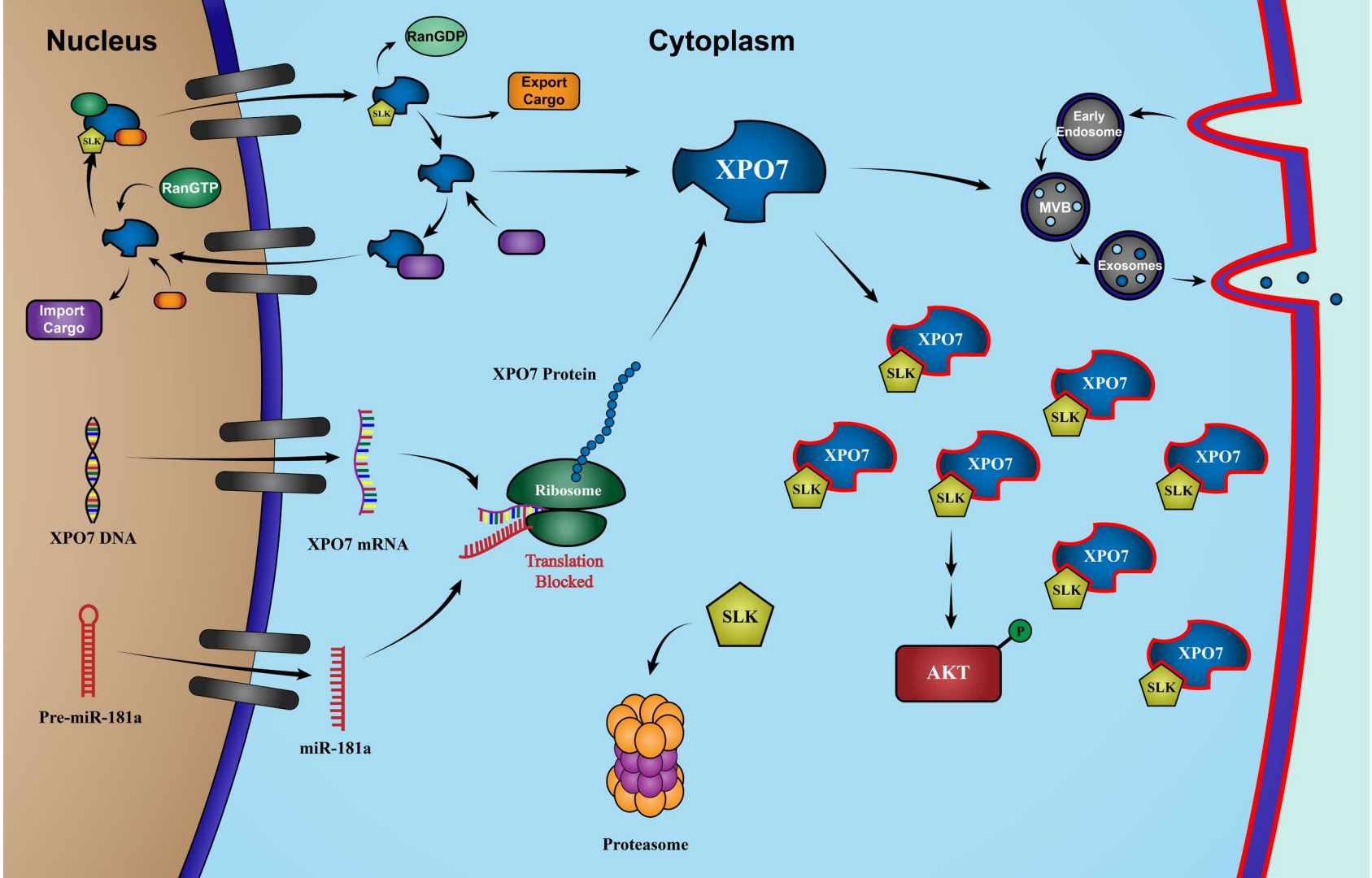
XPO7 mRNA
Ribosome
Translation Blocked
Pre-miR-181a
miR-181a
Proteasome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Cytoplasm
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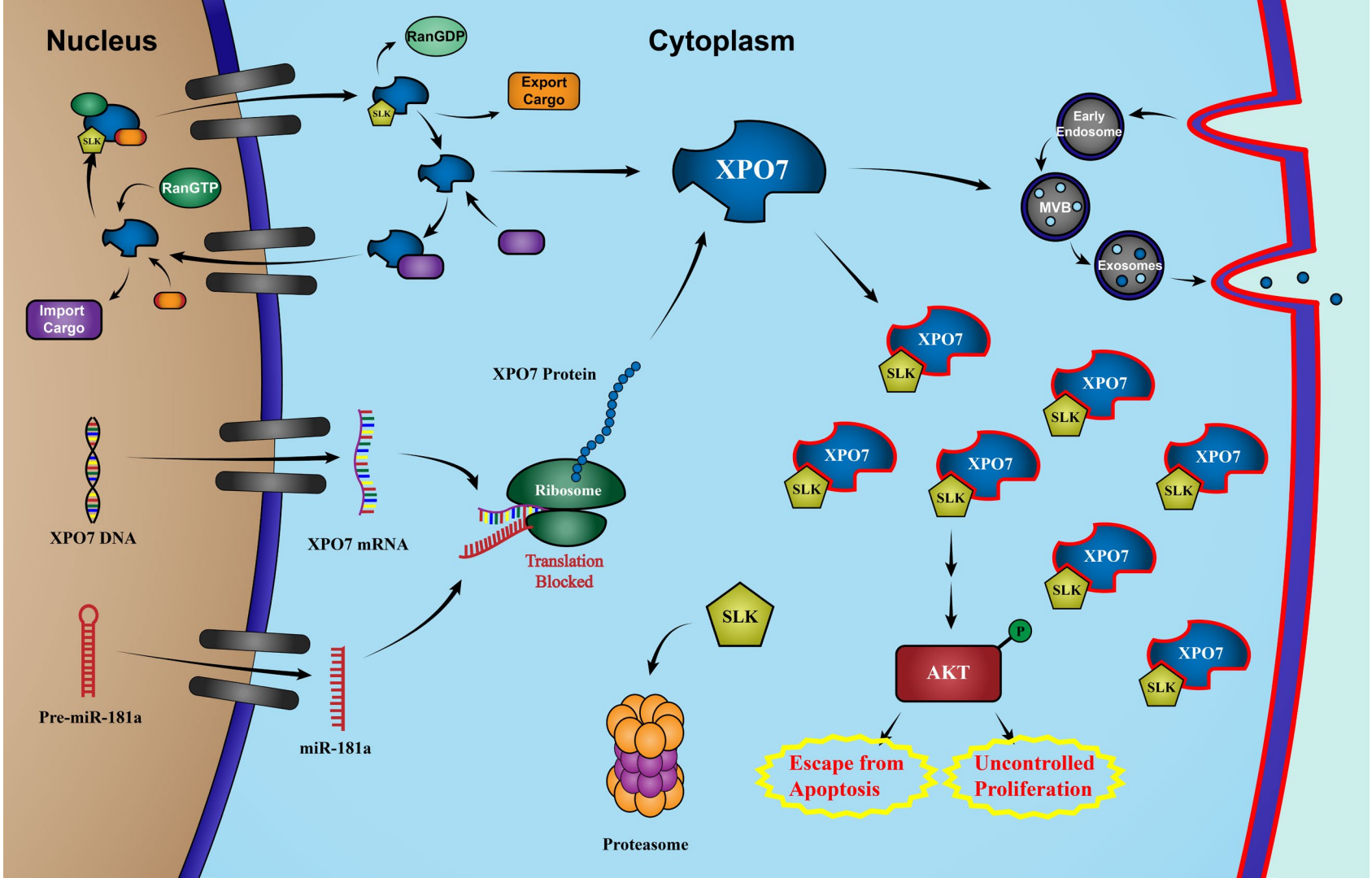
XPO7 mRNA
Ribosome
Translation Blocked
Pre-miR-181a
miR-181a
SLK
Proteasome
AKT
P


Nucleus
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XPO7 DNA
XPO7 mRNA
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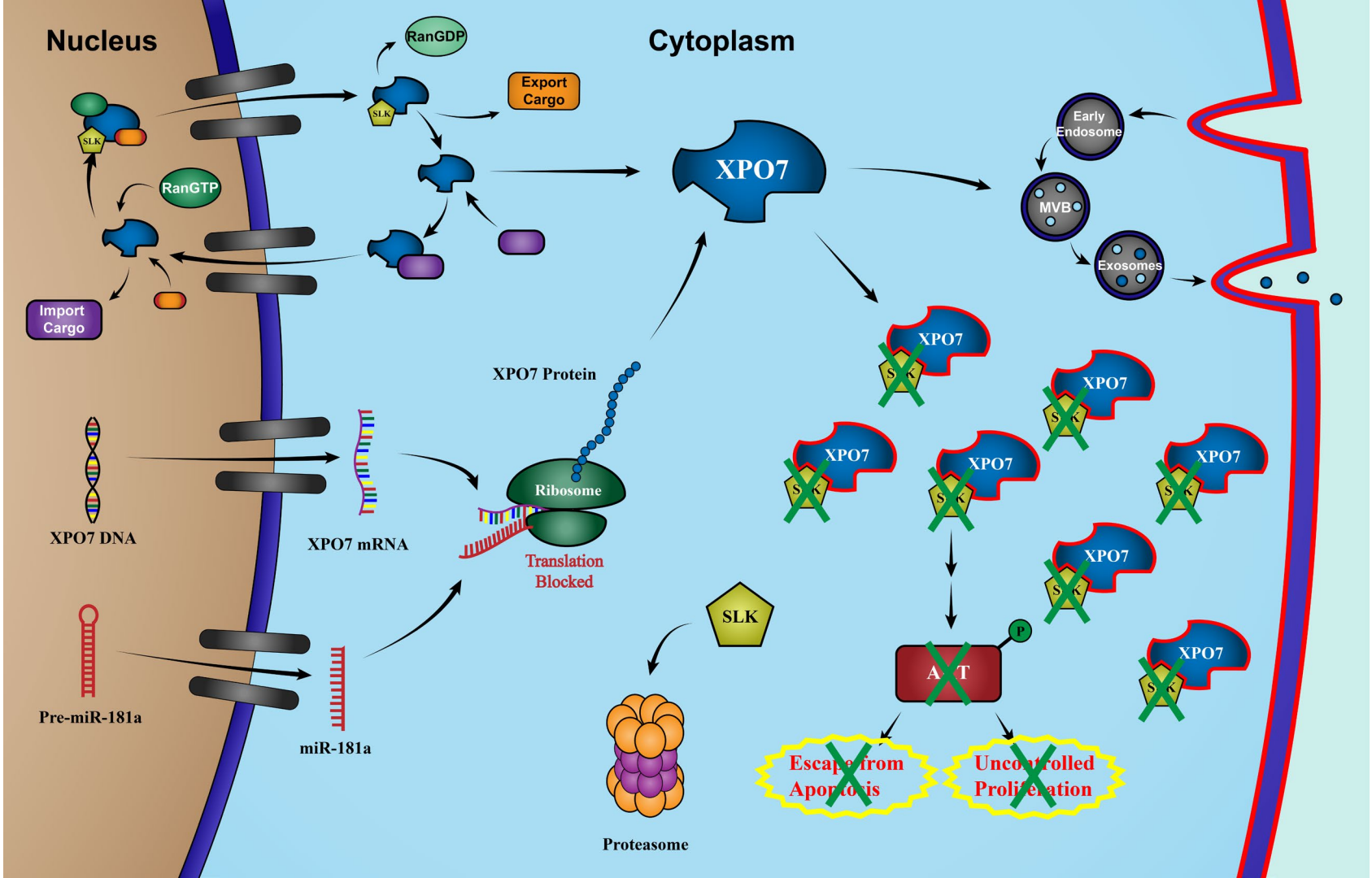
Translation Blocked
Pre-miR-181a
miR-181a
SLK
Proteasome
AKT
P
Escape from Apoptosis
Uncontrolled Proliferation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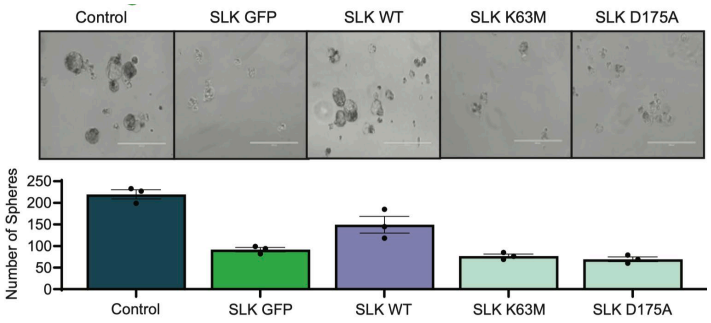
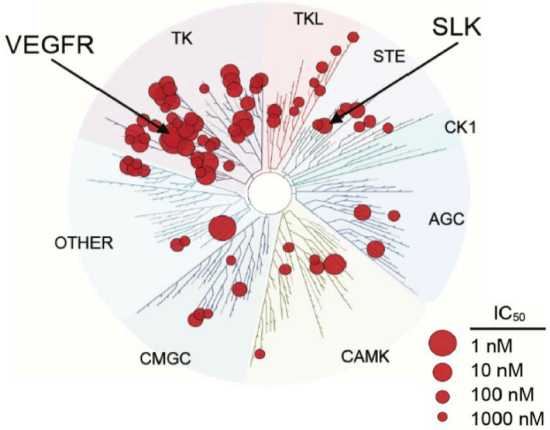
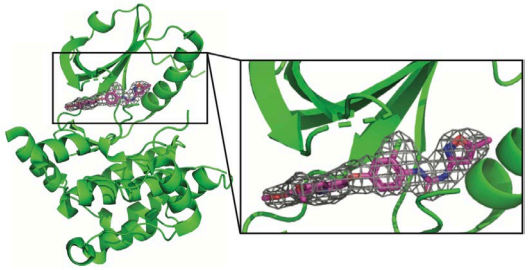
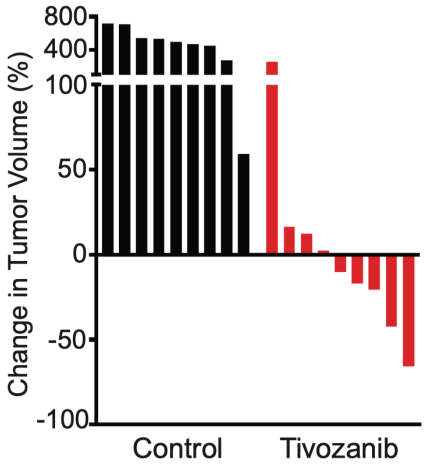
XPO7
Early Endosome
MVB
Exosomes
XPO7 Protein
XPO7 DNA
XPO7 mRNA
Ribosome
Translation Blocked
Pre-miR-181a
miR-181a
SLK
Proteasome
A T
P
Escape from Apoptosis
Uncontrolled Proliferation

Tivozanib Blocks SLK Kinase Activity



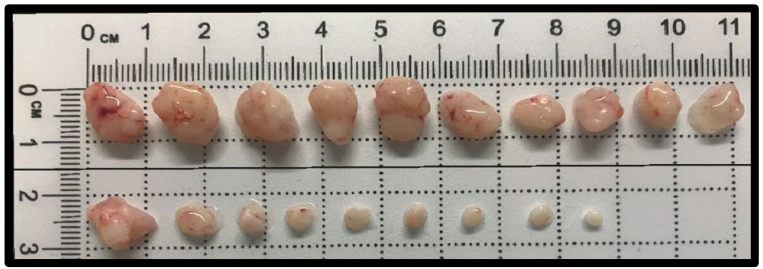






Control

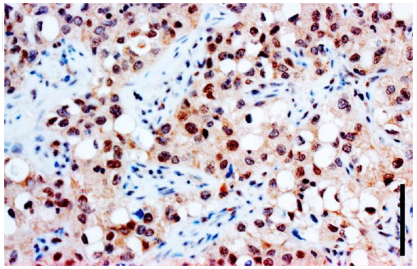
Tivozanib



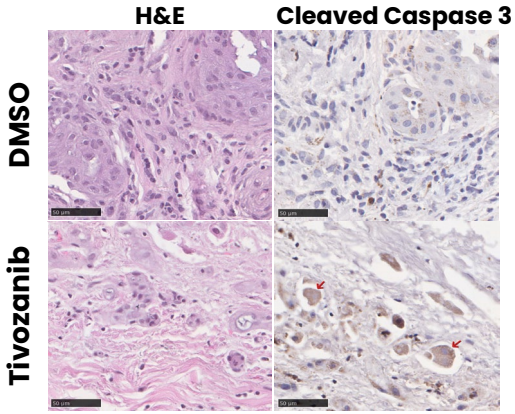
Ayabe, *et al*. In revision. Please do not copy.

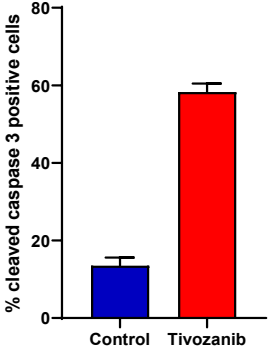
Ayabe, et al. *Cancer Discov*. In revision.

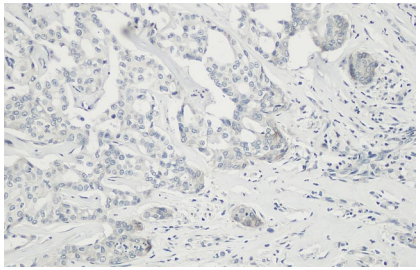
Tivozanib Causes CCA Cell Death Ex Vivo



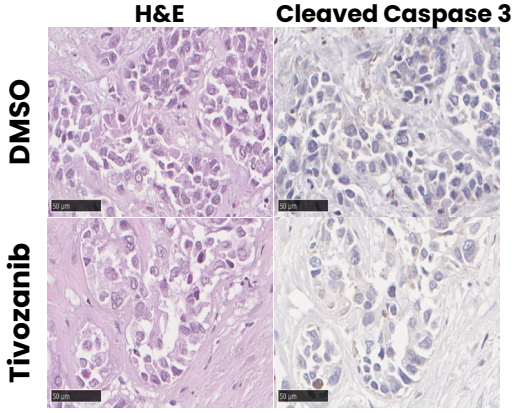
XPO7+ CCA

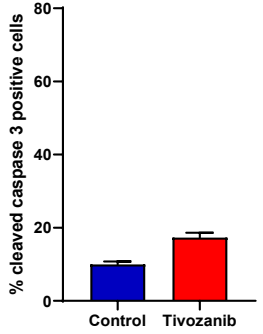






XPO7− CCA





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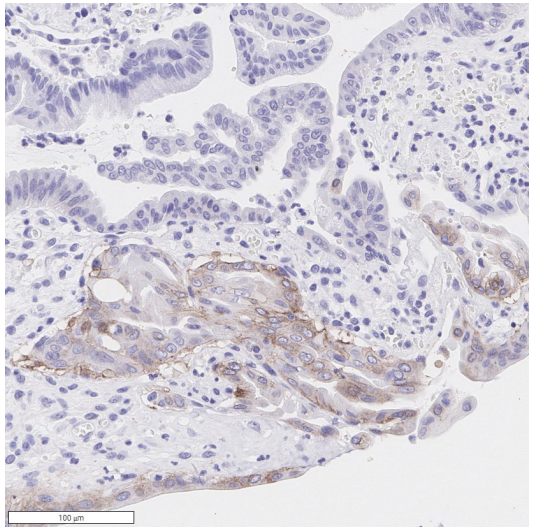
Ayabe, et al. *Cancer Discov*. In revision.

Evaluating Efficacy of Tivozanib (AV-951) in Biliary Tract Cancers

Disease stability with Tivozanib treatment

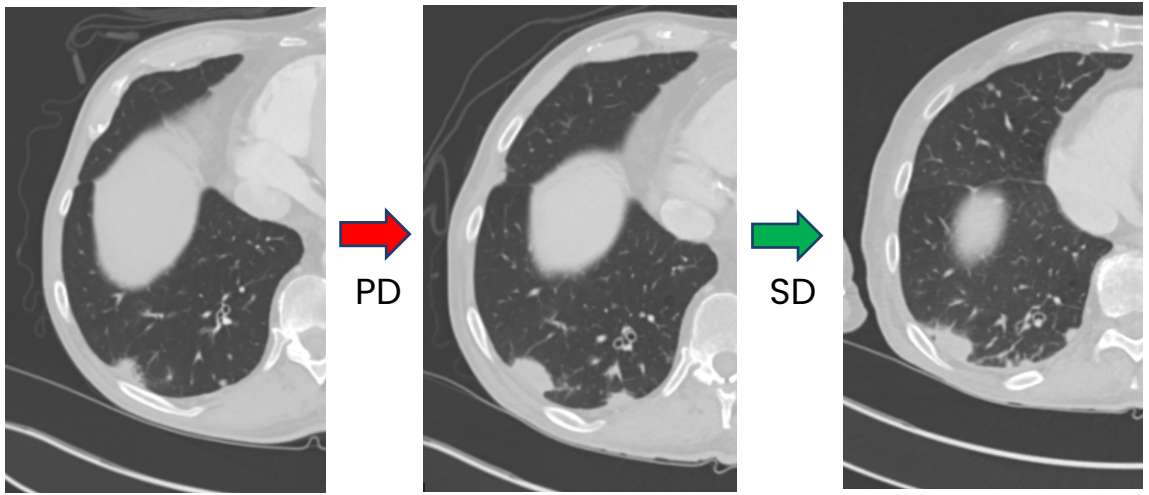
NCT04645160 Pt#3
XPO7+



Gem/Cis

Capecitabine

C2 Tivozanib



PD

SD

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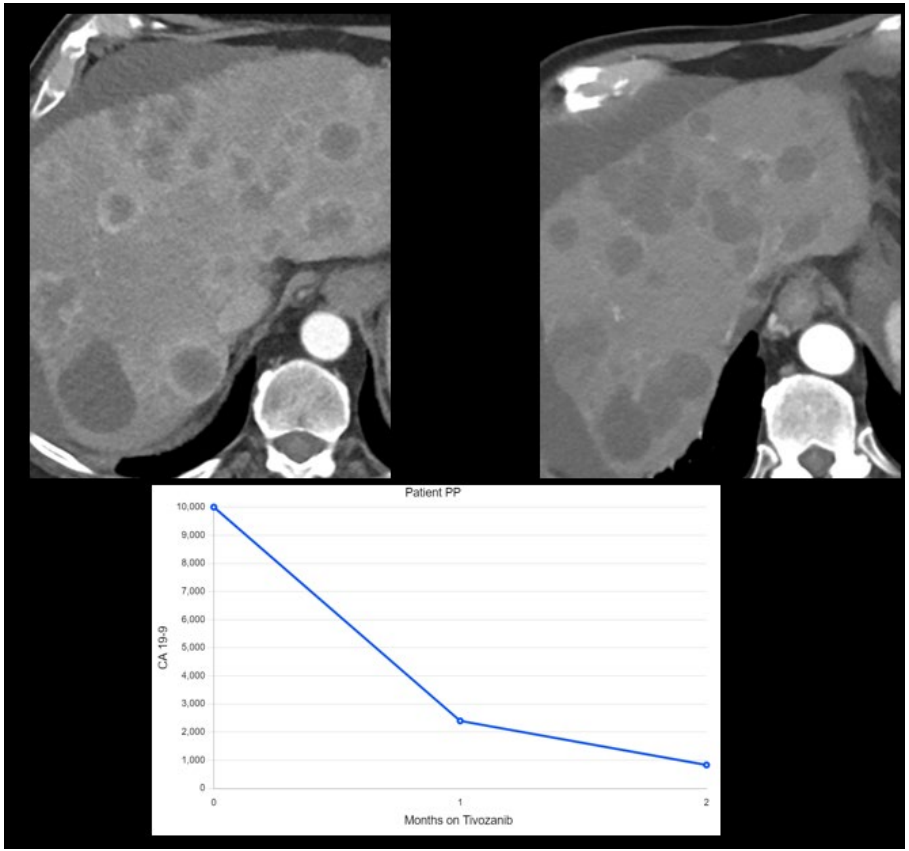
Reduction in CA 19-9 with Tivozanib Treatment



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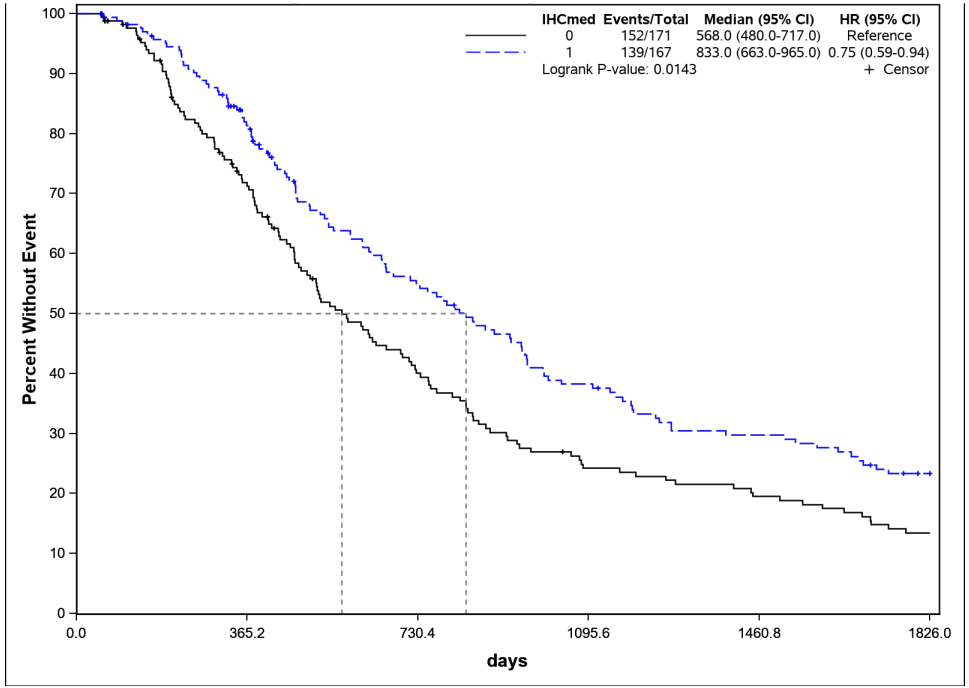
Similar Biology in Pancreatic Adenocarcinoma?

N=339 PDAC in TMA stratified by cytoplasmic staining for XPO7

HR 0.75 (95CI 0.59-0.94)



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Conclusions

CCA remains a challenging disease with limited effective treatment options.

XPO7 is a liquid biomarker for CCA and is linked to an aggressive phenotype through SLK.

SLK is an effective therapeutic target in vivo and ex vivo.

The XPO7/SLK/AKT axis may be at play in other tumor types, including pancreatic cancer.

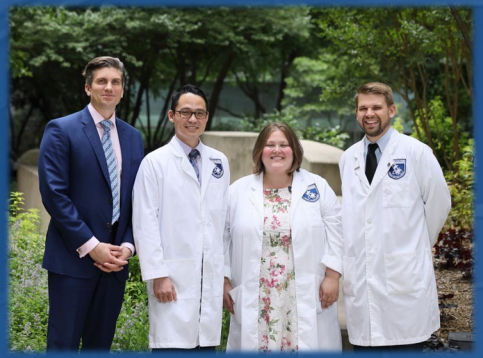
UCI Division of Hepatobiliary and Pancreas Surgery

Zeljka Jutric, MD, MSc

David Imagawa, MD, PhD

Reed Ayabe, MD

Hernandez Lab, National Cancer Institute



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Thank You

rayabe@hs.uci.edu

UCI 趙 Chao Family Comprehensive Cancer Center

Chemoprevention Clinical Trials at UCI:
Past, Present, and Future

Jason A. Zell, DO, MPH
Vice Chief for Academic Affairs, Division of Hem/Onc
Director, Hematology/Oncology Fellowship Training Program

NCI Cancer Prevention Research Programs

https://prevention.cancer.gov/major-programs/cancer-prevention-clinical-trials-network-cp-ctnet

PREVENT Cancer Cancer Prevention-Interception Targeted Agent Discovery Program (CAP-IT)	NCI-Cancer Prevention Clinical Trials Network (CP-CTNet)	NCI-Community Oncology Research Program (NCORP)
• Preclinical Agent Development	• UG1 mechanism • Phase 0-II clinical trials of promising cancer preventin agents	• Phase III cancer preventive agent development • Aimed at demonstrating definitive efficacy

The Past: UCI Chemoprevention Program

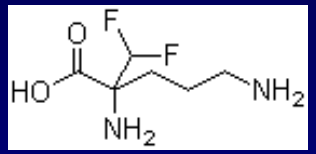
2008 Jun;1(1):32-8

Cancer **Prevention** Research

Difluoromethylornithine Plus Sulindac for the Prevention of Sporadic Colorectal Adenomas: A Randomized Placebo-Controlled, Double-Blind Trial

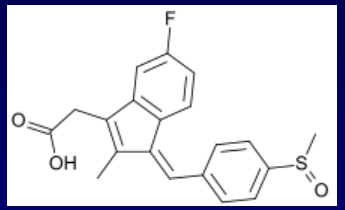
Frank L. Meyskens, Jr.,[1] Christine E. McLaren,[1] Daniel Pelot,[1] Sharon Fujikawa-Brooks,[1] Philip M. Carpenter,[1] Ernest Hawk,[9] Gary Kelloff,[9] Michael J. Lawson,[7] Jayashri Kidao,[3] John McCracken,[4] C. Gregory Albers,[1] Dennis J. Ahnen,[6] D. Kim Turgeon,[5] Steven Goldschmid,[2] Peter Lance,[2] Curt H. Hagedorn,[8] Daniel L. Gillen[1] and Eugene W. Gerner[2]

Eflornithine and Sulindac Effects on Polyamine Metabolism



Eflornithine (DFMO)

Sulindac



PPARγ

Ornithine

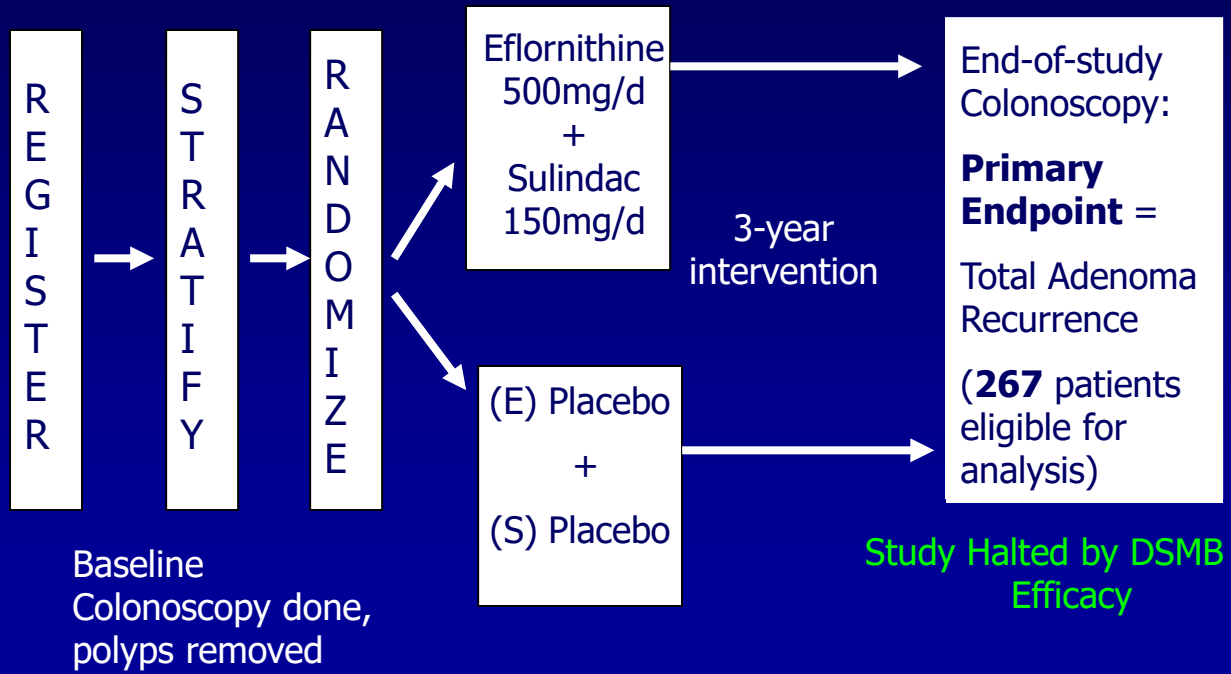
ODC

Polyamines

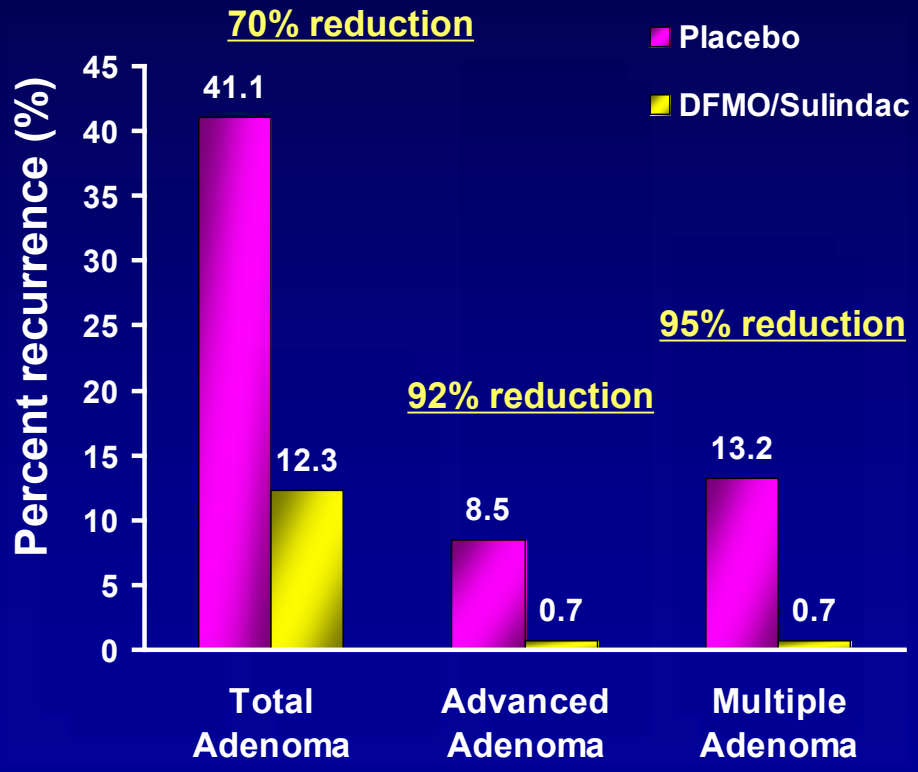
SSAT

Export

Secondary Prevention: UCI 02-06, Eflornithine/Sulindac vs. Placebo in Patients with Colorectal Adenomas



Marked Reduction of Adenomatous Polyps by Eflornithine + Sulindac vs. Placebo



Meyskens, FL, et al. *Cancer Prevention Research,* 2008;*1*:*9-11*

The Past: UCI/NCI Chemoprevention Consortium 2008-2013*

*NCI N01-CN-35160
PI: F Meyskens

The Effect of Difluoromethylornithine on Decreasing Prostate Size and Polyamines in Men: Results of a Year-Long Phase IIb Randomized Placebo-Controlled Chemoprevention Trial

Anne R. Simoneau,[2,4] Eugene W. Gerner,[5] Ray Nagle,[5] Argyrios Ziogas,[3,4] Sharon Fujikawa-Brooks,[4] Hagit Yerushalmi,[5] Thomas E. Ahlering,[2,4] Ronald Lieberman,[6] Christine E. McLaren,[3,4] Hoda Anton-Culver,[3,4] and Frank L. Meyskens, Jr.[1,4]

Research Article — Cancer Prevention Research

A Phase II Randomized, Controlled Trial of S-Adenosylmethionine in Reducing Serum α-Fetoprotein in Patients with Hepatitis C Cirrhosis and Elevated AFP

Timothy R. Morgan[1,2], Kathryn Osann[3], Teodoro Bottiglieri[4], Neville Pimstone[5], John C. Hoefs[6], Ke-Qin Hu[2], Tarek Hassanein[7], Thomas D. Boyer[8], Lorene Kong[9], Wen-Pin Chen[10], Ellen Richmond[11], Rachel Gonzalez[12], Luz M. Rodriguez[11,13], and Frank L. Meyskens[14]

Research Article — Cancer Prevention Research

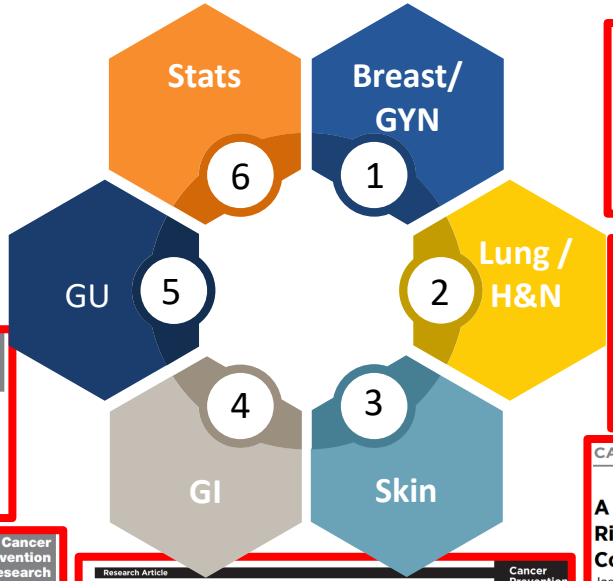
Phase IIa Clinical Trial of Curcumin for the Prevention of Colorectal Neoplasia

Robert E. Carroll[1], Richard V. Benya[1], Danielle Kim Turgeon[2], Shaiju Vareed[2], Malloree Neuman[3], Luz Rodriguez[4], Madhuri Kakarala[2,5], Philip M. Carpenter[2], Christine McLaren[6,7], Frank L. Meyskens, Jr[6], and Dean E. Brenner[2,3,5]

Brief Communication — Cancer Prevention Research

Phase IIA Trial Testing Erlotinib as an Intervention against Intraductal Pancreatic Mucinous Neoplasms

Steven Lipkin[1], John Lee[1], David Imagawa[1], Stephen M. Hewitt[2], Chris Tucker[3], Jason A. Zell[1], Vanessa Wong[1], Angela Garcia[1], Rachel Gonzalez[1], Gary Della Zanna[4], Ellen Richmond[4], L.M. Rodriguez[4], M. Bigg[5], F. Schnoll-Sussmans[6], and Frank Meyskens[1]



Research Article — Cancer Prevention Research

A Phase IIa Randomized, Double-Blind Trial of Erlotinib in Inhibiting Epidermal Growth Factor Receptor Signaling in Aberrant Crypt Foci of the Colorectum

Daniel L. Gillen[1,2], Frank L. Meyskens[2], Timothy R. Morgan[2,3], Jason A. Zell[2,4], Robert Carroll[5], Richard Benya[5], Wen-Pin Chen[2], Allen Mo[6], Chris Tucker[7], Asmita Bhattacharya[8], Zhiliang Huang[8], Myra Arcilla[8], Vanessa Wong[2], Jinah Chung[2], Rachel Gonzalez[2], Luz Maria Rodriguez[9,10], Eva Szabo[9], Daniel W. Rosenberg[6], and Steven M. Lipkin[8]

Research Article — Cancer Prevention Research
See related commentaries by Mulshine and Ondrey, p. 371 and by William and Papadimitrakopoulou, p. 375

Bowman Birk Inhibitor Concentrate and Oral Leukoplakia: A Randomized Phase IIb Trial

William B. Armstrong[1,2], Thomas H. Taylor[1,3,4], Ann R. Kennedy[5], Raymond J. Melrose[6], Diana V. Messadi[7], Mai Gu[8], Anh D. Le[9], Marjorie Perloff[10], Francisco Civantos[11], William Jarrard Goodwin[11], Lori J. Wirth[12], Alexander Ross Kerr[13], and Frank L. Meyskens Jr[1,14]

Research Article — Cancer Prevention Research

A Randomized, Double-Blind, Placebo-Controlled Phase II Clinical Trial of Lovastatin for Various Endpoints of Melanoma Pathobiology

Kenneth G. Linden[1,2], Sancy A. Leachman[6], Jonathan S. Zager[7], James G. Jakowatz[1], Jaye L. Viner[8], Christine E. McLaren[1,3], Ronald J. Barr[2], Philip M. Carpenter[1,4], Wen-Pin Chen[1], Craig A. Elmets[9], Joseph A. Tangrea[10], Sung-Jig Lim[11], Alistair J. Cochran[5], and Frank L. Meyskens Jr[1]

CANCER PREVENTION RESEARCH | RESEARCH ARTICLE

A Phase IIa Trial of Metformin for Colorectal Cancer Risk Reduction among Individuals with History of Colorectal Adenomas and Elevated Body Mass Index

Jason A. Zell[1,2,3], Christine E. McLaren[2,3], Timothy R. Morgan[4], Michael J. Lawson[5], Sherif Rezk[6], C. Gregory Albers[1], Wen-Pin Chen[3], Joseph C. Carmichael[7], Jinah Chung[3], Ellen Richmond[8], L.M. Rodriguez[8,9], Eva Szabo[10], Leslie G. Ford[8], Michael N. Pollak[10], and Frank L. Meyskens[1,3,11]

The Past: UCI Cancer Prevention Program

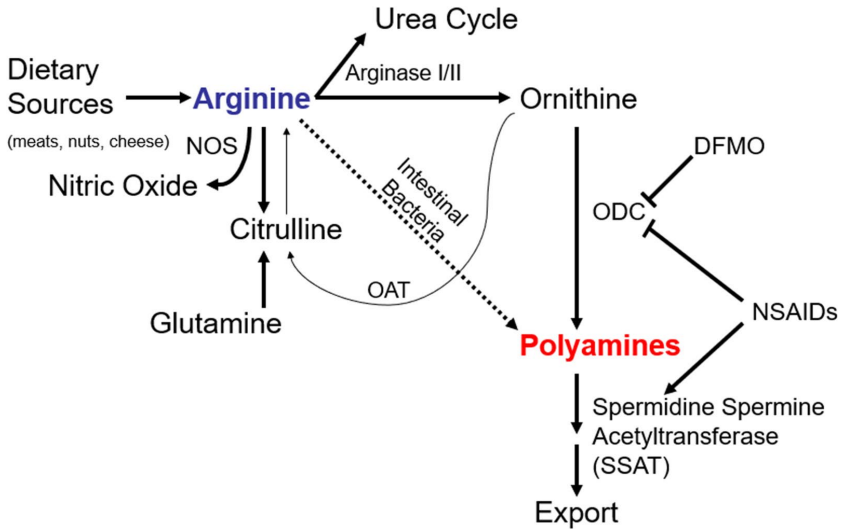
cancers

MDPI

Article

Phase IIa Clinical Biomarker Trial of Dietary Arginine Restriction and Aspirin in Colorectal Cancer Patients

Jason A. Zell [1,2,*], Thomas H. Taylor [3], C. Gregory Albers [4], Joseph C. Carmichael [5], Christine E. McLaren [2,6], Lari Wenzel [2,6] and Michael J. Stamos [5]

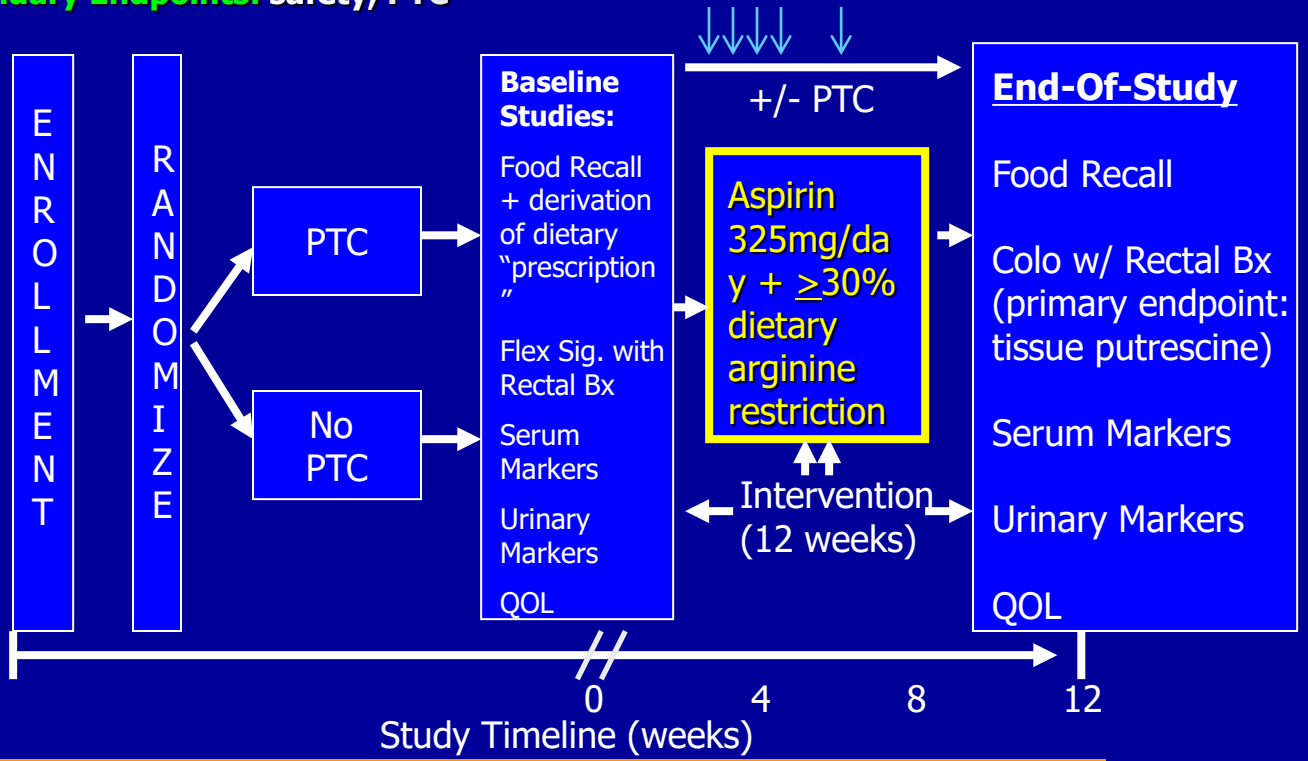


PI: Zell NIH-K23CA133142

Phase IIa clinical biomarker study, UC Irvine: Aspirin and arginine restriction in colorectal cancer patients

Eligibility: stage I-III colon or rectal cancer
Primary Endpoint: decrease tissue putrescine by >50%
Secondary Endpoints: safety, PTC

Accrual: 24



PI: J. Zell

Funding: NIH-NCI K23 CA133142, & ICTS via NCRR M01 RR00827

The Present

15 UCI faculty from the prior Chemoprevention Consortium remain active in research, along w/ new basic, translational, and clinical research faculty.

NCI-NCORP / SWOG Trial: S0820

"A Double Blind Placebo-Controlled Trial of Eflornithine and Sulindac to Prevent Recurrence of High Risk Adenomas and Second Primary Colorectal Cancers in Patients with Stage 0-III Colon or Rectal Cancer, Phase III"

SWOG Lead Investigator:

Jason Zell, DO, MPH
Division of Hematology/Oncology
Dept. of Medicine
School of Medicine
Chao Family Comprehensive Cancer Ctr
University of California, Irvine

SWOG co-PI: Powel Brown, MD, PhD
SWOG Lead Statistician: Joe Unger, PhD
SWOG co-I: Robert Krouse, MD

NCTN co-PI's:

Raymond Bergan, MD (ECOG-ACRIN)
Jennifer Dorth, MD (NRG)
Y. Nancy You, MD (ALLIANCE)

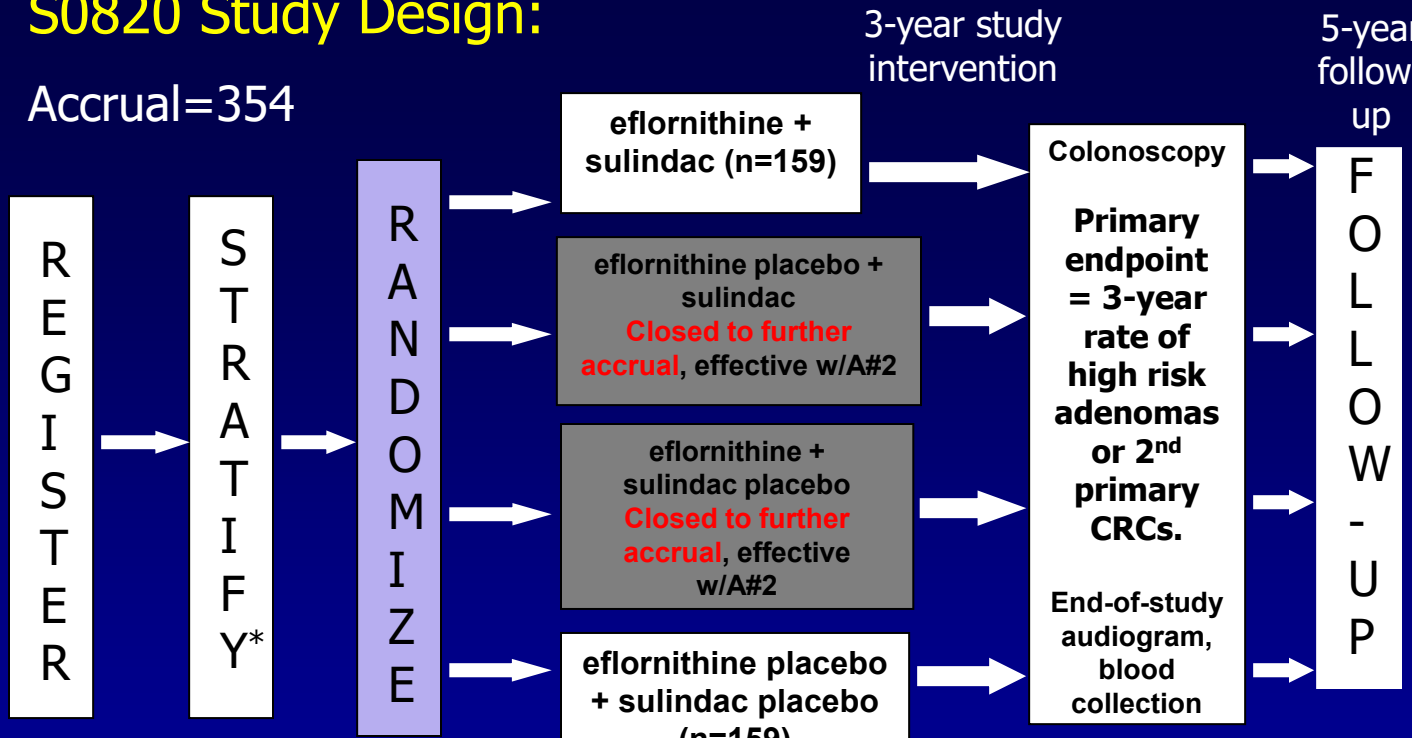
Funding:
1) NCI-NCORP
2) NCI 1R50CA285412-01 (PI: Zell)

S0820 Primary Objective: to assess whether the polyamine-inhibitory combination: eflornithine 500 mg/d and sulindac 150 mg/d (vs. placebos) are effective in reducing the 3-year rate of high-risk adenomas or 2nd primary CRCs in stage 0, I, II, and III colon and rectal cancer patients.

- Primary Endpoint:
  - High risk adenomas (HRA)
    - high-grade dysplasia
    - villous features
    - size ≥ 1 cm
    - Multiple (3 or more) adenomas
  - Second Primary Colorectal Cancers (SPCRC)

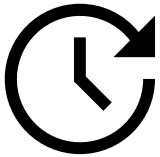
Goal is a 50% *(proposed: 60%) reduction in HRAs or SPCRCs at 3 years for combination E+S vs. combination placebos

S0820 Study Design:



Passed the Single Planned Interim Analysis (for futility): May 2023
Accrual: March 2013 to June 2023

The Future



UC Irvine as Affiliate Organization (AO), U. Arizona-NCI Cancer Prevention Clinical Trials Network (UA-CP-CTNet)

UCI-AO Site PI: J. Zell (1R50CA285412-01)

UA CP-CTNet OBJECTIVES

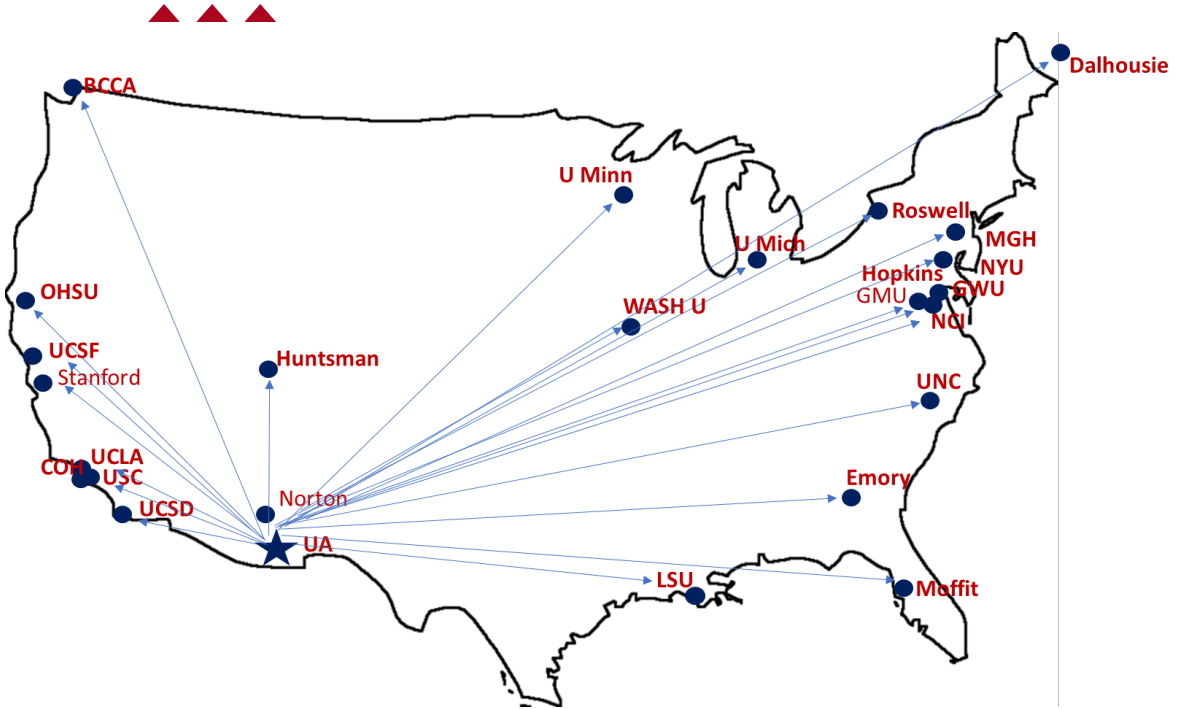
- To design and conduct Phase 0/I/II clinical trials to assess the cancer preventive potential of repurposed drugs, nutraceutical agents, regional/topical drug delivery, alternative dosing regimens, and immune modulators.
- To characterize the clinical activity and biological effects of putative cancer preventive agents.
- To develop further scientific insights into the mechanisms of cancer prevention by the agents studied and to develop novel potential markers as determinants of response and for selecting subpopulations who may differentially benefit from the studied agent.

UA CP-CTNet

LAO: University of Arizona

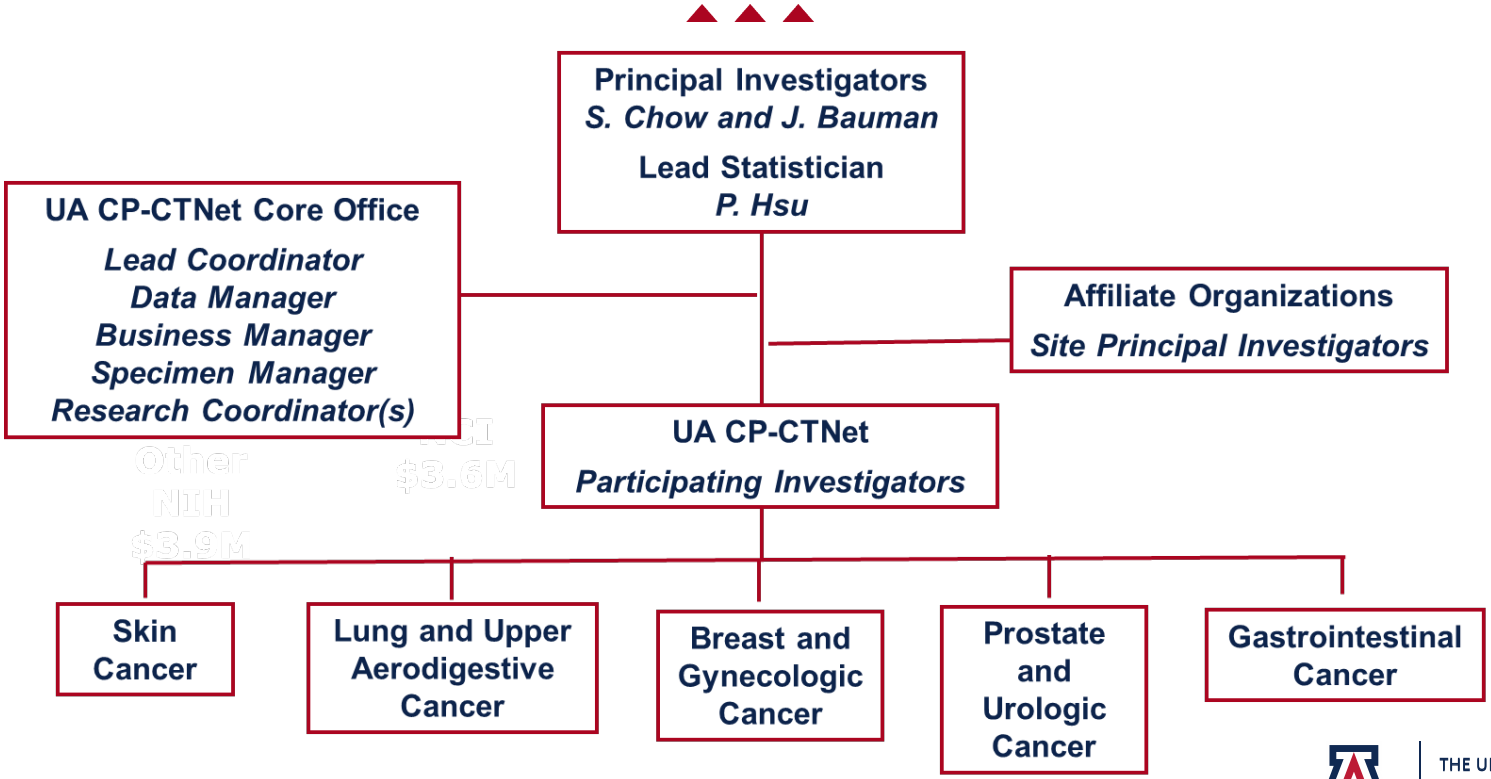
AOs:

- **British Columbia Cancer Agency**
- City of Hope
- **Dalhousie University**
- **Emory University**
- Huntsman Cancer Institute
- George Mason University
- **George Washington University**
- **Johns Hopkins University**
- **Louisiana State University**
- **Massachusetts General Hospital**
- **Moffitt Cancer Center**
- **NCI Clinical Center for Cancer Research**
- **New York University**
- Norton Thoracic Institute
- **Oregon Health & Science University**
- **Roswell Park Cancer Institute**
- Stanford University
- **University of California Los Angeles**
- **University of California San Diego**
- **University of California San Francisco**
- **University of Michigan**
- **University of Minnesota**
- **University of North Carolina**
- **University of Southern California**
- **Washington University**



THE UNIVERSITY OF ARIZONA Cancer Center

ORGANIZATIONAL STRUCTURE



THE UNIVERSITY OF ARIZONA Cancer Center

Current UA CP-CTNet Studies

Protocol	Target Organ	Study Cohort	Agent	Study Site
UAZ20-01-01	Prostate	PCa patients scheduled for prostatectomy	Apalutamide	UA USC Hopkins NCI Clinical Center GWU
UAZ20-01-02	HPV-associated cancers	Healthy teens	N/A; Follow-up on immune response after delayed Gardasil 9 booster	UA UCLA
UAZ20-BIO-01	Skin	Specimens representing melanoma progression (BN, DN, MM)	N/A; Molecular biomarker development	UA
UAZ21-06-01	Lung & upper aerodigestive tract	Current heavy smokers	Broccoli seed & sprout extract	UA Roswell GWU

Current UA CP-CTNet Studies

Protocol	Target Organ	Study Cohort	Agent	Study Site
UAZ21-07-01	Oral	Patients with oral leukoplakia	Metformin	UA UCSD Dalhousie BCCA U Minnesota U Michigan NYU LSU Moffit Emory ~~City of Hope~~
INT21-05-01	GI	Lynch syndrome	TriAd 5 (CEA/MUC1/Brachyury) N-803 (IL15 superagonist)	UA ~~Huntsman~~ NCI Clinical Center

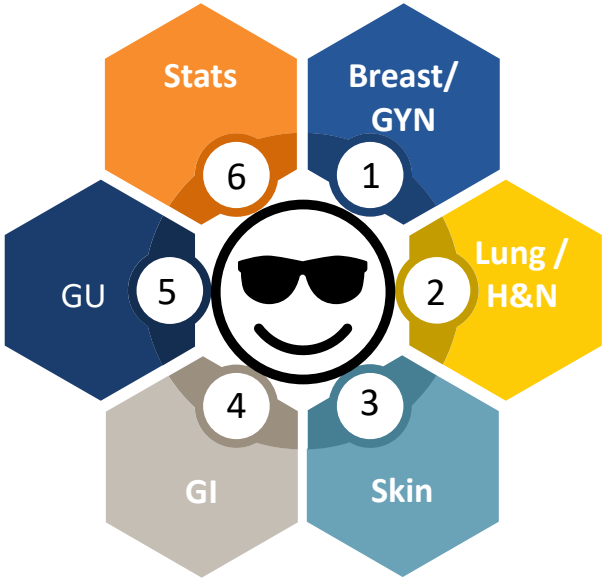
UA-CP-CTNet Affiliate Organization: UC Irvine

Opportunities: 1) Open Phase 0/I/II cancer prevention clinical trials at UCI across all major disease sites
2) Compete as PI for quarterly RFA's, leveraging the 25-site consortia for accruals
3) Develop translational research aims for emerging early phase cancer prevention clinical trials

Statistics
Christine McLaren, PhD
Wen-Pin Chen, MS
Thomas H. Taylor, PhD

Genitourinary
Arash Rezazedeh, MD (Med Onc)
Nataliya Mar, MD (Med Onc)
Xiolin Zi, PhD (Basic Science)

Gastrointestinal
William Karnes, MD (Gastroenterology)
Joseph Carmichael, MD (Colorectal Surgery)
Valerie Vilchez, MD (Colorectal Surgery)
Matthew Whealon, MD (Colorectal Surgery)
Jason Zell, DO (Medical Oncology)



Breast/Gyn
Kiran Clair, MD (GynOnc)
Ritesh Parajuli, MD (Med Onc)
Sayeh Lavasani, MD (Med Onc)

Lung/Head-Neck
Ann Arter, MD (Med Onc)
Shirin Attarian, MD (Med Onc)

Skin Cancer
Kristen Kelly, MD (Dermatology)
Warren Chow, MD (Med Onc)

UCI 趙 Chao Family Comprehensive Cancer Center

Questions?

UCI Chao Family Comprehensive Cancer Center
2024 Scientific Retreat

Pegaspargase Therapy in Acute Lymphoblastic Leukemia (ALL): Therapeutic Drug Monitoring and Toxicity

Van Huynh, MD

Director, Leukemia Program

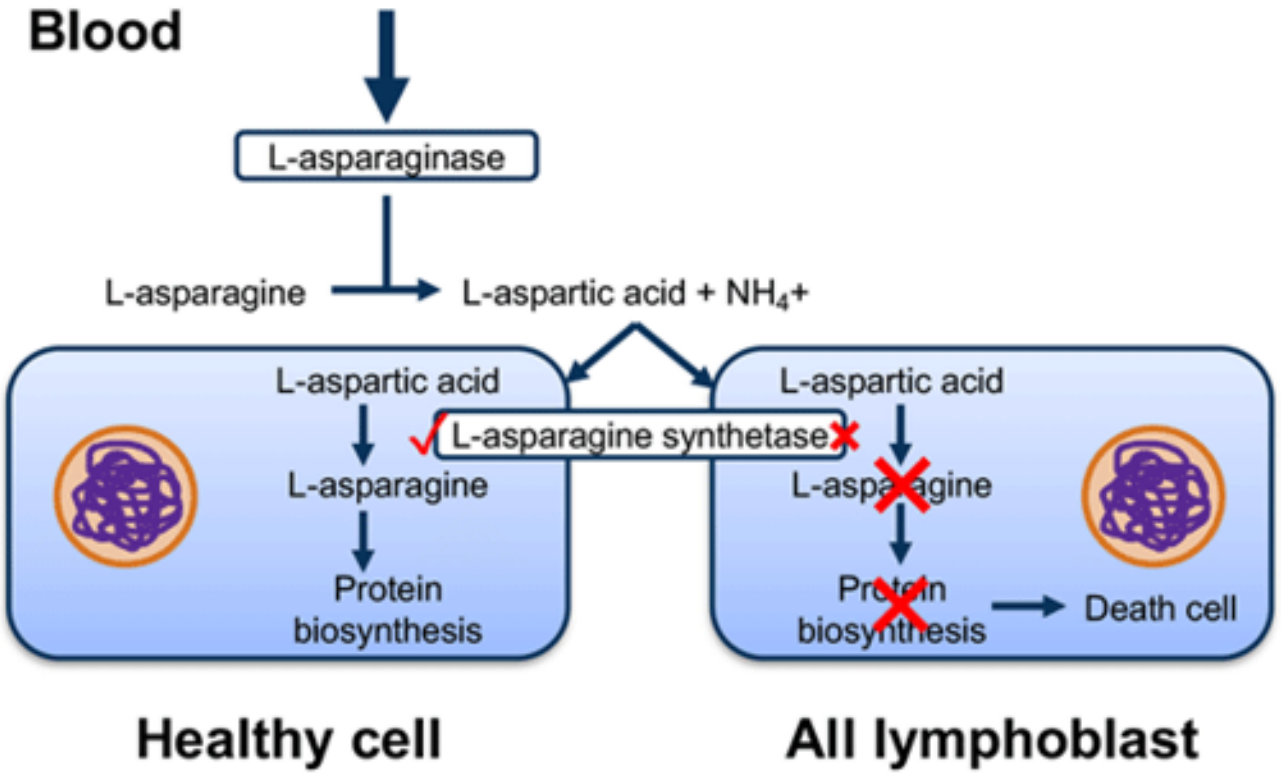
Section Director, CAR T-Cell Program

CHOC Children's Hospital

11/8/2024

Anti-leukemic Affects of Asparaginase

- Children with ALL have overall survival rates >90% versus ~50% in adults
- Asparaginase is key component of pediatric/adolescent ALL therapy
  - 2 to 7 doses given over 2.5 years
  - Levels ≥ 0.1 IU/mL are therapeutic
- Asparaginase high incidence of toxicities and allergic reactions



Multicenter Study to Assess Asparaginase-related Hypersensitivity and Toxicity in Multi-Ethnic Population

- Evaluate pharmacokinetic profile of asparaginase levels at 7 and 14 days after Pegaspargase (PEG)
- Determine if PEG levels vary with obesity, sex, age, race/ethnicity, leukemia type
- Evaluate the incidence of hypersensitivity reactions (HSR) and toxicities related to PEG
- Genome-wide association study (GWAS) to identify pharmacogenomic markers associated with hypersensitivity and Grade ≥3 toxicities

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Results - Demographics

- 358 doses of PEG were administered to 144 patients
- Mean was 8.6 yrs (range 1.1-23.9)
- 61.8% males
- 52.5% Hispanic
- 32.6% obese/overweight
- Hispanic patients more likely to be obese 24.7% vs 10.6% Non-Hispanics

Characteristic	*participants N=144*
Demographics	
Age at diagnosis, years	*7.4 [3.6, 12.1]*
Age at diagnosis ≥ 10 years	*52 (36.1%)*
Gender, male	*89 (61.8%)*
Race/Ethnicity, Hispanic	*73 (52.5%)*
BMI (kg/m^2)	*19.3 (5.6)*
BMI percentile	
Underweight	*10 (6.9%)*
Normal	*87 (60.4%)*
Overweight	*19 (13.2%)*
Obese	*28 (19.4%)*
Clinical status	
B-cell ALL	*125 (86.8%)*
CNS Involvement, CNS1	*118 (82.5%)*
NCI Risk Group, high risk	*52 (36.1%)*
Down Syndrome	*9 (6.3%)*
MRD (day 29) <0.01%	*112 (78.9%)*

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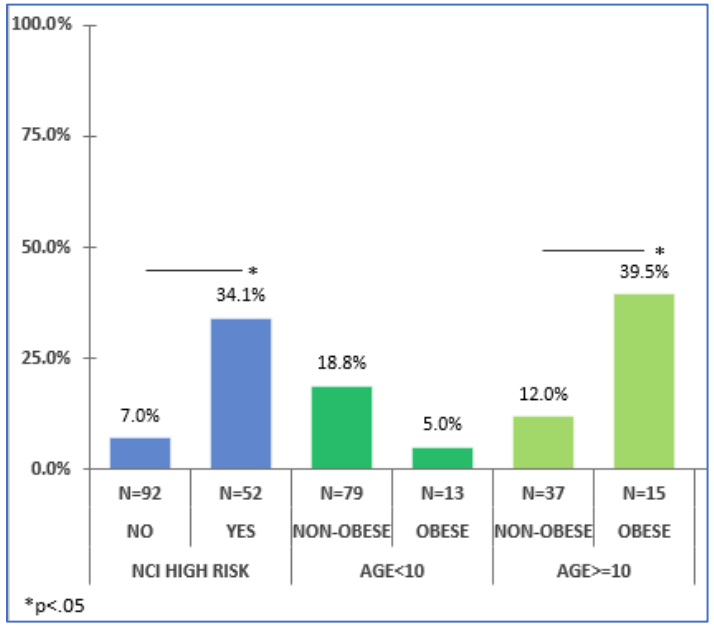
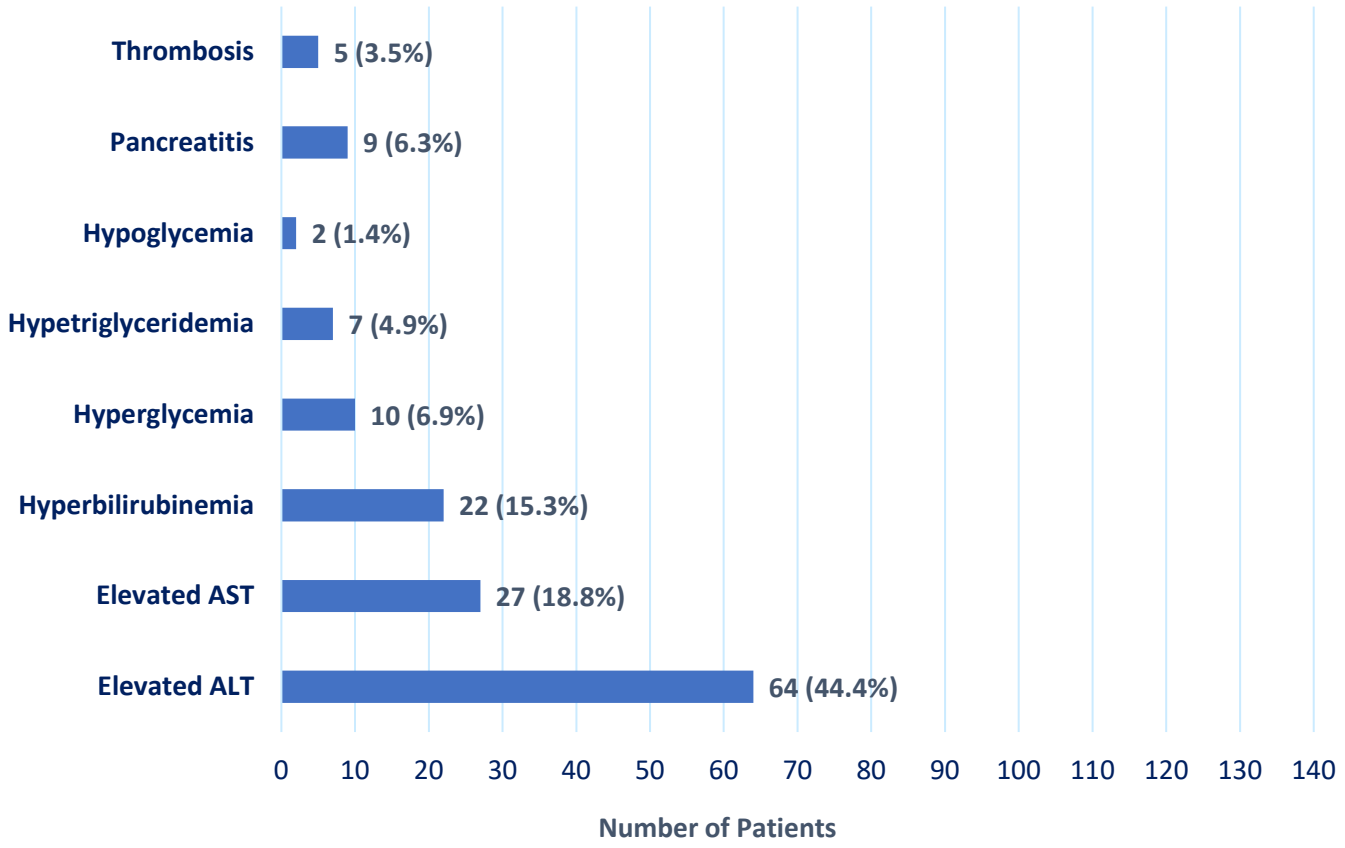
Characteristics associated with increased odds of hypersensitivity reaction (HSR) to PEG

- Incidents of HSR was 19.4% (28 of 144 patients)
- Mean age with HSR 10.5 years
- Fifteen (53.6%) were Hispanic and 10 (35.7%) were obese
- In the bivariate analysis: the likelihood of HSR was increased with obesity (p=0.020), older age ≥10 years (p= 0.036), NCI HR (p=0.013) and non B-ALL



Characteristics	Bivariate	Multivariable
	OR (95% CI), p-value	OR (95% CI), p-value
Sex (Female vs. Male)	1.06 (0.45, 2.49), p=.894	----
Ethnicity (Hispanic vs. Non-Hispanic)	1.30 (0.54, 3.09), p=.556	----
Age at diagnosis (≥10 vs. <10 yrs)	2.47 (1.06, 5.75), **p=.036**	0.41 (0.10, 1.59), p=.195
Obesity (Obese vs. Non-obese)	3.03 (1.20, 7.68), **p=.020**	1.78 (0.40, 7.83), p=.446
CNS status at diagnosis (1 vs. 2 or 3)	0.56 (0.20, 1.51), p=.246	----
NCI risk stratification at diagnosis (High vs. Standard Risk)	2.96 (1.26, 6.95), **p=.013**	6.89 (1.82, 26.13), **p=.005**
B-cell ALL (Y vs. N)	0.35 (0.12, 0.99), **p=.048**	0.29 (0.06, 1.50), p=.139
Time after pre-medication to start PEG infusion (<60 vs. >=60 minutes)	1.51 (0.64, 3.56), p=.344	2.53 (0.87, 7.41), p=.088

Grade 3-4 (severe) PEG-Associated Toxicities



- Toxicities were observed in 41% of patients (59 of 144 pts)
- Most common was liver toxicity (elevated ALT)
- Pancreatitis occurred in 9 patients (6.3%) and all were Hispanics
- The risk factor for PEG-associated toxicity was older age $\geq$ 10 years (OR=2.75 (95% CI 1.31, 5.77), p=.008

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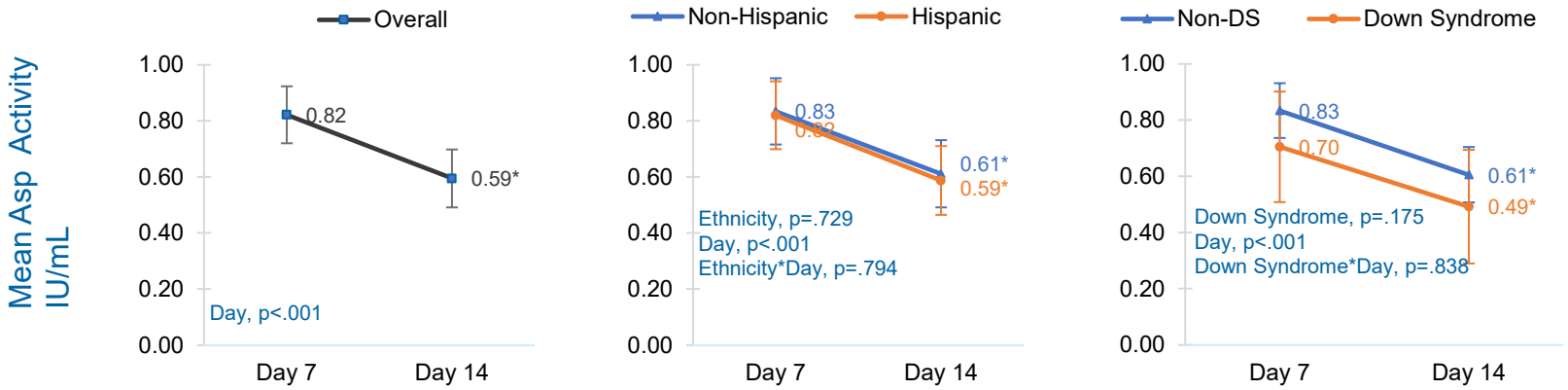
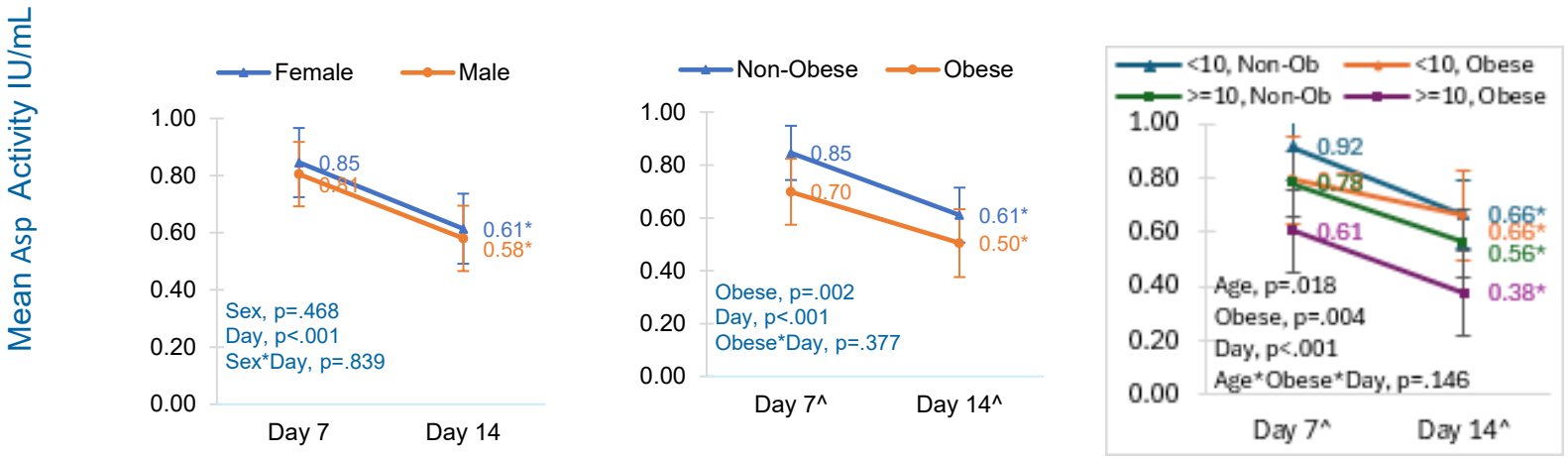
Mean asparaginase activity (AA) levels at Day 7 and 14 after PEG administration by demographic characteristics





- The mean AA levels:
  - Day 7 = 0.82 IU/mL
  - Day 14 = 0.59 IU/mL
- In general – levels are supratherapeutic (need AA >0.1 IU/ml to be effective)

GWAS to identify Pharmacogenetic Markers associated with PEG-related Hypersensitivity and Toxicities

- Abstract: 208260 – 66th ASH meeting in San Diego (Dec 2024)
- Collaboration with Drs. Jatinda Lamba and Vivek Shastri at Univ of Florida
- Infinium GSA-24 v3.0 was used to genotype 650,000 single nucleotide polymorphisms (SNPs) and post standard QC, 233,798 SNPs were tested
- Confirmed SNPS reported in literature

- **Identified novel, unique markers not previously reported**
- 72 SNPs in 59 genes associated with PEG-related hypersensitivity
  - PRKCE, ALX4, STAG1, DAB1, MPK10
- 75 SNPs in 64 genes were associated with PEG-toxicities
  - SPRY4, PALM2-AKAP2 fusion gene, and ALK

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GWAS in Hispanic Population

Hypersensitivity: Adjusted for Hispanic race/ethnicity

- 34 SNPs in 30 genes were associated with hypersensitivity ($p < 0.001$)
- SNPS included: ITPR2, ABHD6, ST6GAL2, RORA, and PAPSS1

Toxicities: Adjusted for Hispanic race/ethnicity

- 25 SNPs in 24 genes were associated with any grade >3 toxicity ($p < 0.001$)
- SNPs included: KCNN2, KCNH5, CLASP1, PON2, WWOX, STIM1, IQCE, and FUT10

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Summary

- 19.4% of patients experienced HSR to PEG therapy
- Risk factors for HSR include age ≥ 10, obesity, NCI HR and non B-ALL. In patients ≥ 10, obesity amplified their risk for HSR.
- A high number of patients (41%) experienced severe PEG-associated toxicity; older age increased the risk for toxicity
- Mean AA levels exceeded the level needed to be therapeutic
- We identified novel, unique SNPs not previously reported that are associated with HSR and toxicities
- Additional studies are warranted to determine whether sequencing can identify populations at risk for HSR and toxicities and can benefit from dose reductions of PEG to minimize toxicity

CHOC

Thank You

- CHOC Children's Hospital
  - Sonia Morales, MD
  - Keri Zabokrtsky, MS
  - Carol Lin, MD
  - Tricia Morphew
- Cincinnati Children's Hospital
  - Christine Phillips, MD
- UCSF Benioff Children's Hospital
  - Beth Winger, MD
- UCSF – Oakland Children's
  - Anu Agrawal, MD
- Lucille Packard – Stanford Children's
  - Catherine Aftandilian, MD
- Kansas - Mercy Children's
  - Keith August, MD
  - Erin Guest, MD
- Lamba Lab – University of Florida
  - Jatinder Lamba, PhD
  - Vivek Shastri, PhD
- Funding
  - CHOC PSF Tithe Grant, CHOC Hyundai Cancer Institute Research Grant, Servier Pharmaceuticals

Thank you to our patients and families

Contact: Van Huynh / vahuynh@choc.org



CHOC
UCI Health

Regulatory T Cells in GVL and GVHD Post-Allogenic Stem Cell Transplant for High-Risk Acute Leukemia.

11-08-2024

Rishi Chavan MD



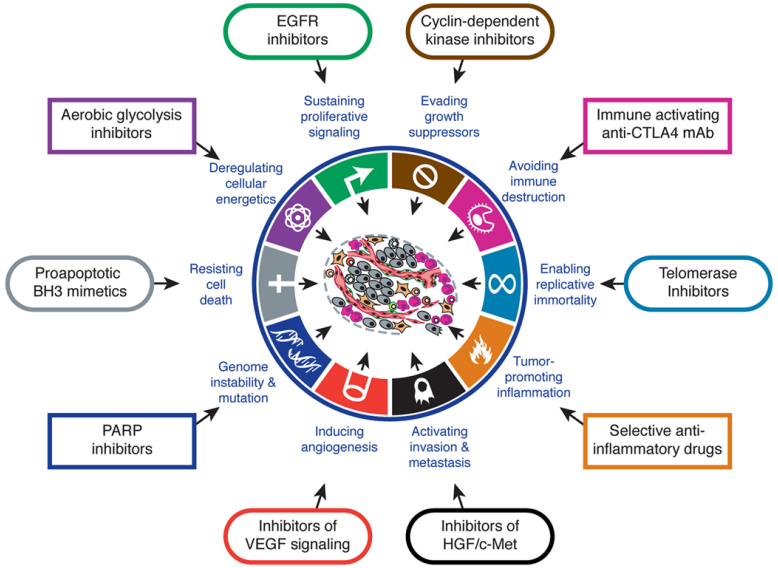
Disclosures

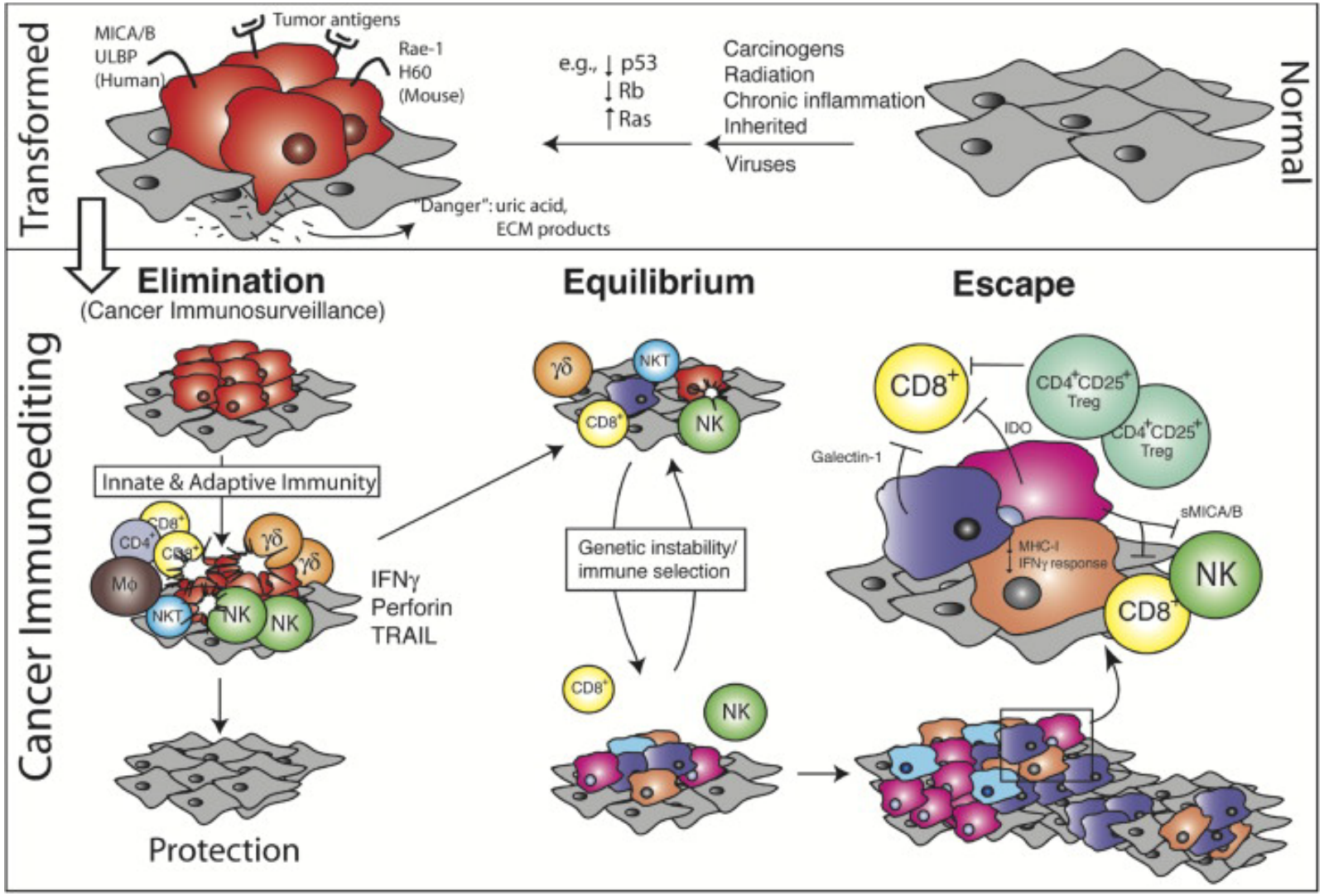
- None

Learning Objectives

- Why certain patients may respond to cancer immunotherapies while others may not.
- The story of Tregs.
- Explore the clinical possibilities of Treg surveillance and optimization in treating cancer and other auto immune conditions.

Is cancer a failure of our Immune system?

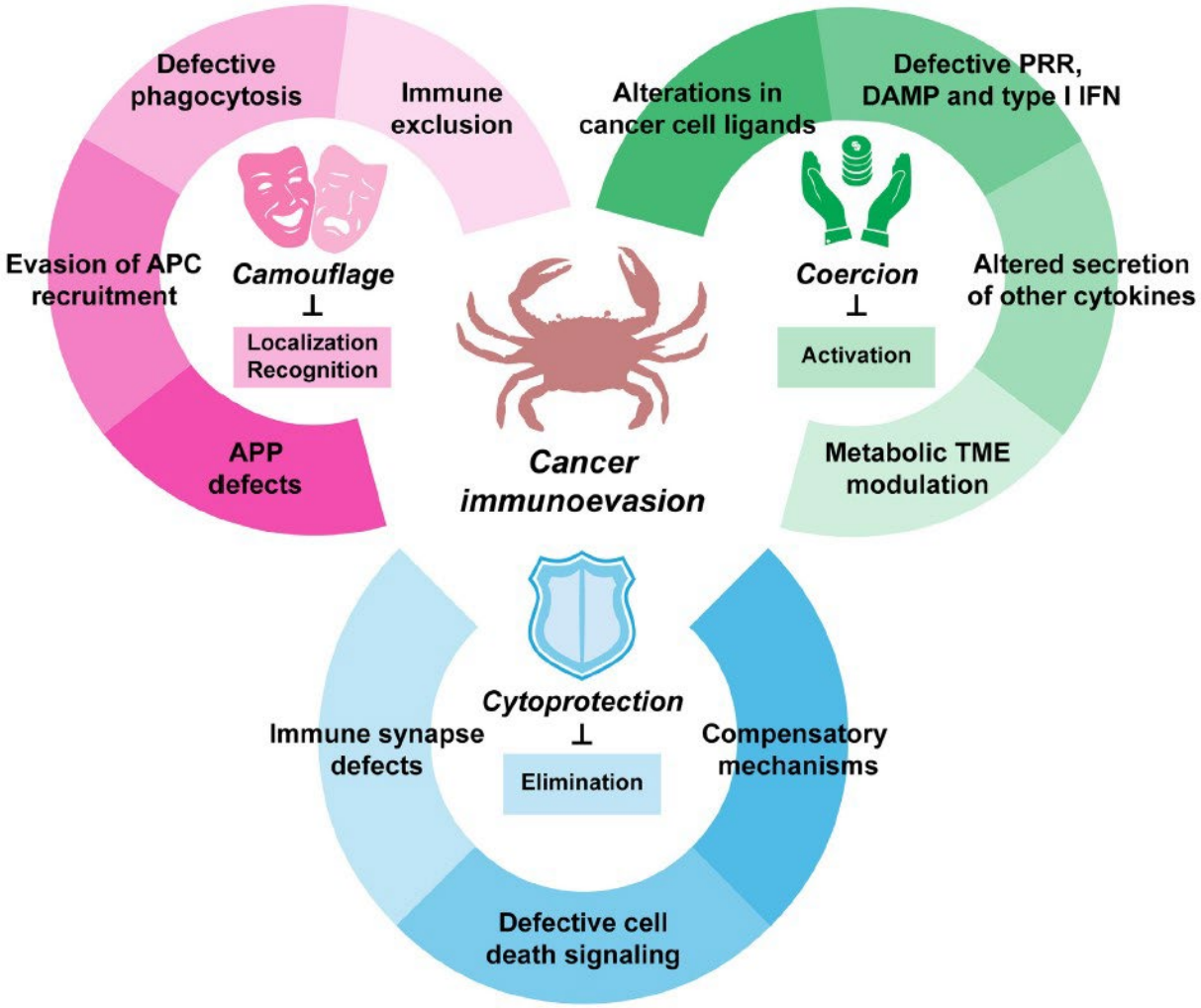




Douglas Hanahan, Robert A. Weinberg et al. **Hallmarks of Cancer: The Next Generation**, Cell 2011

Dunn G et al. **The Immunobiology of Cancer Immunosurveillance and Immunoediting** *Immunity, 2004*

Is cancer a failure of our Immune system?



Three Es model, the host immune system

- eliminates malignant cell precursors and
- contains microscopic neoplasms in a dynamic equilibrium,
- preventing cancer outgrowth until neoplastic cells acquire genetic or epigenetic alterations that enable immune escape.

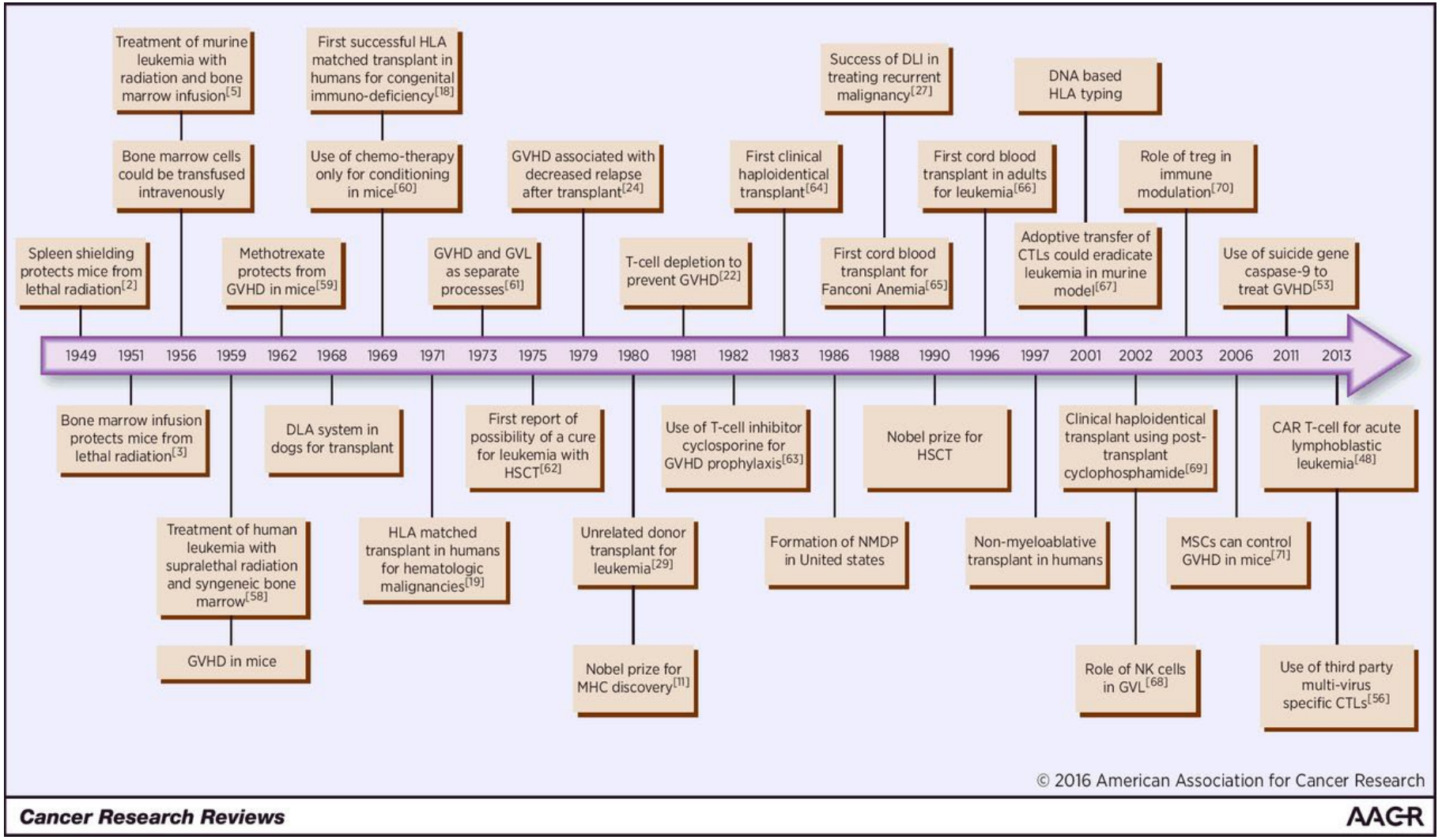
This immune evasive phenotype originates from various mechanisms that can be classified under a novel "three Cs" conceptual framework:

(1) camouflage, which hides cancer cells from immune recognition,
(2) coercion, which directly or indirectly interferes with immune effector cells,
(3) cytoprotection, which shields malignant cells from immune cytotoxicity.

Blocking the ability of neoplastic cells to evade the host immune system is crucial for increasing the efficacy of modern immunotherapy and conventional therapeutic strategies that ultimately activate anticancer immunosurveillance.

Galassi et al., ***The hallmarks of cancer immune evasion***, Cancer Cell (2024)

Allogenic SCT → Autologous CAR T cells → *Allogenic (Donor derived) CAR T cells*



What we:

Want

- Sustained GVL

Don't want

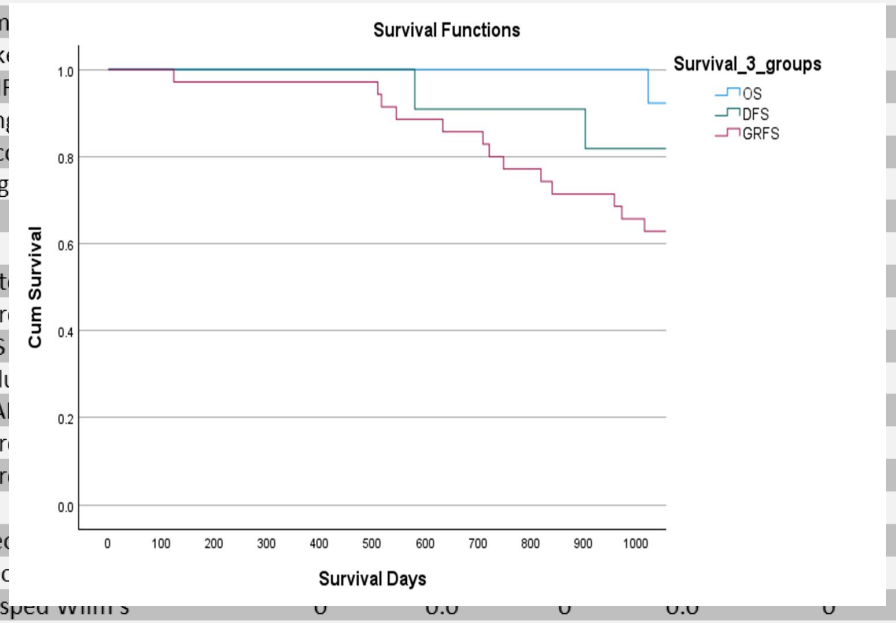
- Severe GVHD
- Infections
- Organ toxicity

Cancer Res. 2016;76(22):6445-6451.
doi:10.1158/0008-5472.CAN-16-1311

CHOC Stem cell transplant and cellular therapy program 2019-2023

Demographics

	ALLO (N=30)		ALLO-HID (N=45)		ALLO-HID Boost (N=2)		AUTO (N=41)		Auto Boost (N=8)		CAR-T (N=20)		ALLO-Unrelated (N=9)		UCBT (N=1)	
CY	N	%;range	N	%;range	N	%;range	N	%;range	N	%;range	N	%;range	N	%;range	N	%;range
2019	6	20.0	12	26.7	0	0	6	14.6	1	12.5	0	0	3	33.3	1	100
2020	5	16.7	6	13.3	0	0	8	19.5	2	25	3					
2021	6	20.0	9	20.0	1	50	6	14.6	1	12.5	5					
2022	8	26.7	6	13.3	0	0	17	41.5	2	25	9					
2023	5	16.7	12	26.7	1	50	4	9.8	2	25	3					
Age	7.7	0.09-21	7.7	0.64-26	15	2.2-17.5	4	0.42-23	4	1.8-17	15					
ALL	7	23.3	17	37.8	1	50	0	0.0	0	0	20					
AML	5	16.7	13	28.9	1	50	0	0.0	0	0	0					
ATRT	0	0.0	0	0.0	0	0	7	17.1	1	12.5	0					
Beta Thalassemia	0	0.0	1	2.2	0	0	0	0.0	0	0	0					
Bone Marrow Failure	0	0.0	1	2.2	0	0	0	0.0	0	0	0					
CGD	1	3.3	0	0.0	0	0	0	0.0	0	0	0					
Diam																
Dysk																
ETMF																
Ewing																
Fanc																
Gang																
HD																
HLH																
Hunt																
Marr																
MDS																
Medu																
MPAI																
Neur																
Neur																
NHL																
Oste																
Pinec																
Relapsed Wilm's																
SAA	5	16.7	1	2.2	0	0										
SCIDS	3	10.0	0	0.0	0	0										
Sickle Cell Disease	1	3.3	1	2.2	0	0										
Wiskott-Aldrich	1	3.3	0	0.0	0	0	0	0.0	0	0	0	0	0	0.0	0	0



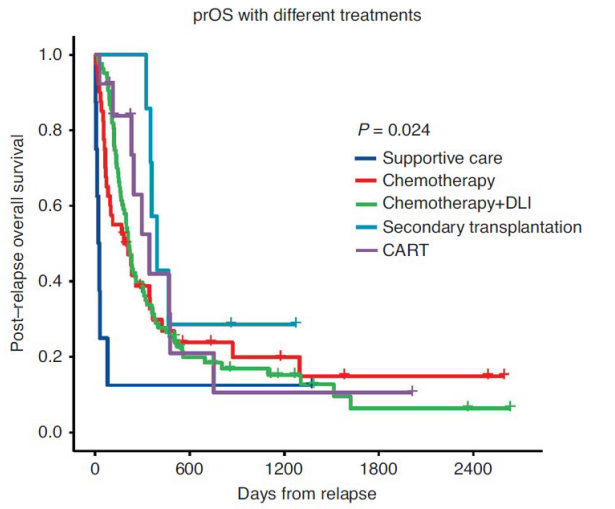
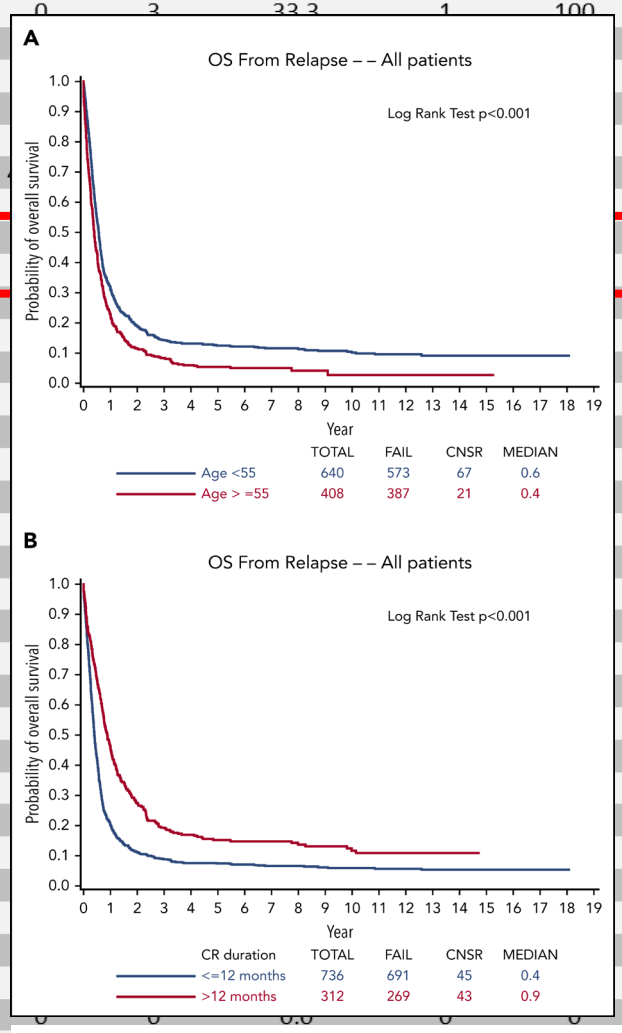


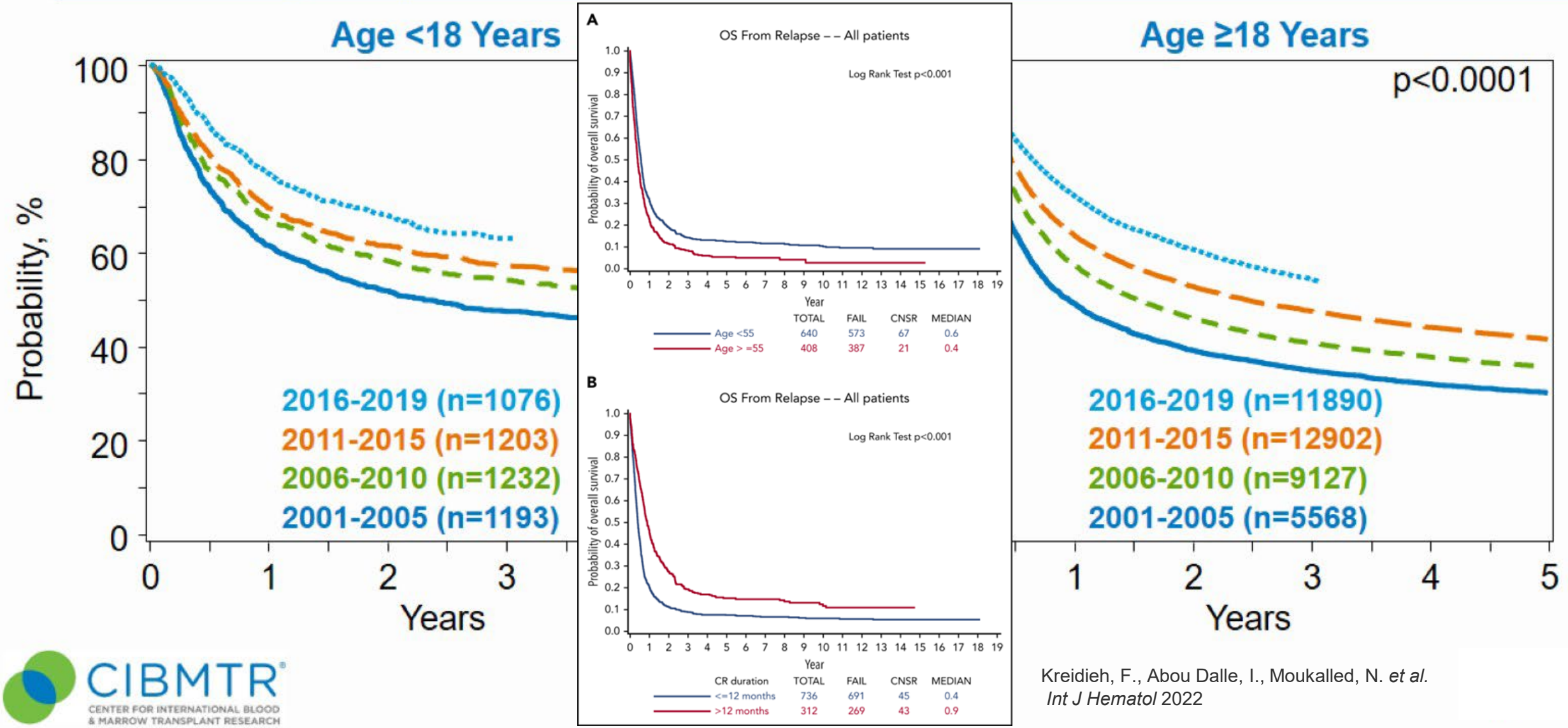
Fig. 4 Post-relapse OS with different treatments. prOS post-relapse overall survival, DLI donor lymphocyte infusion, CART chimeric antigen receptor T cells.

Gao, Y., Wu, H., Shi, Z. *et al. Bone Marrow Transplant* 2023



Kreidieh, F., Abou Dalle, I., Moukalled, N. *et al. Int J Hematol* 2022

Trends in Survival after Allogeneic HCTs for Acute Myelogenous Leukemia (AML), in the US, 2001-2019



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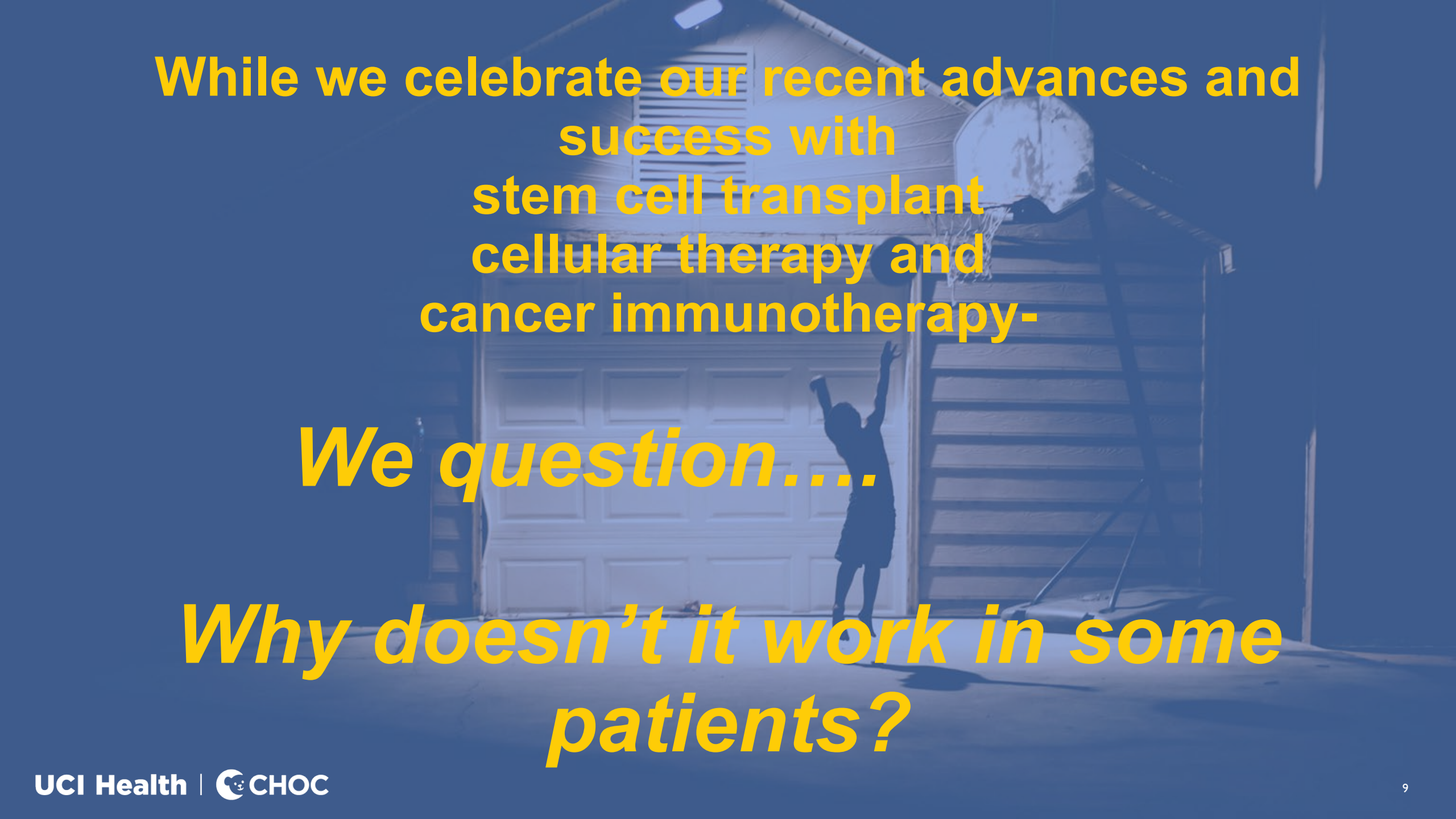
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Kreidieh, F., Abou Dalle, I., Moukalled, N. *et al.* *Int J Hematol* 2022



While we celebrate our recent advances and success with stem cell transplant cellular therapy and cancer immunotherapy-

We question….

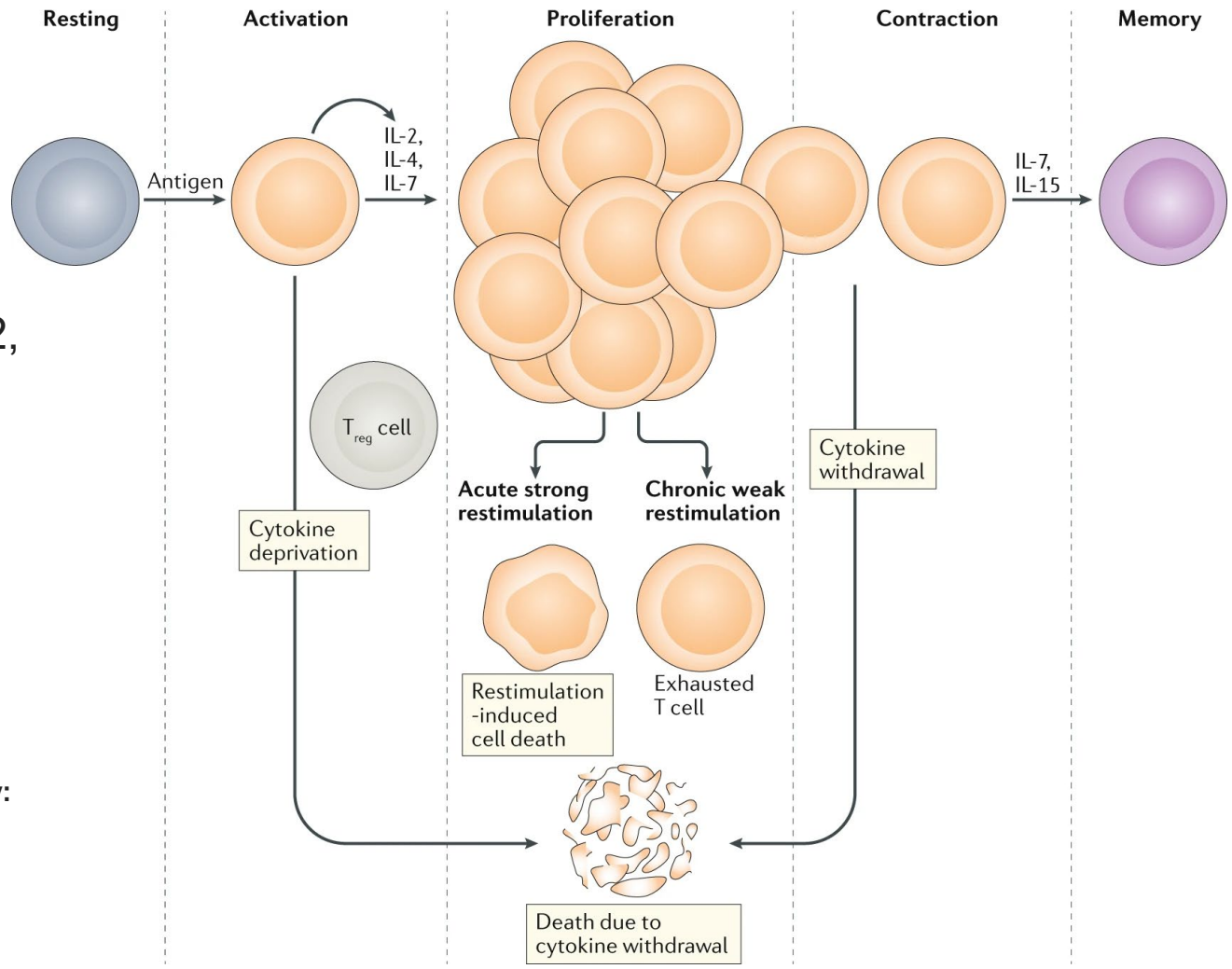
Why doesn't it work in some patients?

T cell primer

Resting T cells become activated after stimulation by cognate antigen in the context of an antigen-presenting cell and co-stimulatory signals.

Activated T cells produce and consume proliferative/survival cytokines, for example, IL-2, IL-4 and IL-7, and begin to expand in number.

If $CD4^+CD25^+$ regulatory T (T_{reg}) cells are present, they can deprive the cycling T cells of proliferative/survival cytokines, especially IL-2, causing them to undergo apoptosis.

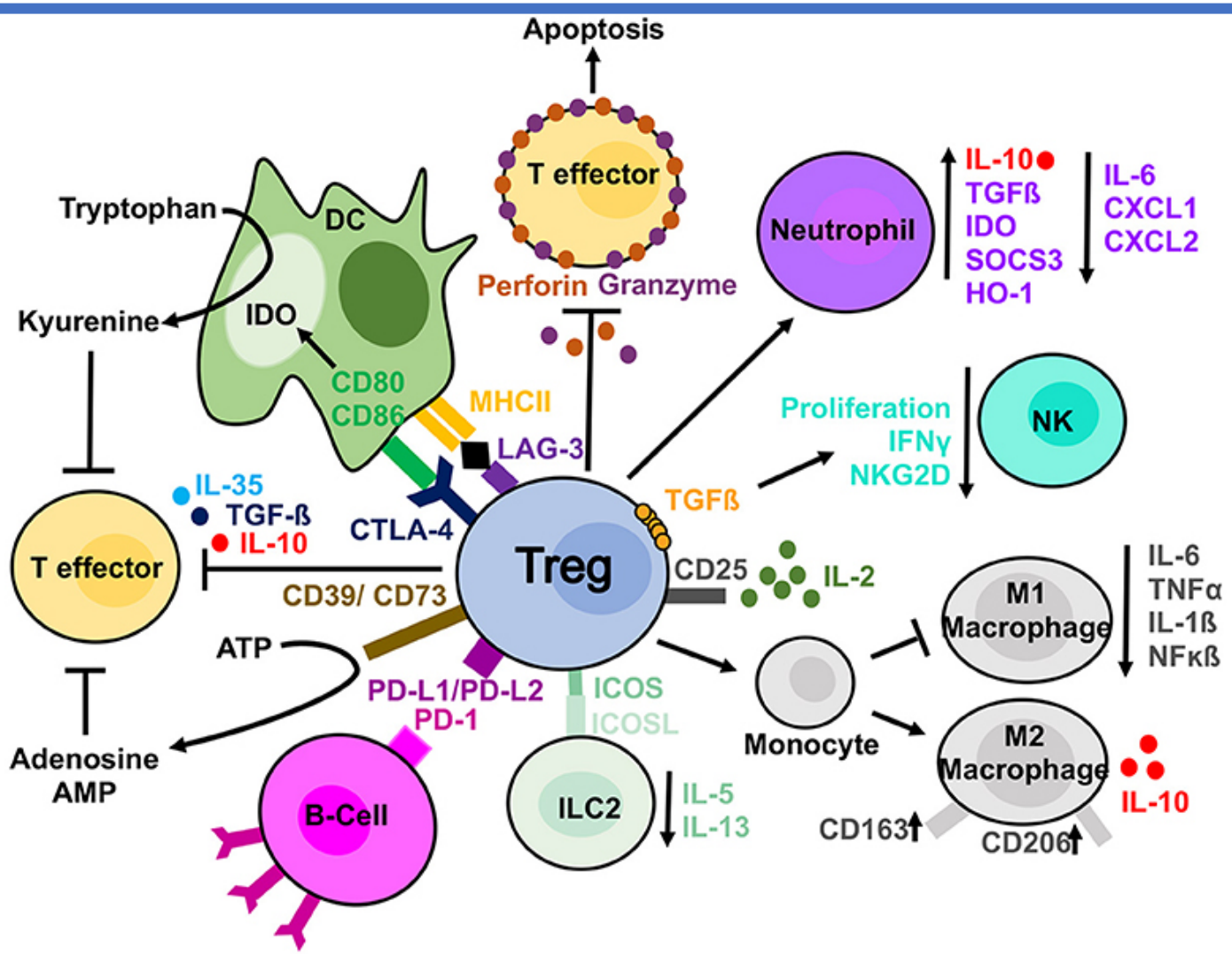


Waldman, A.D., Fritz, J.M. & Lenardo, M.J. **A guide to cancer immunotherapy: from T cell basic science to clinical practice.** *Nat Rev Immunol* **20**, 651–668 (2020).

Currently we have 15 patients and 14 related donors enrolled

Patient / Recipient				Donor			Transplant					GVHD			
Patient ID	Age	Gender	Diagnosis (R/R Leukemia)	Age (yrs)	Gender	Relation to patient	HLA match	Stem cell source	Conditioning Regimen	GvHD prophylaxis	Day of ANC engraft-ment	GVHD	Day of GVHD start	Relapse	Day of Significant infection (+)
CHOC_001	18 y.o	F	VHR B Cell ALL	20	M	Brother	Haplo	Bone Marrow	CY / TBI	ptCY, Tacro, MMF	19	No		No	61
CHOC_002	13 months	F	AML	41	M	Father	Haplo	Bone Marrow	BU/FLU/CY	ptCY, Tacro, MMF	14	Grade 1 (skin)	78	No	11
CHOC_003	19 y.o	F	AML	21	F	Unrelated	MUD 9/10	Peripheral Blood	BU/FLU/CY	ptCY, Tacro, MMF	16	No		No	104
CHOC_004	15 y.o	F	VHR B Cell ALL	19	M	Brother	Haplo	Bone Marrow	CY / TBI	ptCY, Tacro, MMF	17	Grade 1 (skin)	16	No	25
CHOC_005	5 y.o	F	AML	45	M	Father	Haplo	Bone Marrow	Ritux/BU/FLU/CY	ptCY, Tacro, MMF	13	Grade 2 (skin), Grade 3 (liver)	85 / 90	No	10 / 139
CHOC_006	11 y.o	M	VHR B Cell ALL	42	M	Father	Haplo	Peripheral Blood	TestB / CY / TBI	ptCY, Tacro, MMF	14	Grade 3 (skin)	130	No	10
CHOC_007	17 y.o	M	VHR B Cell ALL	43	M	Father	Haplo	Bone Marrow	BU/FLU/TT	ptCY, Tacro, MMF	No	No		Yes	21
CHOC_008	17 y.o	F	AML	21	M	Brother	MRD	Bone Marrow	BU/CY	MiniMTX	13	Grade 1 (skin, possible liver)	24	No	55
CHOC_009	7 y.o	M	Relapsed ALL	21	M	Half-Brother	Haplo	Bone Marrow	cXRT/CY/TBI	ptCY, Tacro, MMF	14	No		No	8
CHOC_010	10 y.o	M	Relapsed ALL	44	M	Father	Haplo	Bone Marrow	TestB / CY / TBI	ptCY, Tacro, MMF	16	No		No	44
CHOC_011	19 y.o	M	AML	30	F	Sister	MRD	Bone Marrow	BU/CY	MiniMTX	17	Grade 1 (liver)	22	No	46
CHOC_012	11y.o	M	VHR B Cell ALL	60	M	Father	Haplo	Peripheral Blood	TestB / CY / TBI	ptCY, Tacro, MMF	15	Grade 1 (skin)	31	No	NA
CHOC_013	18 y.o	M	T cell ALL	40	F	Mother	Haplo	Peripheral Blood	TestB / CY / TBI	ptCY, Tacro, MMF	24	Grade 4 (liver)	68	No	19
CHOC_014	12 y.o	F	VHR B Cell ALL	21	M	Brother	MRD	Bone Marrow	CY / TBI	MiniMTX, CSA, MMF	18	No		No	NA
CHOC_015	17 y.o	M	AML	22	F	Half-Sister	Haplo	Bone Marrow	BU/FLU/CY	ptCY, Tacro, MMF	18	No		No	NA

Regulatory T cells (Treg) primer



Regulatory T (Treg) cells are a subset of CD4+ T cells with immunosuppressive effects through various cellular and humoral mechanisms:

- cytotoxic T lymphocyte antigen 4 (CTLA-4)-mediated suppression of antigen-presenting cells,
- consumption of IL-2 and
- production of immune inhibitory cytokines (IL-10, IL-35, and TGFβ) and
- via molecules like (perforin and granzyme), which damage target cell membrane leading to apoptosis.
- Tregs can sequester, by the high expression of CD25, IL-2 from the microenvironment reducing effector T cells proliferation
- IL-2 starvation reduces NKs from proliferating and exhibiting effector functions as well.
- NKs can be directly affected by Tregs in a membrane bound TGF-ß dependent manner.
- Tregs have a direct effect on B-cells via PDL1/PD-1 interaction and DCs via both CTLA-4 and LAG-3.

Clinical trials to translate research for better patient care

Bedside → Bench

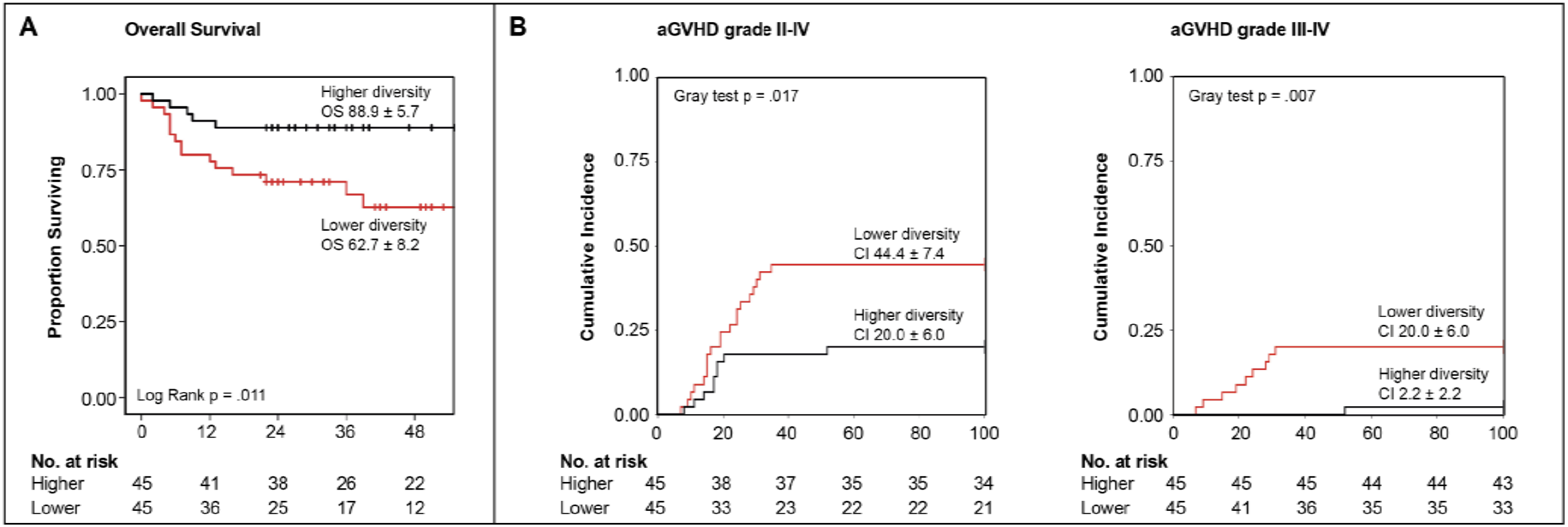
- Tregs:Tcons:NK cells, their respective cytokines and gut microbiome as **biomarkers** in
  - Allogenic SCT
  - CAR-T cell response
  - Inflammatory Bowel Disease
  - Multiple Sclerosis
  - ITP

Bench → Bedside

- Modulating Tregs:Tcon:NK cells and gut microbiome supported by cytokines
  - Sustained GVL in Allogenic stem cell transplant
  - CAR-T cell persistence
  - Transplant for IBD treatment
  - Transplant for MS
  - ITP treatment

Gut microbiota diversity before ALLO HSCT as predictor of mortality in children

Figure 2



Masetti et al Blood 2023

Role of Regulatory T Cells in Predicting Outcomes of HSCT and CAR-T cells

1. Sequential time points for testing Treg percentages for host immune profiling

2. Monitor engraftment, GVHD, disease progression, infections and organ toxicity

7-14 days prior to stem cell transplant (SCT)

Day 0 SCT (on donated product, not recipient)

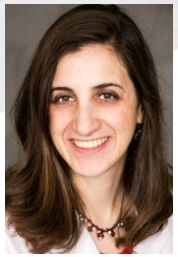
After transplant at Day 30, Day 60, Day 100, and Day 180, Day 270

One year post allogeneic hematopoietic SCT

CHOC Research
GO BEYOND

Keri Zabokrtsky
Nerida Guerrero

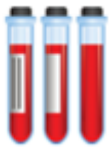
Clinical Co-investigators
- **Dr Van Huynh**
- **Dr Carol Lin**
- **Dr Jamie Frediani**
- **Dr Ivan Kirov**



Flowcytometry protocol

Caitlin Calhoun
BSc, PharmD, RPh
Faith Kim Bsc.

1.) Collect 2-4 ml blood into a purple top collection tube (EDTA)



Storage Protocol:

- Room temp, use immediately, or as soon as possible same day
- Should not exceed more than 30 minutes room temperature for plasma extraction

3.) CD4⁺/CD25⁺/CD127^{dim}/CD56/CD8/L/D

- Cells to analyze: 1.0x10^6
- Custom **MASTERMIX (REA Ab):**
  - CD4 (VioGreen)-V2
  - CD25 (VioBRIGHT 515)-B1
  - CD127(PE)-B2
  - CD56 (PE-Vio770)-B4
  - CD8 (APC Vio770)-R2
  - Viobility 405/452-V1

5.) Analysis of CD45/ CD4⁺/CD25⁺/CD127^{dim}/FoxP3/CD56/ CD8/L/D

- Identify lymphocytes via FSC/SSC
- Identify Live Cells
- Treg identification with CD4/FSC ->CD127(x)/CD25(y)->CD4(y) and FoxP3(x)

1. Collection → 2. Isolation → 3.Cell Surface Staining → 4.Intracellular staining → 5.Flow Analysis → 6.Compiled Data Analysis

2.) StraightFrom Whole Blood CD3+ Microbeads

- Rapid positive selection of CD3+ cells directly from whole blood or marrow.

4.) FoxP3

- Fixation and Permeabilization of surface-stained cells.
- Intracellular staining with Anti-FoxP3 (APC) – R1

5.) Compiled Data Analysis

- Clinical Relevance/Implications after analysis of compiled data
- Figure generation for progress reports, presentations and publications

2.Separation → 3. Storage Bank → 4. Cytokine testing

2.) Plasma separation

- Centrifugation

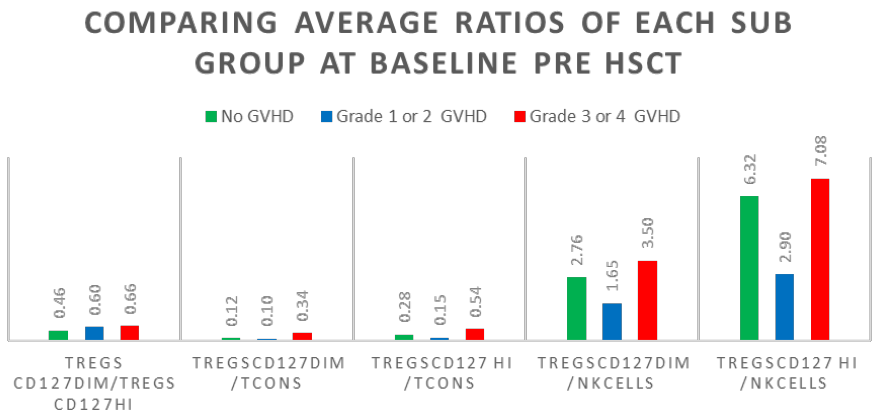
3.) Storage

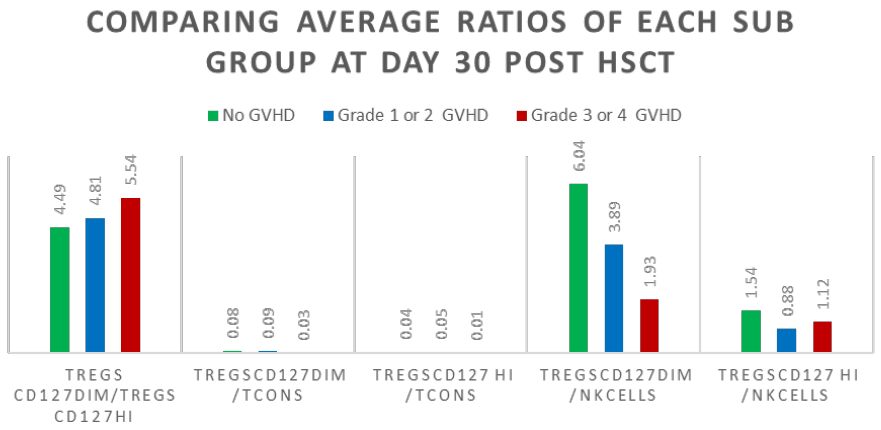
- -80°C up to 6 months

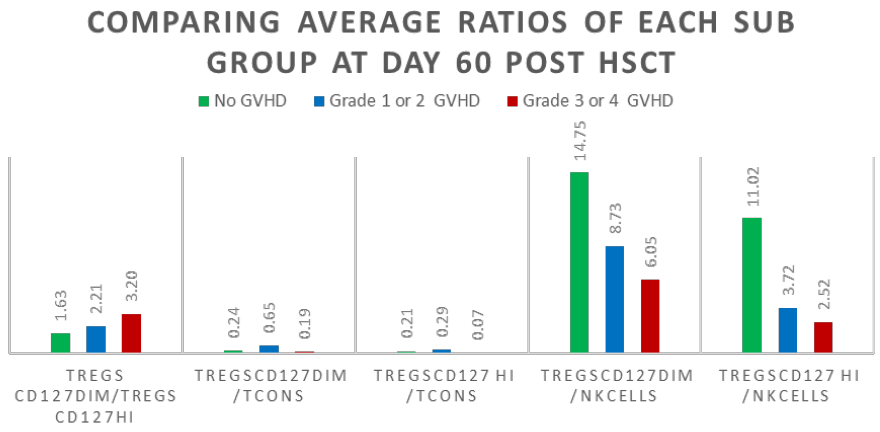
4.) Cytokine Testing

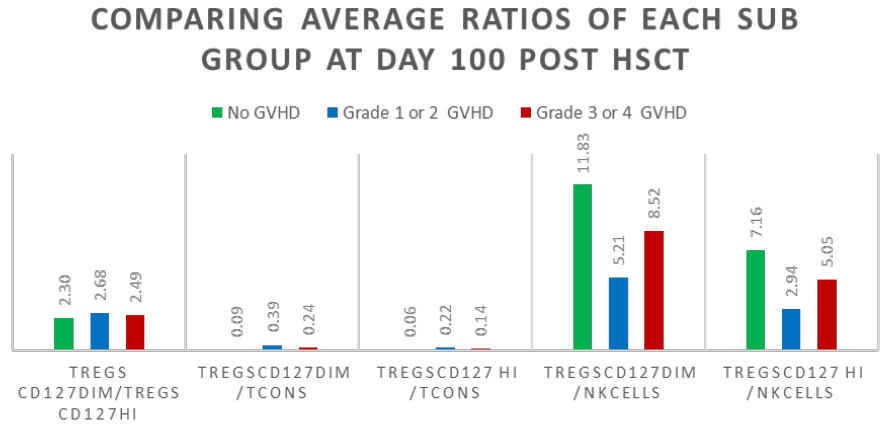
- 7 time points
- Cytokines: IL-2, IL-6, IL-7, IL-10, IL-15, IL-35, INFγ, TNF-a, CTLA-4, TGF-B
- NK/T Kit: GM-CSF, Granzyme B, IFN-γ, IL-2, IL-4, IL-6, IL-10, IL-17A, IL-21, MCP-1 (CCL2), Perforin, and TNF-α

Preliminary data - Patient CHOC 001 – CHOC015









Preliminary clinical analysis of the first 15 samples up to Day 100

Patients/recipients

- Age:13 months to 19 years,
- 8 male and 7 females
- 6 AML and 9 ALL.

GVHD subgroups:

- 7 with no GVHD
- 5 with Grade 1 or 2 GVHD
- 3 with Grade 3 or 4 GVHD.

Relapse free survival : 13 surviving

- 1 death - early relapse
- 1 death – infections, toxicities

Donors: 14 related, 1 unrelated,

- 19 to 44 years, 11 male and 4 female

Are Tregs the bad guys or a good guys?

Sustained GVL – CAR T cell expansion and persistence

- Duell J, Topp MS et al. Frequency of regulatory T cells determines the outcome of the T-cell-engaging antibody blinatumomab in patients with B-precursor ALL. *Leukemia. 2017*
- Good, Z., Spiegel, J.Y., Sahaf, B. et al. Post-infusion CAR T_{Reg} cells identify patients resistant to CD19-CAR therapy. *Nat Med 2022*.
- Gournay V, Chevalier M et al, Immune landscape after allo-HSCT: TIGIT- and CD161-expressing CD4 T cells are associated with subsequent leukemia relapse, *Blood, 2022,*
- Blazar, B.R., Hill, G.R. & Murphy, W.J. Dissecting the biology of allogeneic HSCT to enhance the GvT effect whilst minimizing GvHD. *Nat Rev Clin Oncol* 17, 475–492 (2020).

Acute and chronic GVHD

- Whangbo JS, Koreth J. The role of regulatory T cells in graft-versus-host disease management. *Expert Rev Hematol. 2020.*
- Alho AC, Ritz J. et al. Unbalanced recovery of regulatory and effector T cells after allogeneic stem cell transplantation contributes to chronic GVHD. *Blood. 2016*
- Soares MV,, Lacerda JF. Naive and Stem Cell Memory T Cell Subset Recovery Reveals Opposing Reconstitution Patterns in CD4 and CD8 T Cells in Chronic Graft vs. Host Disease. *Front Immunol. 2019*
- Gooptu M, Cutler CS. Effect of Sirolimus on Immune Reconstitution Following Myeloablative Allogeneic Stem Cell Transplantation: An Ancillary Analysis of a Randomized Controlled Trial Comparing Tacrolimus/Sirolimus and Tacrolimus/Methotrexate (Blood and Marrow Transplant Clinical Trials Network/BMT CTN 0402). *Biol Blood Marrow Transplant. 2019*

Right proportion Treg:Tcon:NKcell at right time

Clinical trials to translate research for better patient care

Bedside → Bench

- Tregs:Tcons:NK cells, their respective cytokines and gut microbiome as **biomarkers** in
  - Allogenic SCT
  - CAR-T cell response
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  - ITP treatment

THANKS !!

- Keri Z, Caitlin C, Faith K, Charrissa C, Sahar N, Nerida G, Kathy D, Dorian C, Kristen K, Yostina A, Regina T, Hiba K, Leia R, Phuong D, Sasha P, Brent D, Terence S and other members of the research institute
- Dien N, Pham T, Karen L, Ruba I, Linda G and other members of the BMT lab
- Scott I, Monika D, Danielle M, Janet T, Ana T, Nancy K, Vivian W, Caitlin G and all our other colleagues on the clinical team
- Patients and their families

RESEARCH SUPPORT

- Stanley Ekstrom Foundation
- CSO Grants
- PSF Grants
- St. Baldrick's Foundation

UCI 趙 Chao Family Comprehensive Cancer Center

Cultural Awareness and Humility in Research

Ursula Worsham, EdD
Diversity Officer
Associate Director, EDI

Discussion Points

1. Commitment to diverse perspectives in research
2. Cultural Awareness - *Competency* vs. *Humility*
3. Considering culture, customs, beliefs and history
4. Fostering Cultural Awareness and Humility
5. Reframing dominant narratives through inclusive language
6. Utilizing a Equity, Diversity, and Inclusion (EDI) lens in research

Commitment to diverse perspectives in research

Make a **personal** commitment to enhance diverse perspectives in research through…

- Self-reflection
- Self-examination of cultural assumptions and bias
- Acknowledgment of personal limitations in cultural **awareness**, knowledge, and understanding
- Lifelong learning

Cultural Humility

Lifelong process of **self-reflection** and **self-critique** accompanied by the commitment to:

- Examine personal beliefs and cultural identities
- Learn about cultures different than your own
- Mitigate the desire to be an “expert” about a particular culture

I am curious about who you are
vs.
I know who you are already

Tervalon & Murray-Garcia, 1998

Cultural Humility

Lifelong process of **self-reflection** and **self-critique** accompanied by the commitment to:

- Learn from diverse communities in the spirit of…
  - ✓ Appreciation vs. Tolerance
  - ✓ Respect for diverse cultures, customs, beliefs, and values
  - ✓ Developing skills to interact with people from any culture

Competency vs. Humility

- ***"Competency"*** implies a finite number of things to know; however, culture and language are always evolving

- ***"Humility"*** acknowledges that we cannot possibly know everything (and that's okay!), but we can keep an open mind for new perspectives

Considering Culture, Customs, Beliefs and History

- Health Beliefs & Customs: Personal beliefs and roles of family members in decision-making.
- Ethnic Customs: Customary gender roles in accepting medical treatment(s).
- Religious Beliefs: Health care-seeking behavior, value alignment with treatment plans and/or desired behavior change(s).
- Dietary Customs: Foods and customary cooking methods.
- Interpersonal Customs: Eye contact, physical touch, etc.
- History of Racial Bias: In U.S. Healthcare System - Mistrust of medical community by communities of color.

Fostering Cultural Awareness and Humility

Community Engagement:

- Actively engage members of the community being explored in research
- Engage subjects in research questions, methods, and interpretation of findings

Culturally Aligned Methods:

- Collaborate with diverse populations
- Consider barriers to participation
- Adapt consent processes, research methods, language, and data collection tools to be culturally aligned and accessible

Address Power Dynamics:

- Recognize and address power imbalances between researchers and participants
- Consider how diverse groups are included or excluded in society

Develop Community Partnerships:

- Engage with community organizations leaders and key stakeholders to recruit diverse participants
- Facilitate bias and cultural humility training for research team members

Reframing dominant narratives through inclusive language

- **Language**: (words) provide an opportunity to convey empathy and understanding to other people.

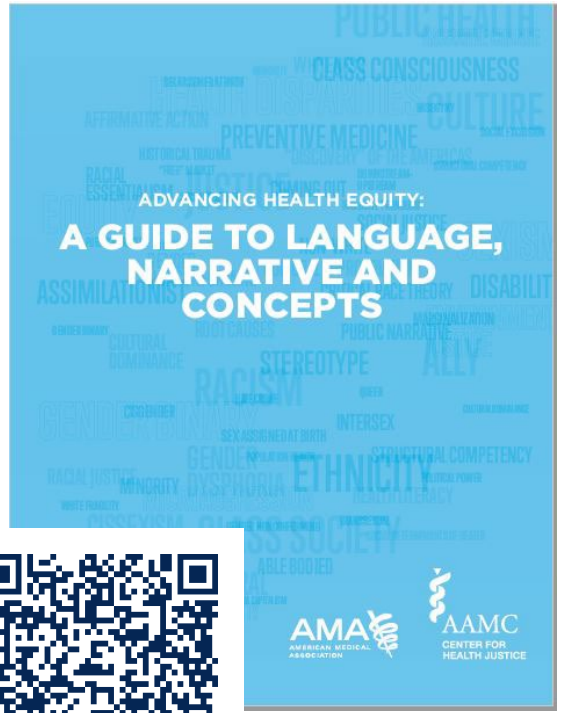
- **Words**: can be exclusionary, have roots in oppression, and reproduce bias- words can make all the difference in creating connections or creating distance with other people.

- **Dominant Narratives:** include historically represented and privileged socioeconomic groups (White, heterosexual, non-disabled, cisgender persons, male, wealthy, English-speaking, Christian, and U.S.-born)

➢ **Opportunity** to utilize language to counteract dominant narratives through inclusivity (ability, gender identity, language, race, ethnicity and more!)

A Guide to Language, Narrative and Concepts

- **Health Equity Language:** Increase awareness of traditional, outdated terms and learn new equity-focused alternatives.
- **Importance of Narratives:** Reflect on the power behind our words and mitigate perpetuating inequities in our communication.
- **Glossary of Key Terms:** Update your health equity communication and concepts!



Utilizing an EDI lens in research…

- Carefully define study population, collaborate with diversity liaisons and key stakeholders.
- Consider disaggregating demographic data into smaller categories/groups to expose hidden trends or patterns when establishing the scope of a problem.
- Identify and stay within the scope of research efforts (true value of interest) (race, ethnicity, ability, sex, sexual orientation, gender identity, etc.)
- When considering historically marginalized communities consider the broader historical and cultural context of social issues.

Ruzycki, S.M., Ahmed, S.B. Equity, diversity and inclusion are foundational research skills. Nat Hum Behav 6, 910–912 (2022). https://doi.org/10.1038/s41562-022-01406-7

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Thank you

Ursula Worsham, EdD
uworsham@hs.uci.edu

Optional Lunch Discussions – Select 1

Community Think Tank

Moderators:
Office of COE &
Community Members
Cliffs

Discussing the community relevance of your research and receiving support for community-centered studies by connecting you with community partners.

Trainee Voices

Moderators:
Ursula Worsham, EdD
Edward Nelson, MD
Claudia Benavente, PhD
Wedge

Discussing the trainee experience at UC Irvine, providing feedback, and sharing your goals to help us enhance programs and support your success.

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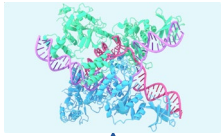
The Future Scope of AI and Machine Learning in the CFCCC

Moderators: BIDD Program Leaders
Anand Ganesan, MD, PhD
Brian Paegel, PhD

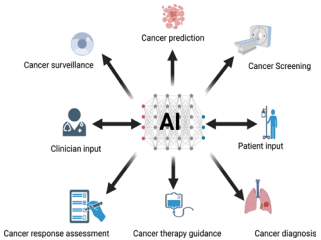
Alpha Fold



Pocket Identification
Dynamic Docking
Drug Development

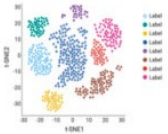
Antibody Design
Protein Design

Feature Selection
Segmentation
Algorithm Design



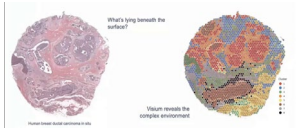
AI in clinical care

AI in Cancer

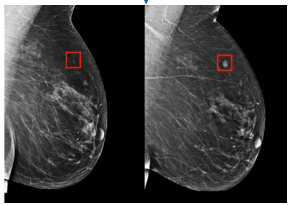


Single Cell Transcriptomics

Feature Selection
Segmentation
Algorithm Design



Spatial Transcriptomics



Feature Selection
Segmentation
Algorithm Design

Diagnosis and Treatment Response

Questions

- What other areas do you see AI/ML application in cancer research and how is that relevant to your work?
- In what ways are you trying to incorporate AI/ML into your work?
- What are bottlenecks in terms of implementing AI/ML strategies in your research (data, classification/analysis, computational resources?)
- What can the cancer center do to better facilitate investigators incorporating AI/ML into their research?

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Using Implementation Science to Accelerate Impact: Insights from Digital Health

Moderator:
Stephen Schueller, PhD
Departments of Psychological Science & Informatics

What is implementation science?

"the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services"

Eccles MP, Mittman BS. (2006) Welcome to implementation science. Implementation Science, 1(1).

Why do we need implementation science: The research-to-practice gap

But first…a quiz

1. How long does it take on average for original clinical research to benefit patients?

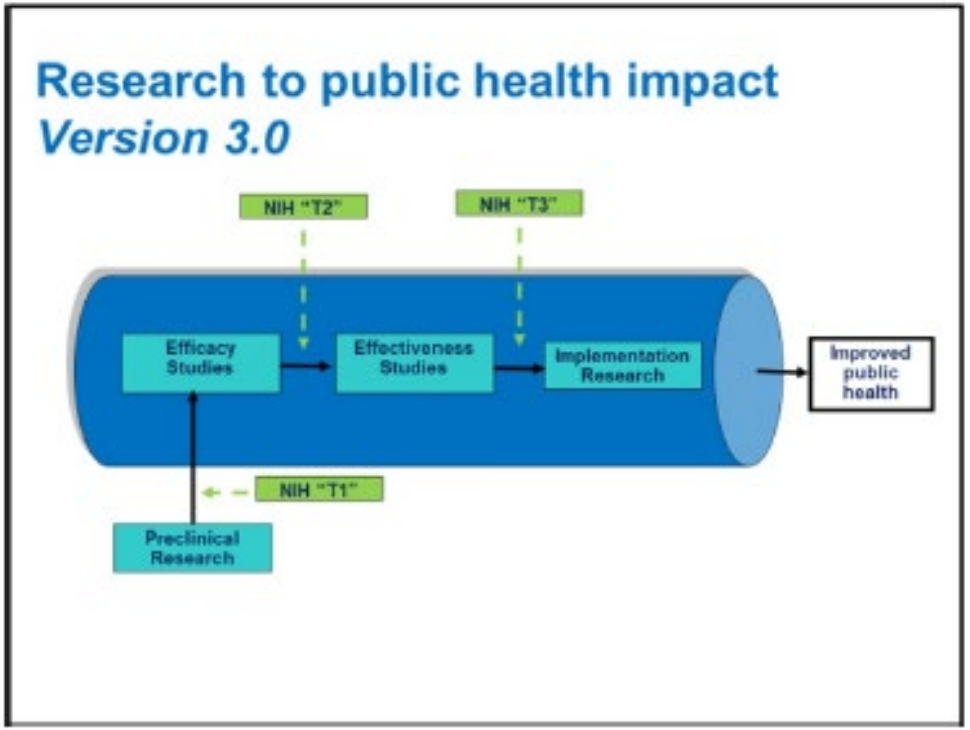
2. What percentage of original clinical research makes its way into practice to benefit patients?

Answers

1. How long does it take on average for original clinical research to benefit patients?
   17 years
2. What percentage of original clinical research makes its way into practice to benefit patients?
   14%

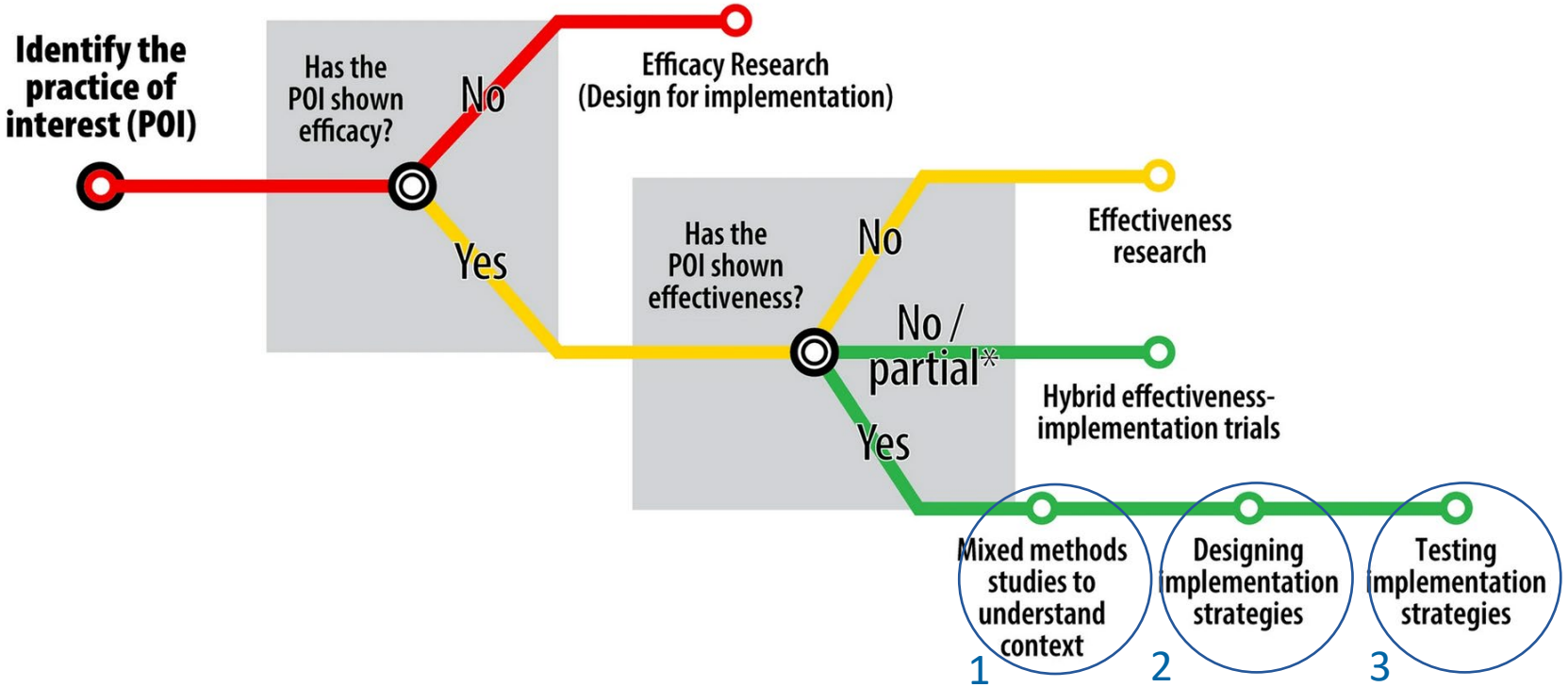
Why?

Traditional Research Approach

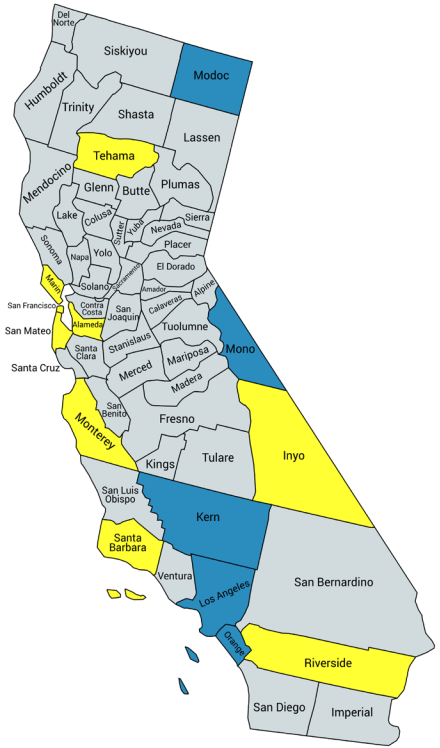


“Traditional Research Approach”

The implementation science subway



Lane-Fall, Curran, & Beidas (2019)



help @ hand™

CONNECTING PEOPLE WITH CARE

- Kern County (completed in 2020)
- Los Angeles County (completed in 2023)
- Marin County (completed in 2023)
- Modoc County (completed in 2021)
- Mono County (completed in 2023)
- Monterey County (completed in 2023)
- Orange County (completed in 2023)
- San Mateo County (completed in 2022)
- Tehama County (completed in 2023)
- Tri-City (completed in 2023)
- City of Berkeley
- Riverside County
- San Francisco County
- Santa Barbara County

Leadership Interviews (Cities/Counties)

Reason for Interview:

- Understand a range of factors and processes that have/might impact the success of the Help@Hand project
- Document changes in the Help@Hand project to assist with the formative evaluation

Methodology:

- Semi-structured interviews with City/County “Tech Leads”
- Duration≈ 45-60 minutes
- Focus on the past year when interview was conducted
- Focus of questions:
  1. Key accomplishments in the Help@Hand project
  2. Challenges experienced, and lessons learned
  3. Changes to the Help@Hand project
  4. Advice for the Help@Hand project and/or similar projects moving forward
  5. Perspectives on technology products in Help@Hand project

Qualitative to Quantitative Approach

Evaluation Type	Administered	Reporting Period	Respondents
Interview 1	Apr. – May 2022	Past Year	10 Tech Leads
Survey 1	July – Aug. 2022	Past Year (since July 2021)	12 Tech Leads
Survey 2	Oct. – Dec. 2022	Current Year (since Jan. 2022)	12 Tech Leads
Survey 3	Mar. – Apr. 2023	Current Year (since Jan. 2023)	11 Tech Leads
Interview 2	June – July 2023	Past Year (since July 2022)	11 Tech Leads
Survey 4	Oct. – Nov. 2023	Past 6 months (since Apr. 2023)	8 Tech Leads

2022 (Year 4) Survey Findings

Surveys (N=24)* Identified the Following Successes, Challenges, Plans, Lessons Learned, and Recommendations in 2022					
Successes		**Challenges**		**Plans**	
Provided digital literacy training	◔	Staff shortages	◔	Outreach to community organizations	◔
Executed a contract	◔	Competing priorities/demands	◔	Outreach to community members	◔
Collaborated with other counties/cities	◐	Contracting difficulties	◔	Evaluate product/deployment	◐
Launched a product	◐	Delayed product launches	◔	Distribute devices	◐
Conducted data analysis	◐	Peer shortages	◐	Launch a product	◐
		Pandemic related disruptions	◐		
Lessons Learned		**Lessons Learned**		**Recommendations**	
Unanticipated delays required **flexible timelines**	●	**Engaging** all stakeholders from the start is essential	◐	Create a **roadmap** of activities (with budget implications) and allow counties/cities to decide if they want to participate in an activity	◐
Innovation projects benefit consumers, Peers, staff, and other core members	◔	Technologies change quickly and as such require continued **adaptations and flexibility**	◐	Work on **disseminating** information and learnings from Help@Hand project to non-participating counties/cities	◐
Technology projects require staffing with **specialty skills**	◔	Access to **devices and digital literacy** should be examined	◐	Create new opportunities to **review evaluation reports and learnings** together	◐
Dedicating staffing is necessary for project success	◔	**Contracting** requires knowledge that has not been present in current teams	◐	Create more **smaller sub-groups** within the project to share learnings in specific areas or domains	◐

*Two surveys were conducted in 2022, one in July-August 2022 and one in October – December 2022. 12 Tech leads responded to each survey resulting in 24 responses overall. ◐ 26-50%; ◔ 51-75%; ● 76-100%

2023 (Year 5) Survey Findings

Surveys (N=19)* Identified the Following Successes, Challenges, Plans, Lessons Learned, and Recommendations in 2023					
Successes		**Challenges**		**Plans**	
Outreached to community organizations and community members	◔	Staff shortages	◔	Improve digital literacy of community members	◔
Provided digital literacy training	◔	Consumer engagement challenges	◔	Outreach to community organizations	◐
Executed a contract	◔	Contracting difficulties	◐	Finish a pilot project	◐
Distributed devices	◔	Peer shortages	◐	Apply lessons learned to projects outside Help@Hand	◐
Launched a product	◐				
Hired a new staff member	◐				
Lessons Learned		**Recommendations**		**Recommendations**	
Dedicated **staffing** is necessary for project success	◔	Continue **collaboration and outreach** to increase access to care at a larger scale	◔	Create a plan for **informing users** about project completion	◐
Innovation projects can benefit consumers, Peers, staff, and other stakeholders	◔	Have more **dedicated staff** and support staff with **carved-out** time for training and project operations	◔	Create new opportunities to **review evaluation reports and learnings** together	◐
Project delays require **flexibility** to amend and adapt project timelines	◔	Create a **roadmap** of activities (with budget implications) and allow counties/cities to decide if they want to participate in an activity	◔	Create more **smaller sub-groups** within the project to share learnings in specific areas or domains	◐
Unanticipated delays in projects are likely	◐	Work on **disseminating** information and learnings from Help@Hand project to non-participating counties/cities	◔	Secure **funding and resources** to sustain the project after Help@Hand ends	◐
Initial assumptions about access to devices and knowledge to use technology need to be examined/reconsidered	◐				
A full **staff** is necessary for project success	◐				

*Two surveys were conducted in 2023, one in April 2023 and one in October – November 2023. 11 Tech leads responded to Survey 1 and 8 Tech Leads responded to Survey 2 resulting in 18 overall. ◐ 26-50%; ◔ 51-75%

Interview Findings

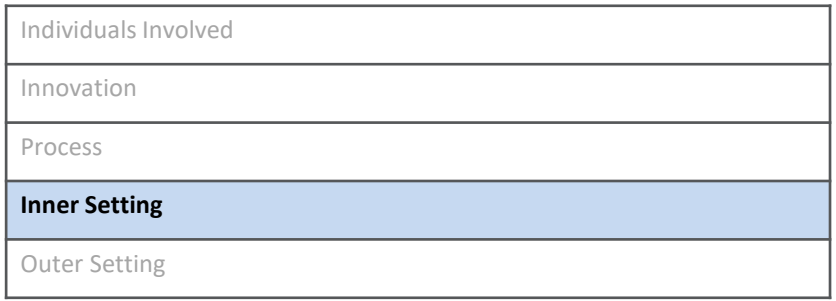
Individuals Involved
Innovation
Process
Inner Setting
Outer Setting

"The vendor provided us with the additional staff we needed to get the project off the ground". Another noted, "The county itself cannot do it all, but partnering with other organizations can help."

"The vendor wasn't willing to change the contract terms even when it became clear that we needed adjustments."

- Vendor flexibility benefited technology customization and contracting
- Vendors optimized county/city capacity with additional staffing and expertise
- Communication and coordination between vendors and counties/cities

Interview Findings

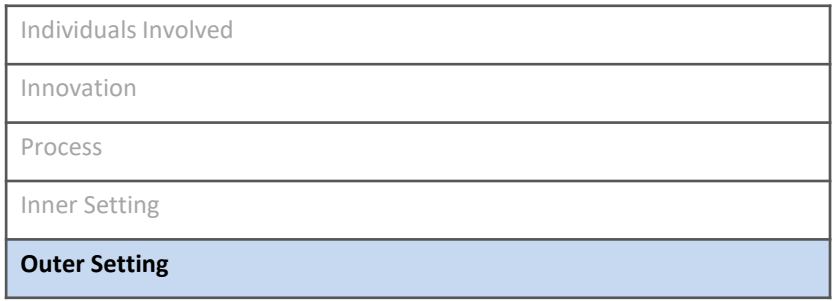


"Our county has always been forward-thinking, and that made it easier for us to embrace new technology and adapt to the changes."

"Lack of dedicated staffing impeded project success. We were already stretched thin, and we couldn't allocate enough resources to this project."

- Expanding the workforce to address digital mental health implementation
- Limited county/city capacity to manage technology projects internally
- Culture and readiness for implementation
- Lack of a clear implementation strategy

Interview Findings



"We worked closely with community stakeholders to make sure the tools we were implementing would actually meet their needs."

"While external partnerships helped us in some areas, managing these relationships was difficult and caused delays in communication and decision-making."

- Counties/cities worked with external organizations to fill gaps
- Community and stakeholder needs were central to decision-making

Some takeaway thoughts

Major challenges related to staffing and contracting

- Digital mental health requires skills not often present in county/city behavioral health teams

Collaborative model useful

- Smaller counties/cities with bigger counties
- Counties/cities with vendors

Maintaining flexibility and adaptability is critical

- In products, implementation, and evaluation

Implementation Strategies

Strategies are interventions … on the system

Sometimes called “implementation interventions”, but the field has moved away from that

Methods or techniques used to enhance adoption, implementation, sustainment, and scale-up/out of a program or practice

Do **not** have a direct effect on client/patient-level health outcomes

Often multilevel

Evaluating strategy effectiveness is the primary focus of implementation research

NIH Definition of Implementation Research

The scientific study of the use of strategies to adopt and integrate evidence-based health interventions into clinical and community settings

Implementation Strategies

Strategies are interventions … on the system

- Sometimes called “implementation interventions”, but the field has moved away from that

Methods or techniques used to enhance adoption, implementation, sustainment, and scale-up/out of a program or practice

- Do **not** have a direct effect on client/patient-level health outcomes
- Often multilevel

Evaluating strategy effectiveness is the primary focus of implementation research

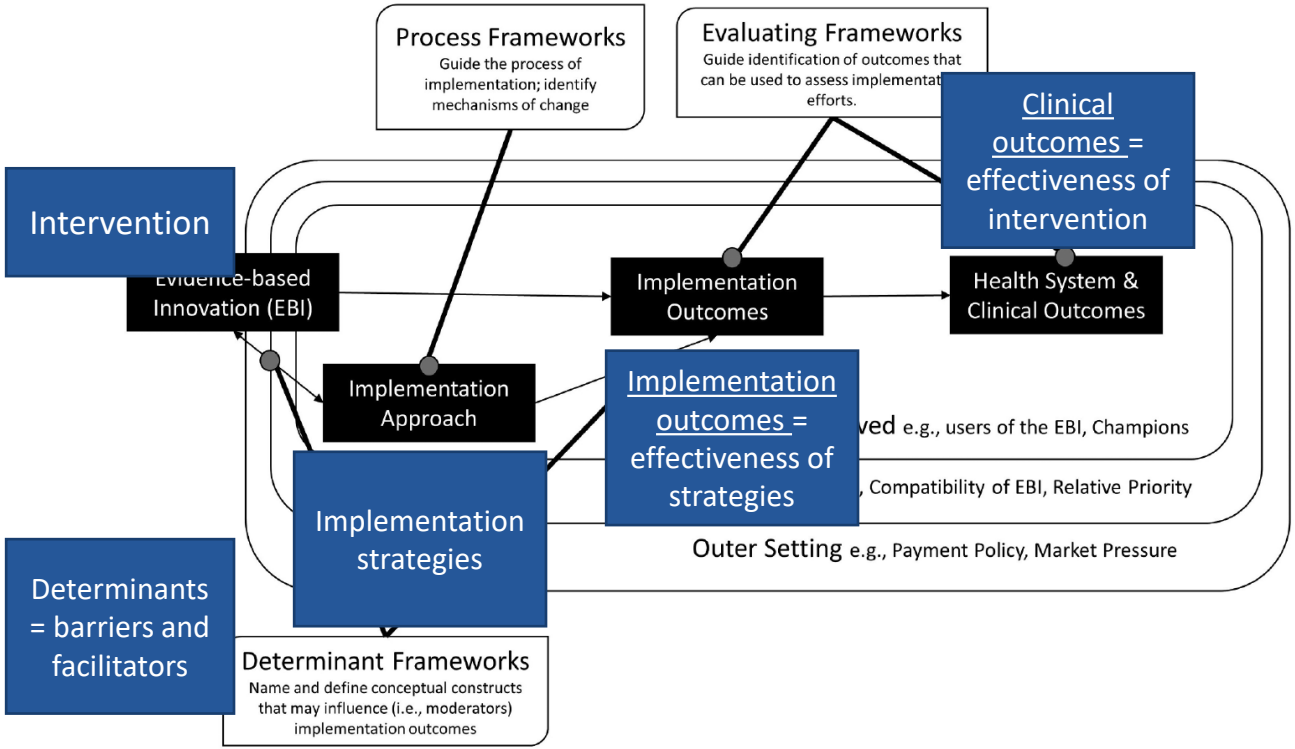
Scope

- Discrete (e.g., reminders)
- Multifaceted/packaged (e.g., training + consultation)
- Blended/protocolized (e.g., Getting to Outcomes)

Target and/or interact with <u>determinants</u> to achieve <u>implementation outcomes</u>

- Rarely one-to-one relationship between strategy and determinant

Implementation Strategies



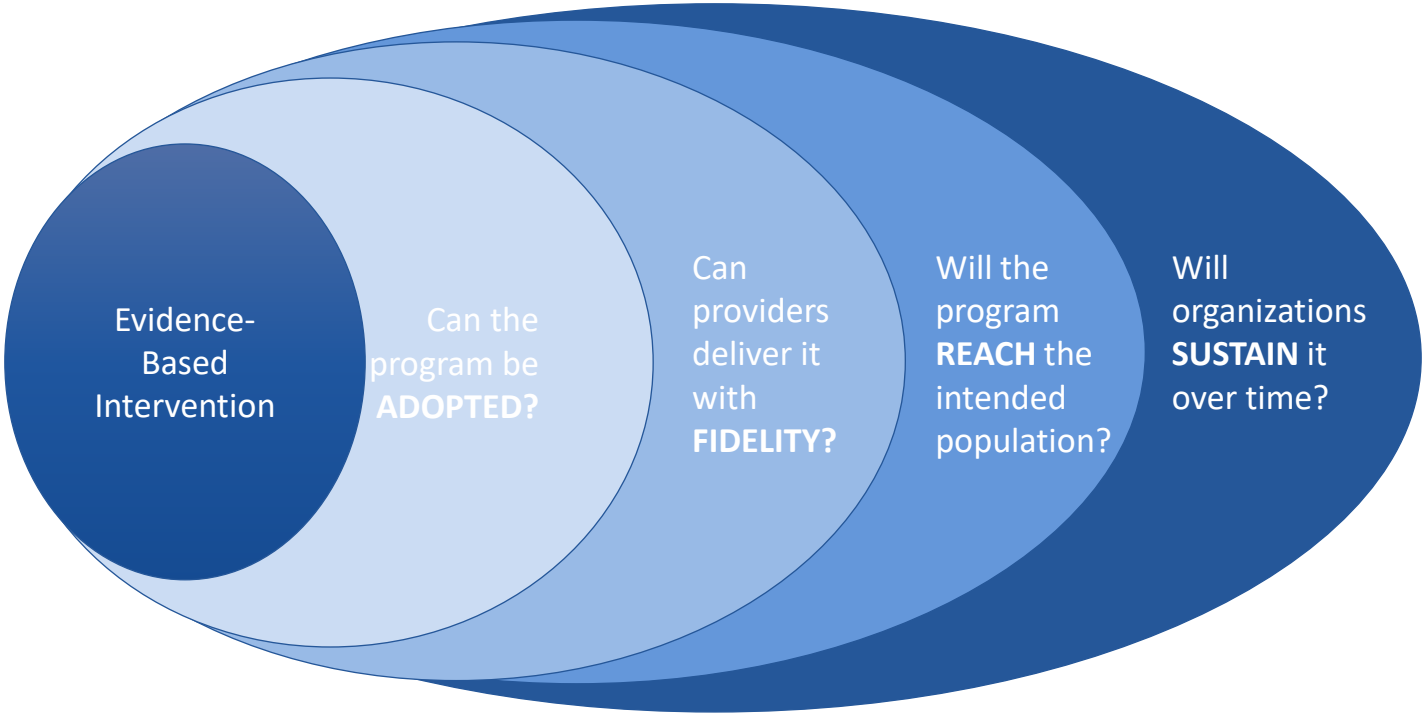
Damschroder, 2020

Implementation Strategies

Clinical/preventive intervention	→	"The Thing" that improves people's health
Implementation	→	Doing "The Thing"
Implementation research	→	How to best do "The Thing"
Implementation strategies	→	Actions that change agents take to help other people do "The Thing"
Implementation outcomes	→	**How much / how well did others do "The Thing"**

Curran, 2020

Evaluation of Implementation



Implementation Outcomes Defined

The effects of deliberate and purposive actions to implement new treatments, practices, and services (Proctor et al., 2011)

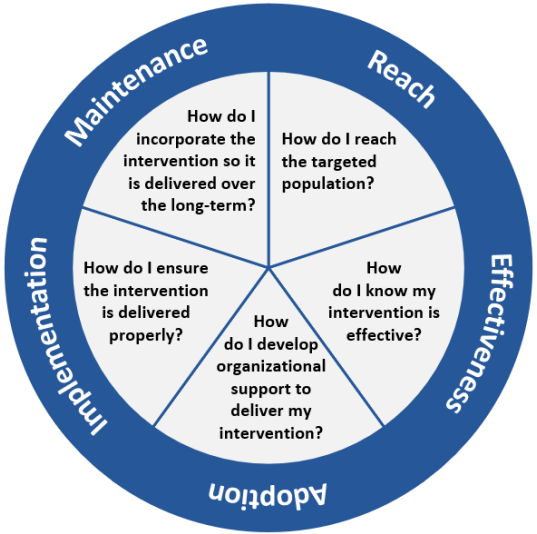
Three functions (not mutually exclusive)

1. Indicator of implementation success (e.g., reach, adoption)
2. Proximal indicators of implementation process (e.g., adoption)
3. Intermediate outcomes relative to service system and clinical outcomes (e.g., must reach before having a clinical effect)

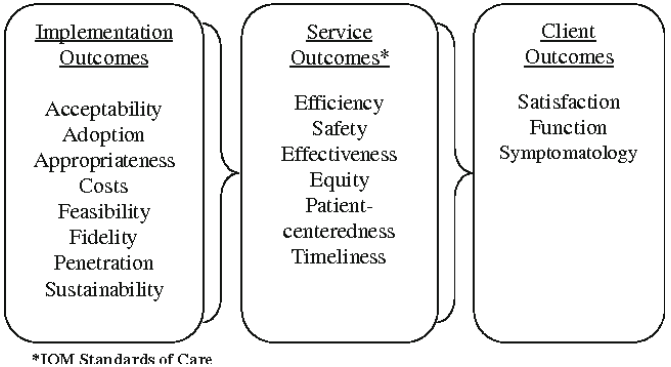
Evaluation/Outcomes Frameworks

RE-AIM (Glasgow et al)

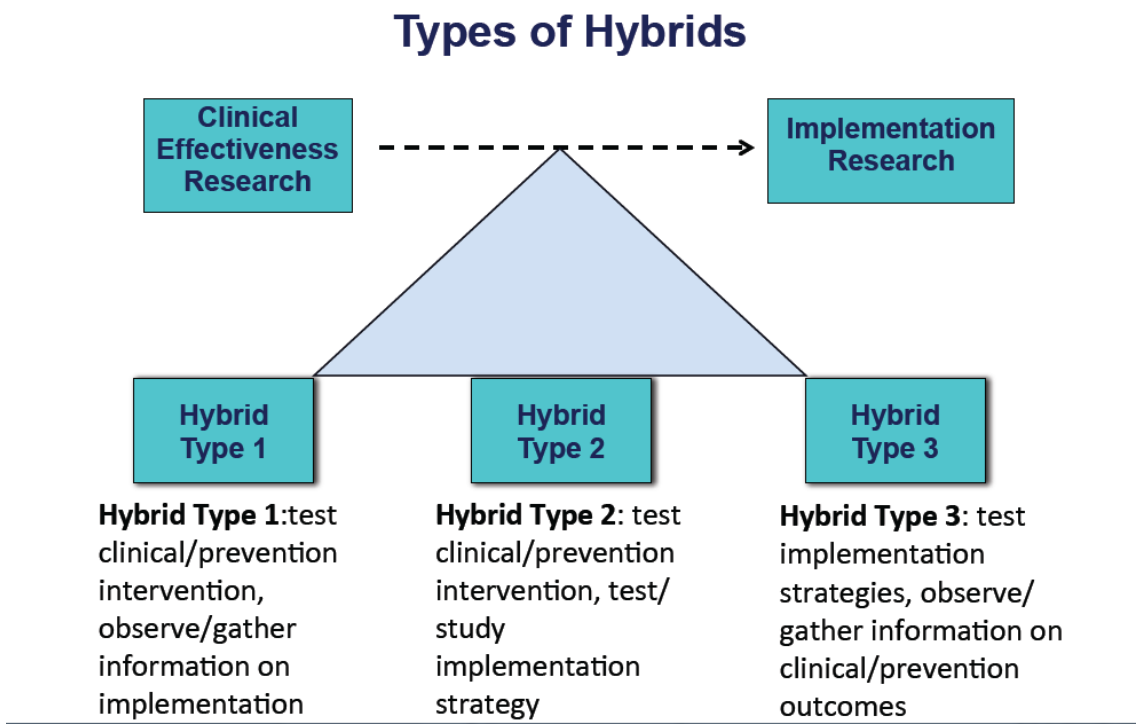
Figure 1. Elements of the RE-AIM Framework



Proctor et al.



Hybrid Trials: Combining Effectiveness and Implementation



My Well-Being Guide (R37 CA255875, PI: Yanez)

Aim 1a: Evaluate the effective of my well-being guide on depressive symptoms

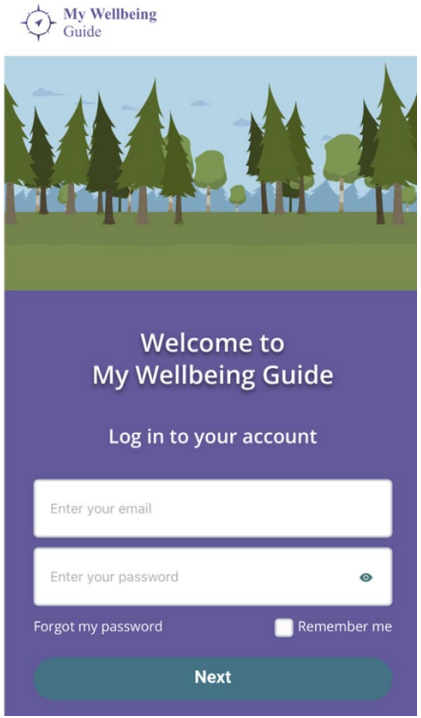
PROMIS Depression at baseline, eight weeks, six months, and 12 months

Aim 1b: Evaluate the process of implementing my well-being guide and its impact on patient and system-level outcomes

Clinician and administrator interviews and EHR data

Aim 2: identify facilitators and barriers to wide-spread implementation and expansion of my well-being guide

Focus groups at both recruitment sites to gather feedback from clinicians, hospital administrators, and patients



Yanez, Czech, Buitrago, Smith, Schueller, Taub, Kircher, Garcia, Bass, Mercer, Silvera, Scholtens, Peipert, Psihogios, Duffecy, Cella, Antoni, & Penedo, 2023

SUPERA: Supporting Peer Interactions to Expand Access

(R01 MH126664, MPI: Schueller, Aguilera)

Aim 1: Evaluate patient-level randomization on effectiveness of digital cognitive-behavioral therapy (dCBT)

Depression, anxiety, engagement

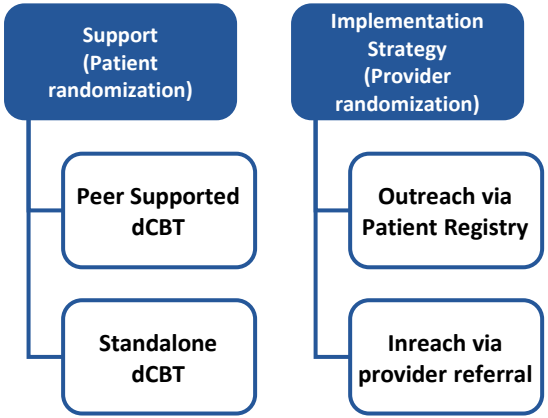
Aim 2: Evaluate provider-level randomization on the effectiveness of implementation strategies

Reach, adoption, cost

Aim 3: Evaluate putative mechanisms of change

Mixed-methods: surveys, interviews, and focus groups

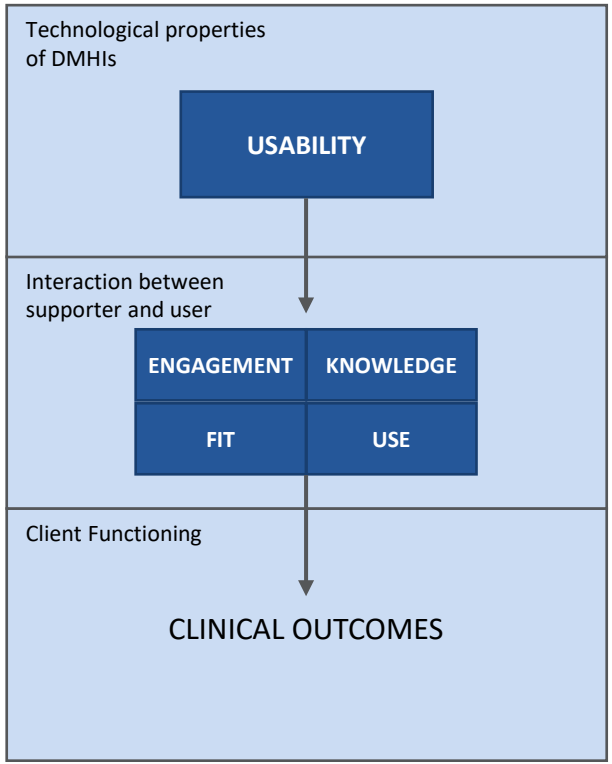
Attitude towards intervention, implementation climate, clinical readiness, potential for sustainability



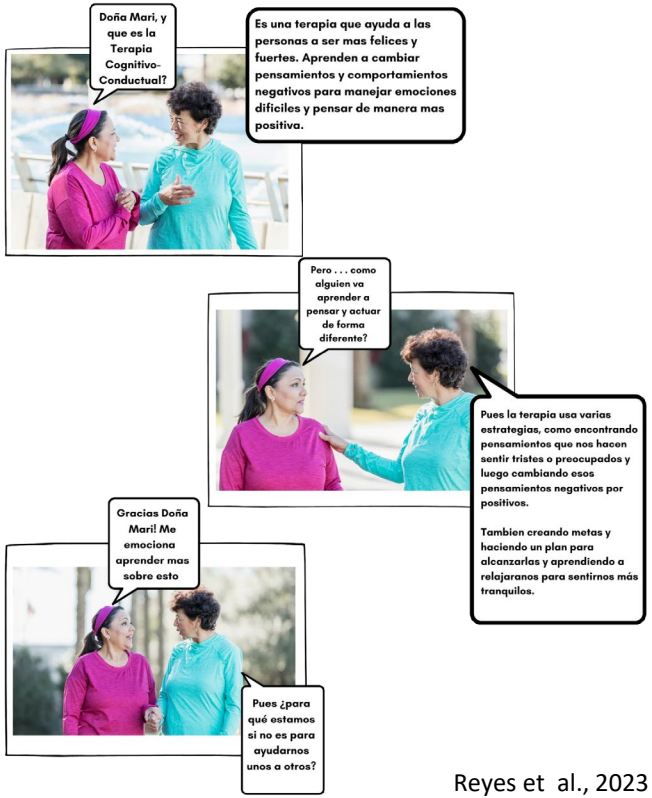
SUPERA

Aguilera, Avalos, Rosales, Reyes, Hernandez-Ramos, Ramos, Garcia, Hoang, Ochoa-Frongia, Fortuna, & Schueller, 2024

Adapting our model of support for community peers



Schueller, Tomasino, & Mohr, 2017



Reyes et al., 2023

RE-AIM applied to *My Well-Being Guide* and *SUPERA*

RE-AIM Dimension	Definition	My Well-Being Guide	SUPERA
Reach	Proportion of the target population that participated in the intervention	Proportion of participants who enroll (Spanish, severity, source)	Proportion of eligible individuals contacted and onboarded (age, gender)
Effectiveness	Success rate if implemented as planned	Improvement in depression (primary) and secondary outcomes	Improvements in depression and anxiety (primary) and secondary outcomes
Adoption	Number of settings and people who are willing to initiate the program	Proportion of clinician-initiated referrals of patients to the intervention	Percent of providers with at least one enrolled patient and characteristics
Implementation	Extent to which intervention is implemented as intended in the real world	Fidelity of participants (number who complete 5 of 7 modules)	Fidelity to the protocol and costs associated with implementing
Maintenance	Extend to which program is sustained over time	Program sustainability and assessment tool, sustained improve in depression overtime	Future work

Some takeaway thoughts and messages

- **Implementation science is the study of integration of evidence-based innovations into routine care settings**
  - Some key implementation science concepts
    - **Implementation strategies:**
      Actions that change agents take to help other people do the evidence-based innovation
    - **Implementation outcomes:**
      How much or how well did other people do the evidence-based innovation?
    - **Hybrid Effectiveness-Implementation Designs:**
      Trials that simultaneously evaluate effectiveness and implementation
      - Hybrid Type 1: Effectiveness > Implementation
      - Hybrid Type 2: Effectiveness = Implementation
      - Hybrid Type 3: Effectiveness < Implementation

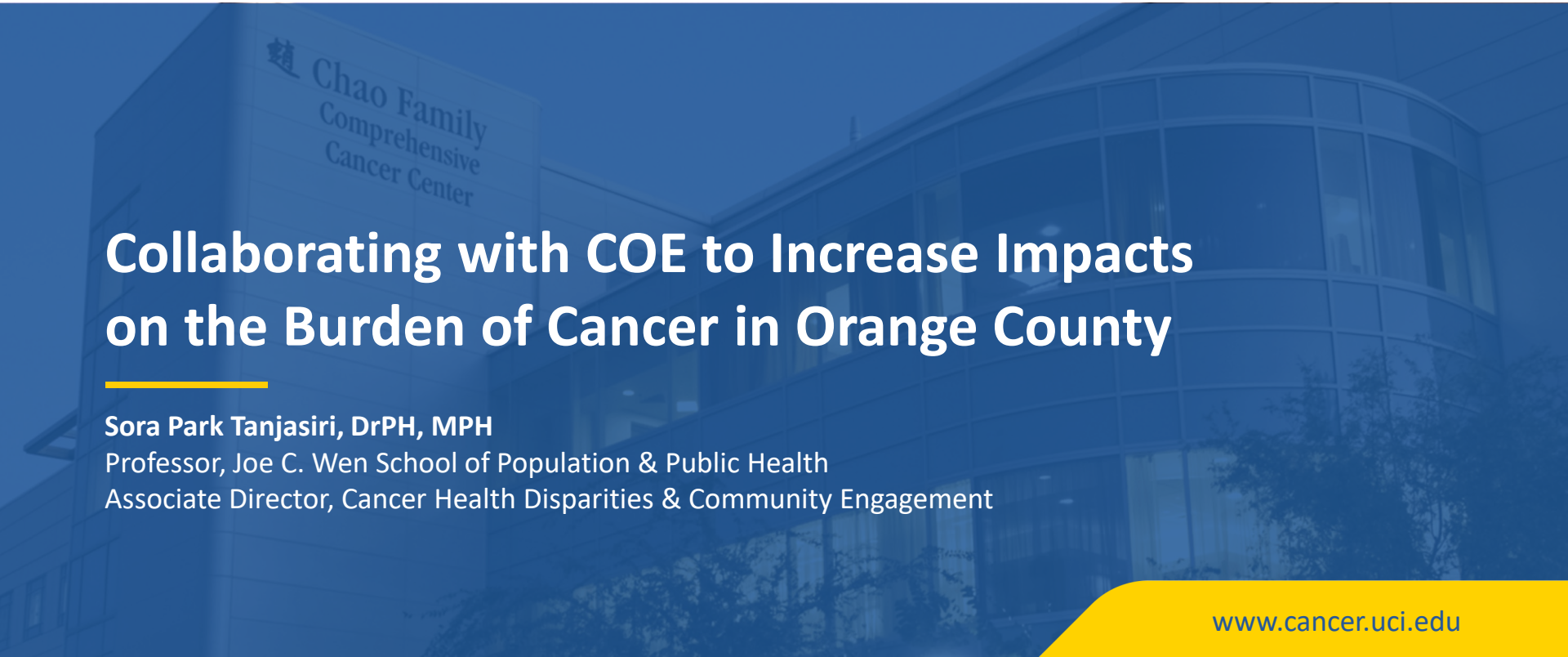
- **Implementations rarely succeed or fail due their effect size, they fail due to contextual variables**
  - Settings, people involved, policies, etc.

Thanks!

Questions?

Contact:
s.schueller@uci.edu
@steveschueller

UCI 趙 Chao Family Comprehensive Cancer Center



Collaborating with COE to Increase Impacts on the Burden of Cancer in Orange County

Sora Park Tanjasiri, DrPH, MPH
Professor, Joe C. Wen School of Population & Public Health
Associate Director, Cancer Health Disparities & Community Engagement

01

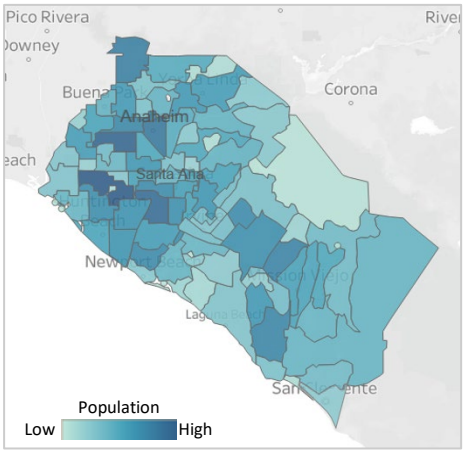
Catchment Area

CFCCC Catchment Area

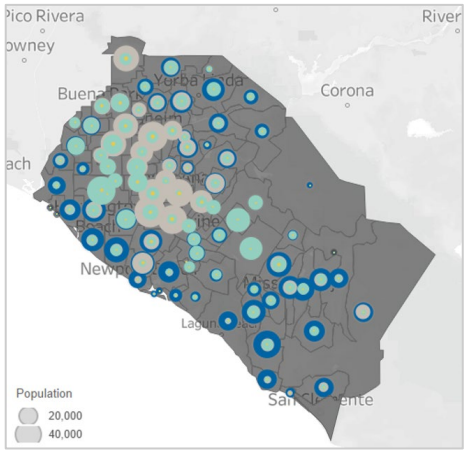
Orange County, CA: Historically minoritized groups are the majority (62%)

State

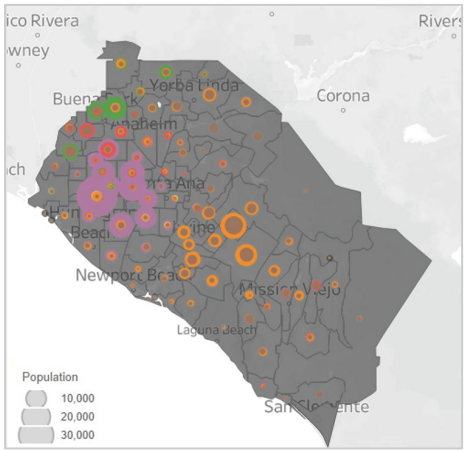
County



Racial & Ethnic Diversity



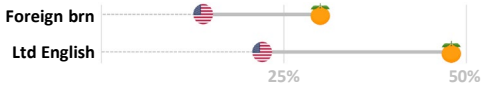
Asian Ethnic Diversity (24% of OC)



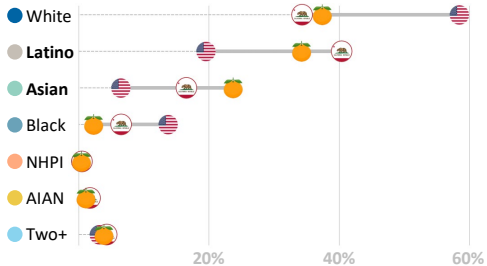
6th most populous county in the US
Home to **3.2M residents** (~10% of CA)

Age Distribution 🍊 = 🇺🇸
Poverty 🍊 = 🇺🇸

Double the national average of foreign born and limited English residents



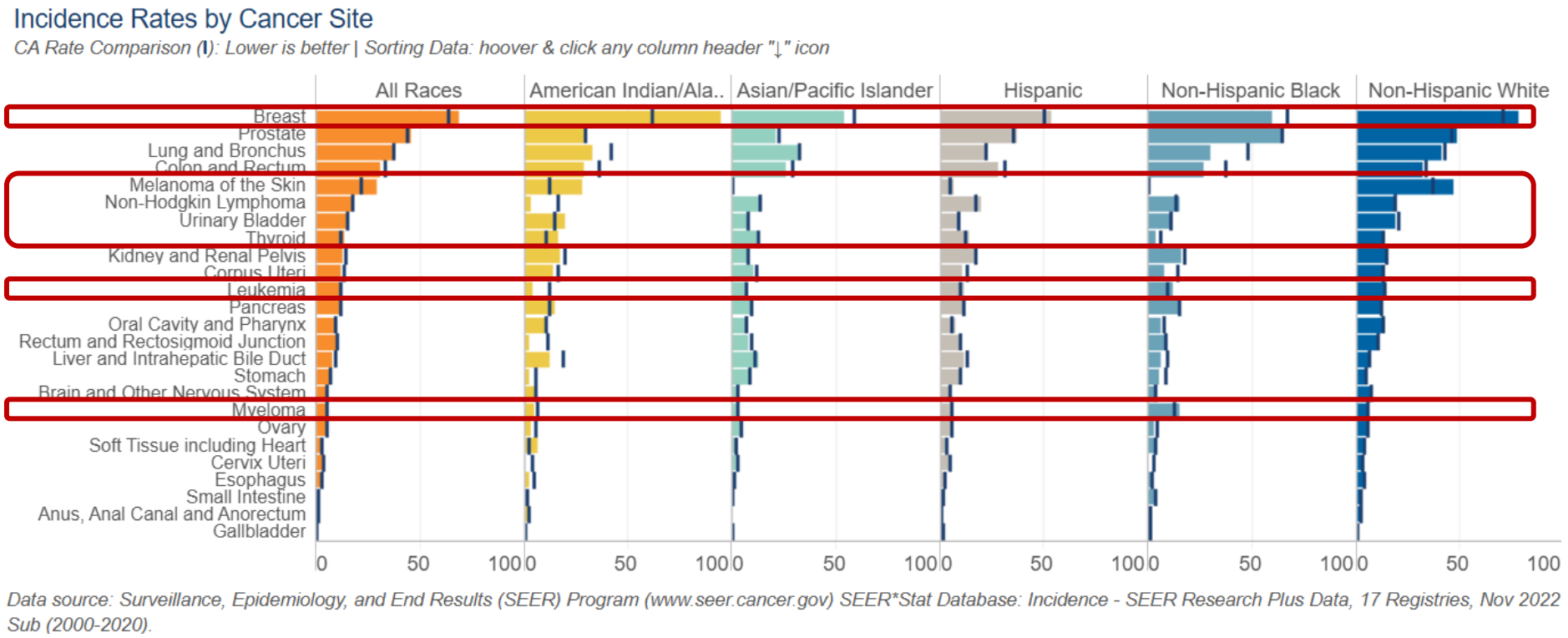
Latino and Asian populations surpass national averages (US Census 2023)



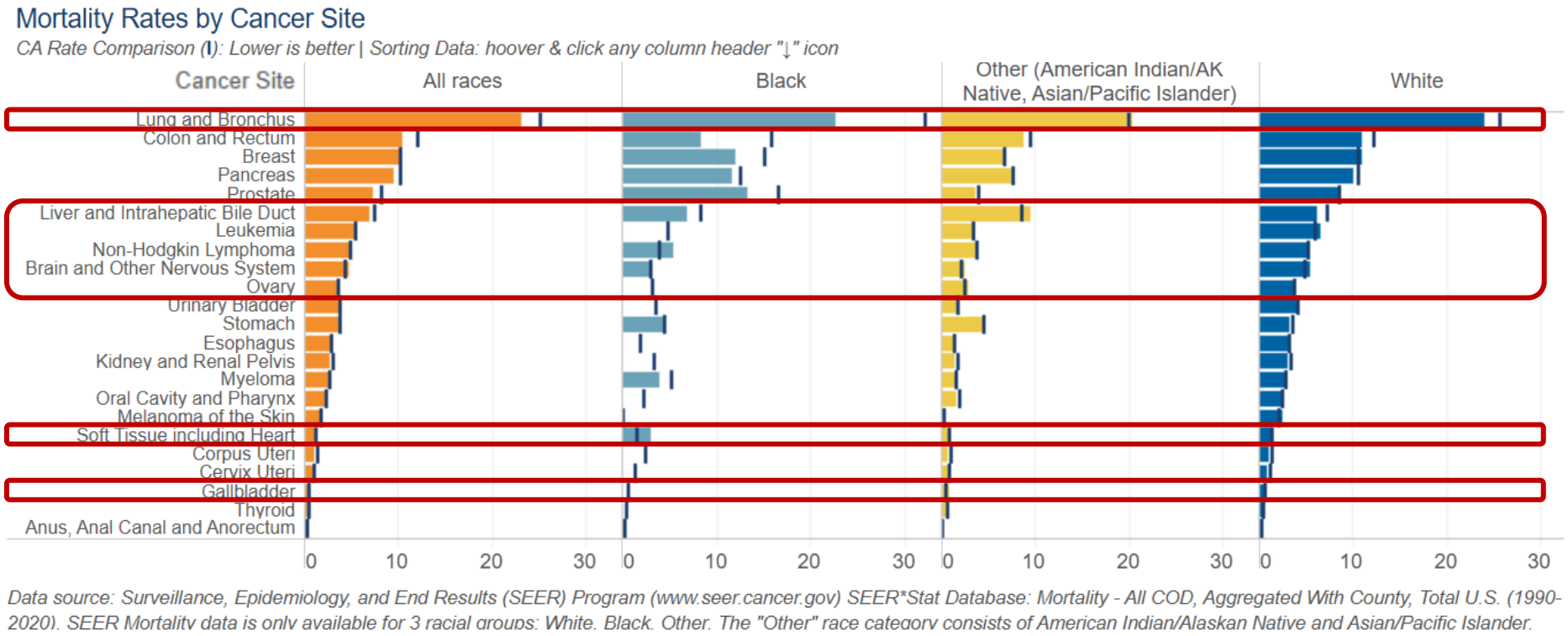
Home to the largest Vietnamese community outside of Vietnam

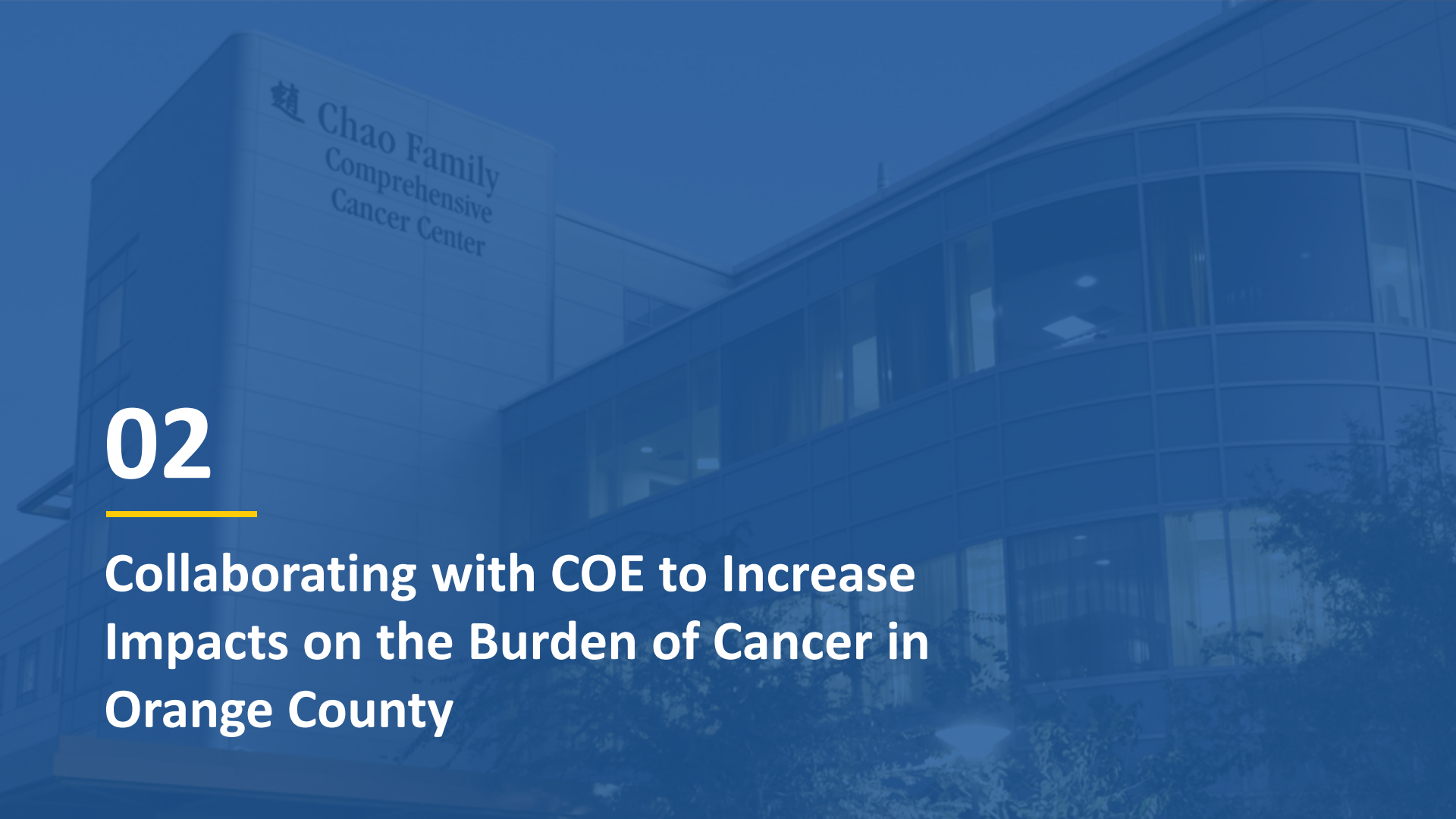
Vietnamese	**31%**	Asian Indian	9%
Chinese	19%	Japanese	5%
Korean	15%	Other Asian	9%
Filipino	12%		

CFCCC's Catchment Area: Cancer Incidence Burdens



CFCCC's Catchment Area: Cancer Mortality Burdens

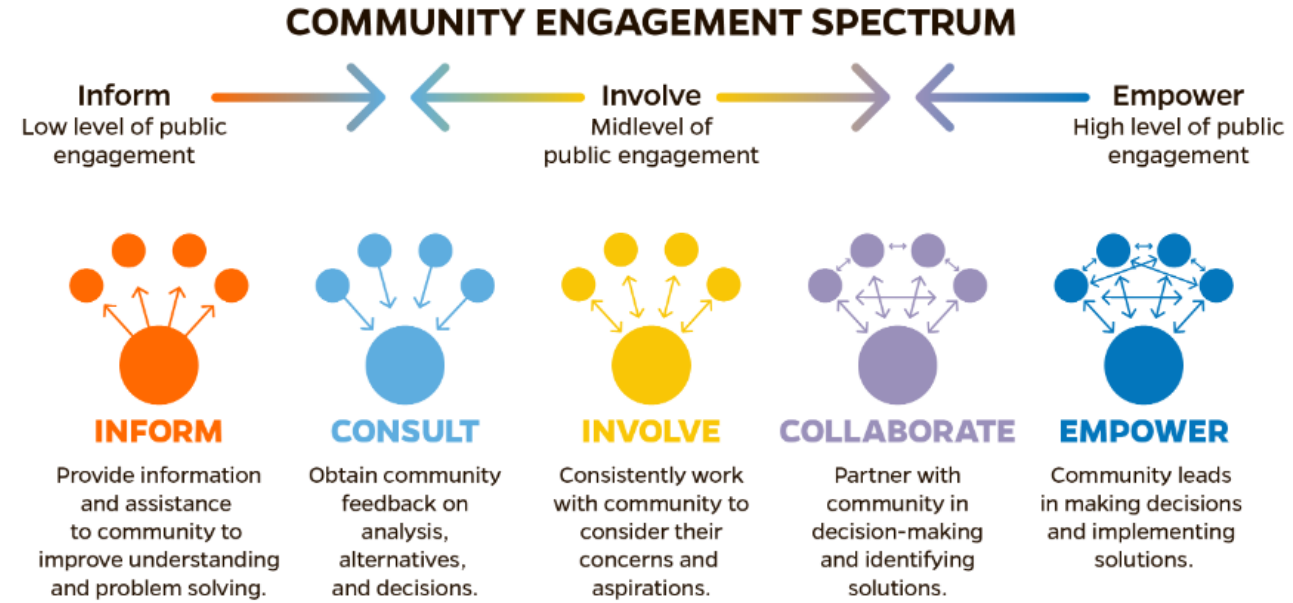




02

Collaborating with COE to Increase Impacts on the Burden of Cancer in Orange County

Office of COE: Spectrum of Community Engagement



COE Liaisons

Community Equity Board

Office of Community Outreach and Engagement (COE)

Office of COE: COE Liaisons

COE Liaisons

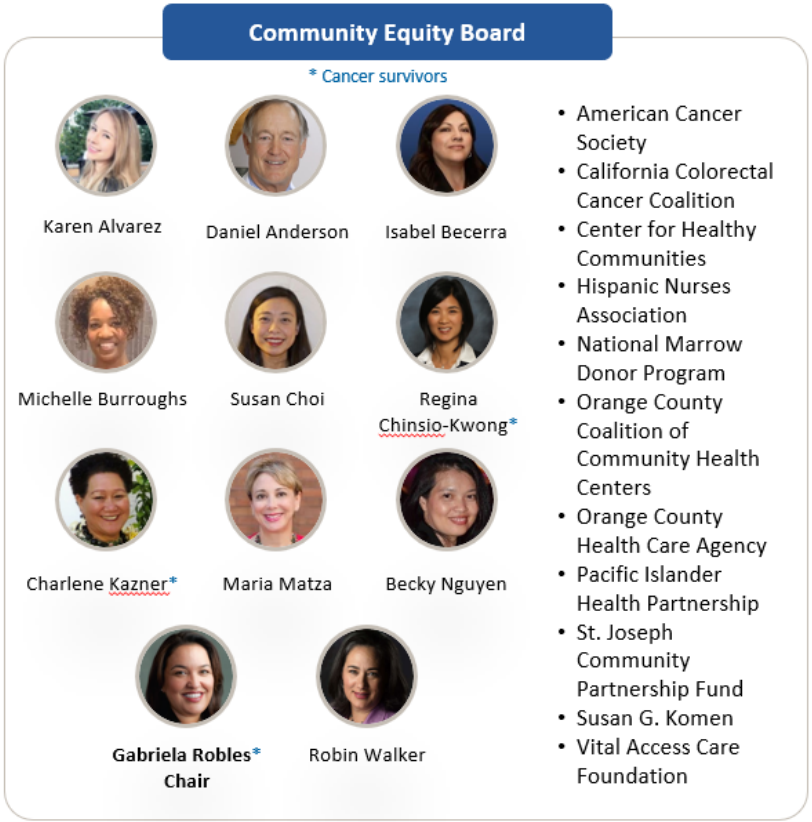
Shawn Griffin, Pharm D
Systems, Pathways & Targets

Gelareh Sadigh, MD
Cancer Control

Darci Trader, PhD
Biotechnology, Imaging & Drug Development

1. Work with Research Program leaders to promote catchment-area related research
2. Facilitate bidirectional communication between Research Programs and COE team to advance community engaged research
3. Help develop priorities and approaches for increasing integration of research with community
4. Present information on COE initiatives at Research Program meetings
5. Participate in:
   - COE Liaison quarterly meetings
   - Community Equity Board biannual meetings

Office of COE: Community Equity Board



- Members from **Key Health Organizations:** Partnerships with the American Cancer Society, California Colorectal Cancer Coalition, Orange County Coalition of Community Health Centers, and more.
- Healthcare **Leaders and Professionals:** Including experts from the National Marrow Donor Program, Orange County Health Care Agency, and Susan G. Komen.
- Community **Health Advocates:** Expertise in working with vulnerable populations including Latino, Vietnamese, Black, and low-income communities.
- **National/State Presence:** Hispanic Nurses Association, Pacific Islander Health Partnerships.
- Cancer **Survivors as Members:** Firsthand experience in addressing the needs of cancer-affected communities
- **Support Network:** involvement from St. Joseph Community Partnership Fund and Vital Access Care Foundation.
- **Health and Wellness Advocacy:** Focus on social determinants of health and improving access through Orange County Health Care Agency and Center for Healthy Communities.
- Innovative **Strategies and Resources:** Engaging solutions developed in collaboration with Local and national partners.

Office of COE

Office of COE

Daniel Rivas, MA
COE Director (Spanish)

Iris Duran
Community Health Educator (Spanish)

Vy Lê
Community Health Educator (Vietnamese)

Troy Tang
Patient Navigator (Vietnamese)

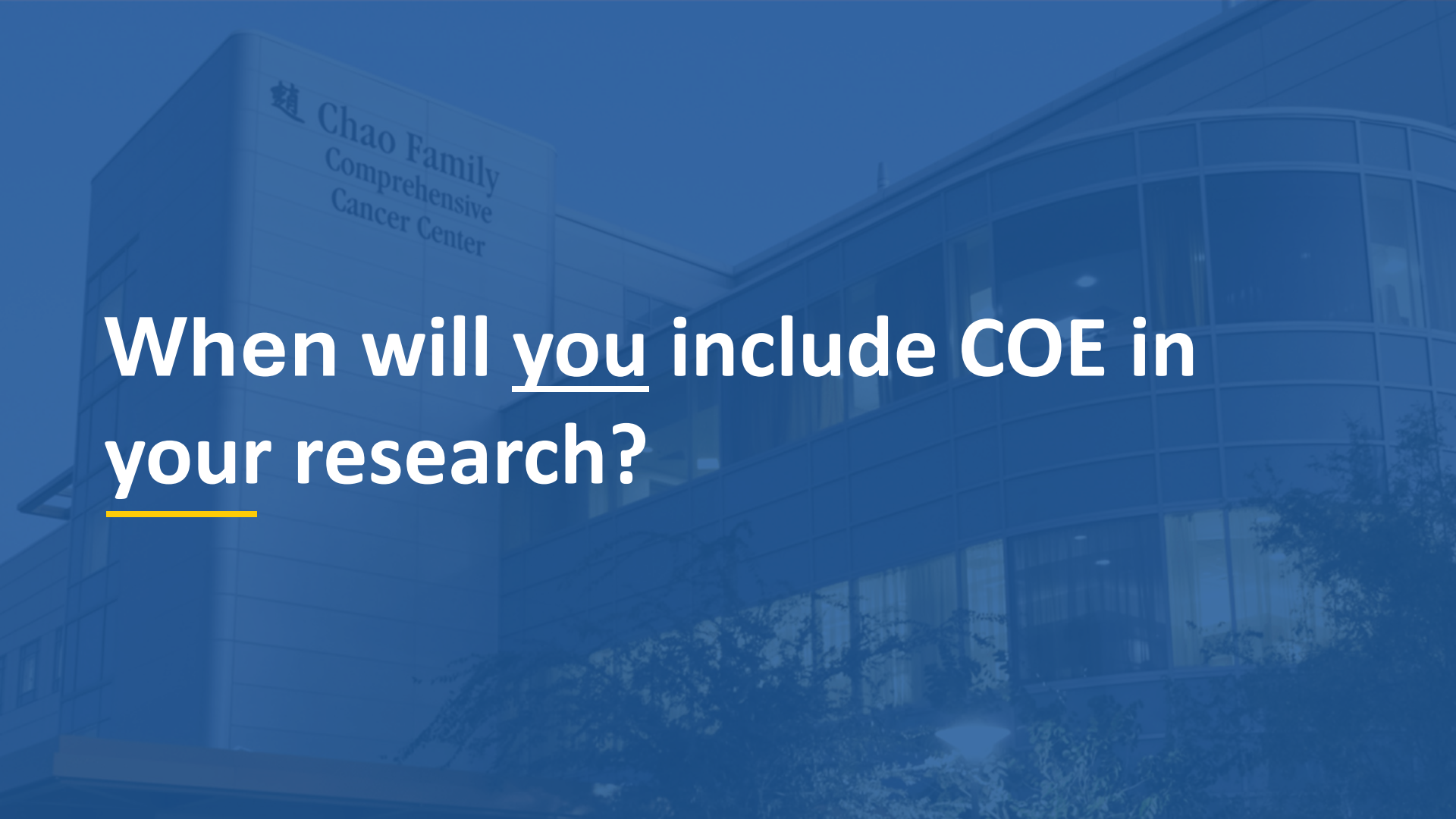
- **Data-Driven Research Insights:** Access to the Catchment Area Dashboard for precise data on cancer trends, social determinants of health, and community needs.
- **Established Community Networks:** Leverage partnerships with FQHCs, community organizations, and local leaders to facilitate participant recruitment and outreach.
- **Culturally Tailored Recruitment:** Expertise in creating in-language. Culturally relevant materials to engage diverse populations effectively.
- **Community-Embedded Workforce:** Programs like the Community Science Worker (CSW) initiative and Community Scientist Academy (CSA)
- **Enhanced Trial Diversity:** Proven methodologies to increase clinical trial enrollment from underrepresented groups, improving the generalizability of research findings.
- **Bidirectional Feedback Mechanisms:** Systems for incorporating community input into research design, fostering relevance and higher participant retention.
- **Health Equity Focus:** Opportunities to collaborate on research that addresses disparities, aligns with funding priorities, and drives impactful outcomes.
- **Policy Impact Potential:** Engage in research that informs policy changes and demonstrates real-world impact beyond academic publication.

Office of COE: Impact on Research

"I found community engagement is impactful but complicated. COE helped me in supporting letters for grant applications and for future community engagement. It ensures that the research is patient-centered, relevant, and impactful." (Liangzhong Shawn Xiang, PhD, Biomedical Engineering)

"We received valuable feedback on the financial education materials, resources, as well as our patient outreach materials. I have a better understanding of the role of COE, and how they can partner to make the research more applicable to the community." (Gelareh Sadigh, MD, Radiological Sciences)

"Community engagement is a way to build trust and provide knowledge about cancer risks… I feel this really made my application stand out including a section on community engagement where part of our budget is allocated to meeting with patient survivors and advocates to discuss our research. COE has expertise in health equity, is plugged into the community, and can promote policy change to address disparities." (Nicholas Pannunzio, PhD, Biological Chemistry)



When will you include COE in your research?

UCI 趙 Chao Family Comprehensive Cancer Center

Transgenic Mouse Facility (TMF)

Shimako Kawauchi, PhD | *Manager*
Grant MacGregor, DPhil | *Director*

Mission and Leadership

MISSION

Facilitate use of the mouse as a mammalian experimental system to investigate mechanisms of oncogenesis and testing of cancer therapeutics

To fulfill this mission, **TMF**:

- Advises investigators wishing to use genetically engineered mouse models (GEMMs) in their research program, on experimental design and analysis, helps write grant proposals & manuscripts and provides letters of support.
- Provides access to specialized expertise and equipment to develop GEMMs, provides technical support, and sources additional reagents required to manipulate the mouse genome and analyze the consequences thereof.
- Communicates awareness of novel mouse-related resources via workshops, seminars, e-mail or the TMF Shared Resource website, facilitates their acquisition for Cancer Center members, and provides practical assistance with their use.
- Assists researchers by importing, or helping to develop, new experimental approaches necessary to address specific experimental questions in their research.

LEADERSHIP

Grant MacGregor, DPhil

Director

Shimako Kawauchi, PhD

Manager

Services

Services cover design, development, re-derivation, cryopreservation, and re-animation of GEMMs in an efficient and cost-effective manner, including:

- Consultation, at no cost to PI, on strategies to engineer the mouse genome.
- Design and targeted engineering of loci in mouse zygotes via CRISPR (>300 projects completed to date).
- Targeted transgenesis at the *Hipp11* and *ROSA26* loci.
- Targeted engineering of endogenous loci in mES cells including CRISPR-mediated humanized gene replacement.
- Southern analysis of targeted loci in ES cells and animals, including PFGE.
- Insertion of conventional multi-copy transgenes and bacterial artificial chromosomes (BAC) at random loci via pronuclear injection of DNA.
- Cryopreservation, import, export, rederivation or reanimation of GEMMs via IVF or embryo transfer.
- Breeding and genotyping of GEMMs.
- Development of RT-PCR-based genotyping assays.
- High-throughput analysis of standard PCR assays using Fragment Analyzer.
- Production of large cohorts of genetically defined mice for studies, by IVF and embryo transfer.
- Annual lectures and workshops on genome engineering methods.
- Provision of language and figures for grant proposals and manuscripts, plus letters of support, at **no cost to PI**.

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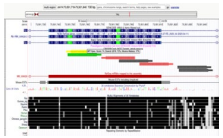
current high-demand services

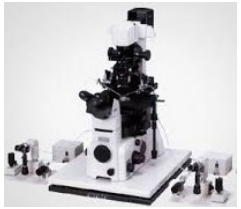
Key Equipment & Technologies

- Bioinformatic analyses of mouse and human genomics to facilitate strategies for genome engineering

- TaqMan, rhAMP based genotyping via two Bio-Rad RT-PCR systems

- High-throughput (3 x 96-well tray) analysis of standard PCR reactions using Agilent capillary array Fragment Analyzers (two instruments)



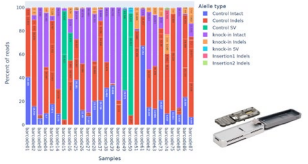
- Microinjection, electroporation and culture of zygotes / preimplantation embryos (two systems)

- Culture and cryogenic storage of sperm, embryos, mES cell lines

- PFGE and Southern analysis using Bio-Rad CHEF Mapper


- IVF-based mouse production (multiple incubators)

- Multiple animal holding rooms with ventilated cage racks and sterile caging.



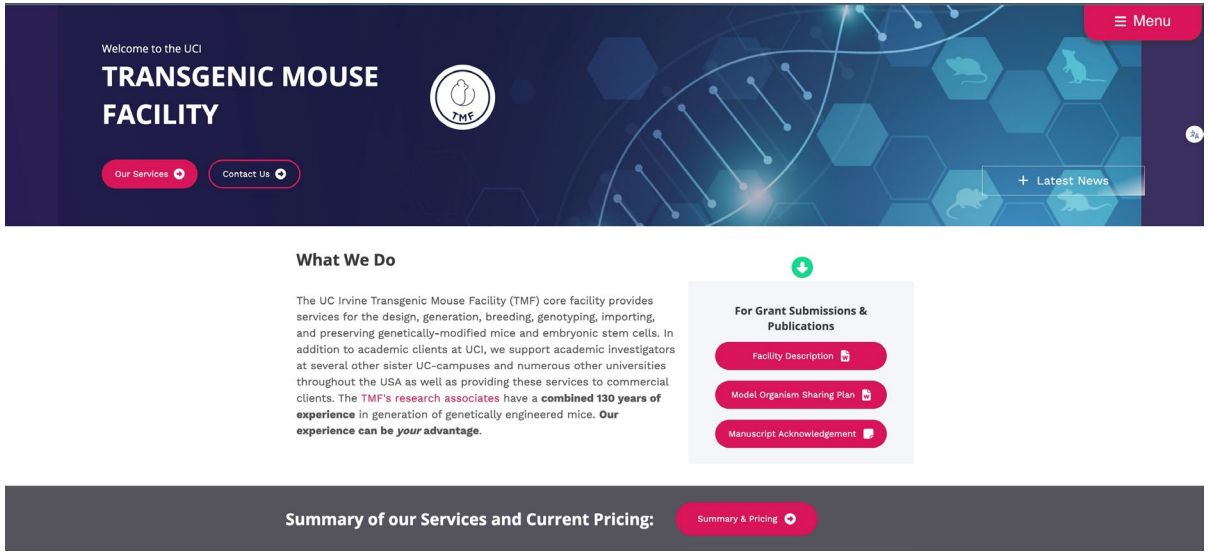
- Deeper and faster CRIPSR modification analysis with ONT sequencing

- Tissue culture suite with incubators, hoods and electroporation apparatus for ES cell culture (not shown)

Questions? Contact Us!

Website: https://transgenic.uci.edu/

Email: **TMF@uci.edu**



UCI 趙 Chao Family Comprehensive Cancer Center

Thank You

UCI 趙 Chao Family Comprehensive Cancer Center

Optical Biology Core (OBC)

Rahul Warrior, PhD
Director

Mission and Leadership

MISSION

OBC is a matric of 4 cores that provide access to cutting-edge imaging and sorting capabilities

To fulfill this mission, **OBC** operates the:

- **Self-Use Facility (SUF)** offers confocal, lightsheet and two photon microscopes for deep tissue, whole tissue, and fluorescence lifetime (FLIM) and Super Resolution imaging
- **Laboratory of Fluorescence Dynamics (LFD)** is dedicated to the development and application of advanced fluorescence microscopy techniques for studying molecular dynamics and interactions in biological systems.
- **Non-Linear Optical Microscopy (NLOM)** Laboratory specializes in multiphoton microscopy-based imaging with large fields of view and rapid scanning for diagnosing skin cancers and other skin conditions and monitoring skin therapies. NLOM focuses on collaborative equipment use, development and protocol design
- **Flow Cytometry Facility (FCF)** operates a suite of multi-parameter flow cytometers equipped for fluorescence activated cell sorting and/or analysis

LEADERSHIP

Rahul Warrior, PhD
Director

Michelle Digman, PhD
Manager, LFD

Adeela Syed, PhD
Manager, SUF

Mihaela Balu, PhD
Manager, NLOM

Michael Hou, PhD
Manager, FCF

Services

Self-Use Facility (SUF)

Walk-up use of suite of microscopes

- 4 confocal microscopes with training on advanced imaging techniques such as Airyscan imaging, Spectral Imaging and 2-photon microscopy
- Single plane illumination microscope (SPIM) able to analyze both live sample and cleared tissues. The Z1 has four laser lines (405 nm, 488 nm, 561 nm, 633 nm) and a custom chamber for organically cleared samples
- Super Resolution Lattice SIM with SMLM capabilities and 60nm resolution with SIM2 for live super resolution (255fps/60nm)

Laboratory for Fluorescence Dynamics (LFD)

A national research resource center for biomedical fluorescence spectroscopy with over 12 instruments for dynamic imaging

- The LFD designs, tests, and implements advances in the technology of hardware, software, and biomedical applications
- Dynamic imaging modalities include: metabolic Imaging, NADH metabolism, OXPHOS/Glycolysis, Bioluminescent immune reporters and fluorescence metabolic reporters

Non-Linear Optics Microcopy (NLOM) Laboratory

Develops biophotonics technologies for basic research and pre-clinical/clinical applications via nonlinear optical microscopy (NLOM)

- NLOM for optical coherence tomography, diffuse optical spectroscopy and imaging, spatial frequency domain imaging, laser speckle imaging, Coherent anti-Stokes Raman Scattering (CARS) and FLIM to enable multi-photon deep tissue imaging

Flow Cytometry Facility (FCF)

Self use of suite of cytometers

- 4 multi-parameter flow cytometers including one equipped for fluorescence activated cell in a BSL2 cabinet featuring downstream applications of single cell cloning and single cell analysis.
- Access to: High-end workstations for data analysis, including advanced 3D/4D analyses and cell sorting analysis

All four components of the OBC provide:

- Letters of support, training and research consultation
- Grant preparation: Assistance with study design, data processing, analysis strategies and letters of support
- Imaging and Flow Cytometry Workshops offered multiple times throughout the year for Faculty, Students, Staff and visiting scholars

More information regarding all services can be found at: https://cancer.uci.edu/optical-biology-core

Training and Education Activities

Self-Use Facility and Laboratory of Fluorescence Dynamics

- Extensive training sessions on the use and capabilities of the newly installed LSM 980 microscope and other instruments and Image analysis software
- Participants, from Community College and high schools in OC participated in a program to foster scientific interest. The main aim was to expose students to technology driven science research. Students were given lectures on the basics of microscopy, optics, imaging methods, biophotonics and computational data analysis. They selected specific research topic and performed experiments, implement experimental design and use advance computational methods to test their hypothesis. In addition, they attended lectures by a group of faculty members, postdocs and students.
- LFD and OBC partnered to host Hand-on workshop on Advanced Dynamic Imaging. > 50 researchers from around the world attended a 4 days workshop at UCI in October that included lectures and training on Image Correlations, FLIM, super-resolution and Deep tissue imaging

Non-Linear Optics Microcopy (NLOM) Laboratory

- FlowJoTM Software v10 Training: Intro/Refresher (2h), Comp (1h), QC/Norm samples (1h), and Height parameter using algorithms (2h)
- BD Biosciences flow cytometry lunch and learn: Fundamentals of flow cytometry panel design & Breaking barriers with BD FACSDiscoverTM S8 Cell sorter: Increase experimental capabilities and discover what was previously impossible

Flow Cytometry Facility (FCF)

- Lectures and hand-on activities on the imaging resources in our lab offered as part of the on-campus workshop in Advanced Fluorescence Imaging and Dynamics, the Annual Short Course on Multiscale Biophotonics and the course on Modern Imaging and Cancer offered by Cancer Research Institute at UCI
- Regular hands-on training on the use and capability of the Leica SP8 Falcon/CARS in our lab

The OBC provides:

- Letters of support, training and research consultation
- Grant preparation: Assistance with study design, data processing, analysis strategies and letters of support
- Imaging and Flow Cytometry Workshops offered multiple times throughout the year for Faculty, Students, Staff and visiting scholars

UCI 趙 Chao Family Comprehensive Cancer Center

Thank You

www.cancer.uci.edu

UCI 趙 Chao Family Comprehensive Cancer Center

Genomics Research & Technology Hub (GRT Hub)

Suzanne Sandmeyer, PhD
Director

Mission and Leadership

MISSION

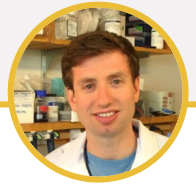
To provide emerging and state-of-the-art genomics technologies and training to CFCCC members

To fulfill this mission, **GRT Hub**:

- Supports adoption of current and developing – omics technologies to combat cancer
- Trains and supports cancer center researchers in the strategic application of -omics technologies
- Promotes rigorous analytical approaches in –omics including: providing user training, bioinformatic and statistical analysis, and support for data interpretation and documentation, archiving, and sharing

LEADERSHIP

Suzanne Sandmeyer, PhD
Director
Genomic Technologies



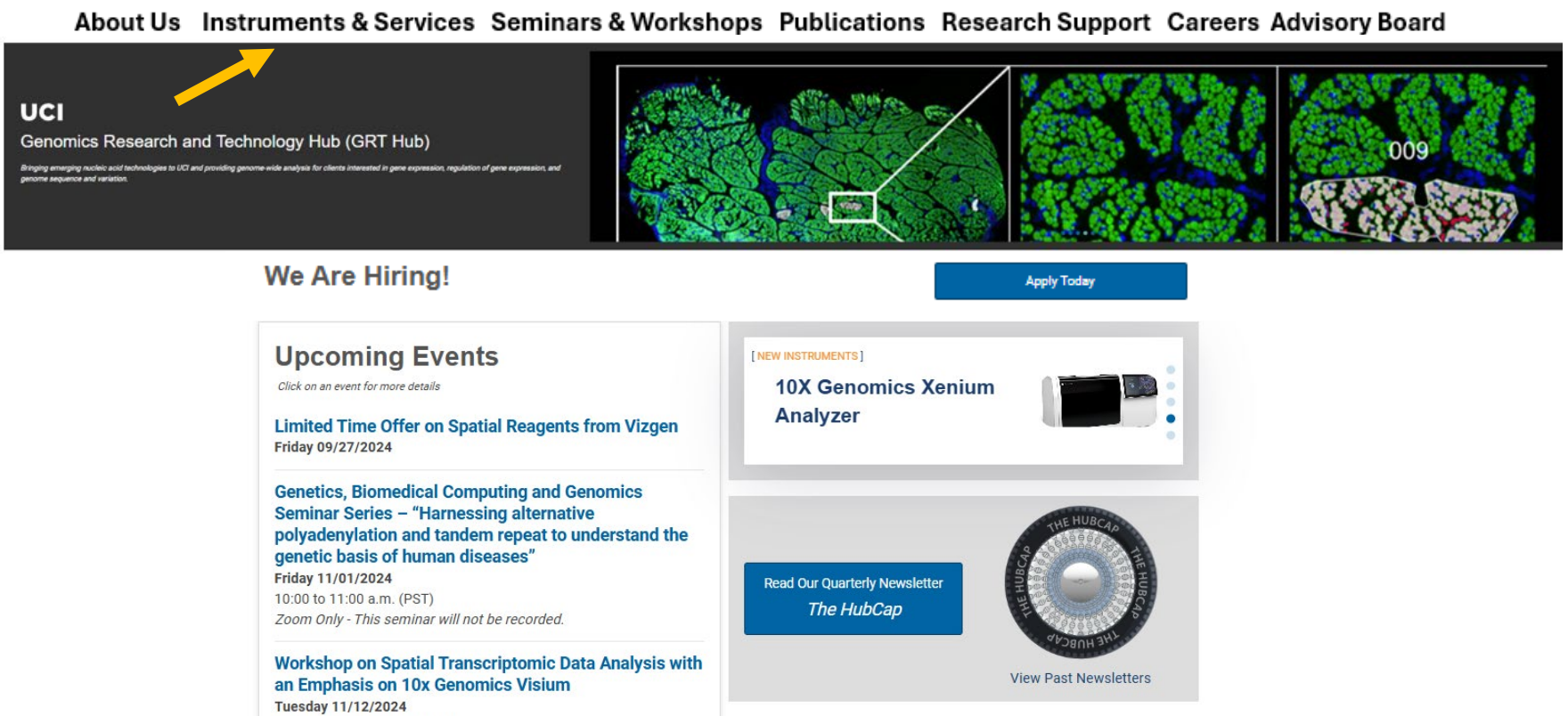
Remi Buisson, PhD
Assistant Director
GRT Hub SR

Melanie Oakes, PhD
Manager
Technical Operations

Jenny Wu, PhD
Director, Bioinformatics
Transcriptomic Analysis

Ivan Chang, PhD
Bioinformatics Engineer
Data Sharing

Home Page


About Us
Instruments & Services
Seminars & Workshops
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Research Support
Careers
Advisory Board
UCI
Genomics Research and Technology Hub (GRT Hub)
Bringing emerging nucleic acid technologies to UCI and providing genome-wide analysis for clients interested in gene expression, regulation of gene expression, and genome sequence and variation.
009
We Are Hiring!
Apply Today
Upcoming Events
Click on an event for more details
Limited Time Offer on Spatial Reagents from Vizgen
Friday 09/27/2024
Genetics, Biomedical Computing and Genomics Seminar Series – "Harnessing alternative polyadenylation and tandem repeat to understand the genetic basis of human diseases"
Friday 11/01/2024
10:00 to 11:00 a.m. (PST)
Zoom Only - This seminar will not be recorded.
Workshop on Spatial Transcriptomic Data Analysis with an Emphasis on 10x Genomics Visium
Tuesday 11/12/2024
9:00 a.m. to 1:00 p.m. (PST)
Sprague Hall, Room 105
[NEW INSTRUMENTS]
10X Genomics Xenium Analyzer
Read Our Quarterly Newsletter
The HubCap
THE HUBCAP
View Past Newsletters

Instruments Page

PacBio Revio Long-Read Sequencer

10X Genomics Xenium Analyzer

10X Genomics CytAssist

Illumina NovaSeq X Plus Short-Read Sequencer

Illumina NovaSeq X Plus Short-Read Sequencer

The Illumina NovaSeq X Plus installed in the middle of June, comes with state-of-the-art short read sequencing. Two flow cells (2*8 lanes) produce up to 25 B reads each (2x150bp) in 48 hr while maintaining quality of 85% >Q30 and reducing price by 30 %. According to Illlumina specifications, technical improvements include reduced input requirements, higher density flow cells, XLAP-SBS chemistry, new optics, enzymes, and modifications in cycle blocking and unblocking. Dragen software can be used to facilitate analysis. FASTQ files will continue to be made available to users. This reduces runs for short read 30X coverage with 128 genomes per dual flow cell and deeper sequencing for single cell transcriptomics.

More Information from the Manufacturer

Related Services: Short-read Sequencing & Library Construction |

Seminars

Upcoming

Genetics, Biomedical Computing and Genomics Seminar Series – "Harnessing alternative polyadenylation and tandem repeat to understand the genetic basis of human diseases"

Friday 11/01/2024
10:00 to 11:00 a.m. (PST)
Zoom Only - This seminar will not be recorded.

Ya (Allen) Cui, PhD
Research Assistant Professor in the Wei Li lab
UCI Department of Biological Chemistry

Dr. Ya (Allen) Cui is a research assistant professor in Prof. Wei Li's lab in the Department of Biological Chemistry at the University of California Irvine. Dr. Cui will open his own lab early next year. Dr. Cui's research is focused on understanding the genetic association of tandem repeat (TR) and alternative polyadenylation (APA) association with complex traits and diseases, such as cancer, neurological, cardiovascular, and metabolic diseases. Dr. Cui will present his recently developed alternative polyadenylation transcriptome-wide association method (3'aTWAS) to identify APA-linked susceptibility risk genes (Nature Communications 2023) and an extremely exciting new research direction: TR-gnomAD, now known as TR-Atlas, a biobank-scale TR reference map for diverse ancestries (Cell 2024 and Nature Genetics accepted).

Zoom Link

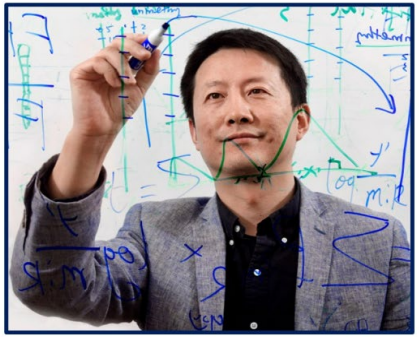
Previous

Genetics, Biomedical Computing and Genomics Monthly Seminar

Tuesday 06/04/2024
10:00 to 11:00 a.m. PST

Emerging Genetic Drivers of Human Diseases: A genome-wide spectrum of tandem repeat expansions in 338,963 humans

In this talk, Dr. Li will present an extremely exciting new research direction: the Tandem Repeat Genome Aggregation Database (UCI TR-gnomAD; ***Cell*** 2024). This groundbreaking project has positioned UCI as a leader in human and medical genetics. TR-gnomAD provides the first genetic reference maps for approximately 0.8 million Tandem Repeat (TR) expansions, such as the CAG expansion in Huntington's disease, across 340,000 humans. It revolutionizes TR-based disease-association studies, health disparity research, and clinical diagnostics. The international research and medical communities, including scientists, physicians, and genetic counselors, will heavily rely on TR-gnomAD for interpreting TR expansions in genetic diseases,



Genetics, Biomedical Computing and Genomics Monthly Meeting – "Translational Science at CFCCC-Opportunities for Collaboration and Clinical Trials", Farshid Dayyani, MD, PhD

Tuesday 05/07/2024
10:00 to 11:00 a.m. (PT)

Dr. Dayyani is a Professor of Clinical Medicine in the Division of Hematology/Oncology at University of California Irvine and board certified in Medical Oncology. He is also the Associate Director for Translational Science and the Medical Director of the Clinical Trials Unit at the Chao Family Comprehensive Cancer Center at UC Irvine.

Dr. Dayyani performs clinical and translational research in gastrointestinal and hepatobiliary carcinomas. He manages a wide portfolio of investigator initiated, NCI funded and industry sponsored clinical trials to develop novel treatment options and establish new biomarkers. He obtained his MD/PhD from LMU Munich, Germany, followed by a research fellowship and residency in internal medicine at Harvard Medical School, Boston. He then completed a combined clinical and research fellowship in medical oncology at the UT MD Anderson Cancer Center, Houston, TX. Dr. Dayyani also has industry experience as Global Clinical Lead for Oncology at Roche Diagnostics, Int. in Rotkreuz, Switzerland, prior to joining UC Irvine.

Workshops

Upcoming

Workshop on Spatial Transcriptomic Data Analysis with an Emphasis on 10x Genomics Visium

Tuesday 11/12/2024
9:00 a.m. to 1:00 p.m. (PST)
Sprague Hall, Room 105

This workshop will introduce data analysis workflow with both sequencing- and imaging-based spatial transcriptomics platforms, using 10x Genomics Visium and Xenium as examples. The topics will include an overview of preprocessing and data visualization with both 10x Genomics proprietary software and the state-of-the-art open-source software. New topics such as Visium HD and Xenium 5k data analysis will be discussed including cellular niche and spatial differential analysis methods. A guided tour will be provided on how to run the latest visualization and data exploration tools to support spatial transcriptomics via command line and Jupyter Hub on HPC3. ***Attendees are encouraged to bring their own project data for analysis and discussion.***

Registration is required – $50 and limited to 20 attendees

Register Today!

Previous Workshops

Spatial Transcriptomic Data Analysis & Software

Tuesday 02/27/2024
8:00 a.m. to 12:00 p.m. - Light continental breakfast provided
Sprague Hall, Room 105

Genomics Research and Technology Hub (GRT Hub) Workshop

Required: Personal laptop (Mac or Windows) and HPC3 account

Instructors: Jenny Wu, PhD and Ivan Chang, PhD

This workshop introduces data analysis workflow with both sequencing and imaging based spatial transcriptomics platforms, using 10x Visium and Xenium as examples. The topics included an overview of data quality control, preprocessing and visualization, cellular segmentation etc. with 10x proprietary software and state of the art Open-source software. A guided tour was provided on how to run the latest visualization and data exploration tools to support spatial transcriptomics via both the command line and the Jupyterhub of HPC3.

- Computing on the HPC3 for Spatial Omics Ivan Chang, PhD
- Introduction to 10x Visium and Xenium spatial platform data analysis workflow and analytical tools Jenny Wu, PHD
- Interactive Computing on the HPC3 for Spatial Omics, Ivan Chang, PhD
- Introduction to 10x Visium and Xenium Spatial Platform Data Analysis, Jenny Wu, PhD

10x Genomics Spatial Workshop Series – Three Sessions

Thursday 01/11/2024 – Wednesday 01/24/2024
This text for testing only
Webinar

Because cells reside within microenvironments, their functions are influenced by the network cells surrounding them, sending and receiving messages. Spatially resolved biology, including whole transcriptomic and targeted in situ methods, allows scientists to build a more complete view of cellular function in a morphological context, representing a paradigm shift in the study of biological systems. Visium from 10x Genomics is a NGS-based spatial discovery platform that allows whole transcriptome profiling of tissues. The Xenium In Situ platform is an imaging-based solution that provides precise localization of thousands of RNA targets with subcellular resolution, offering true single cell spatial analysis. Insights from these spatial techniques can be combined with single cell data to bring greater resolution and enable a deeper understanding of gene expression patterns, helping researchers develop and refine hypotheses.

January 11. 2024 – Xenium – Accelerating the Master of Biology
January 18, 2024 – Xenium
January 24, 2024 – Visium Gene Expression

Research Support

Experimental Planning

Staff of the GRT Hub are experts excited to assist you in the overall conception and framing of the experimental workflow. If you are new to using the Hub or working with a particular instrument or technique, it is advised to meet as much in advance as possible with the Hub Manager, Melanie Oakes, PhD, in order to understand the workflow, expertise and resources that may be required as well as the time frame and cost to go from concept to product. In addition, for planning with regard to numbers of samples required for statistical robustness, meeting with the Director for Bioinformatics, Jenny Wu, PhD, is advised. For understanding your own computer resources that may be required, meeting with our expert in bioinformatic engineering, Ivan Chang, PhD, may also be helpful, particularly if your experiments are data intensive and you are new to UCI or the HPC3.

Grant Applications

Strategic planning for grants including experimental workflow, time for execution, data collection and analysis performed in the GRT Hub should be addressed as much in advance of the grant deadline as possible to ensure time to provide complete support. Direct assistance in grant writing is a recharged expense, however, grant planning, costing etc. is not.

Letters of support (LOS) The GRT Hub can provide either a standard LOS, or a customized version. In either case, when requesting such a letter, please provide the PI name(s), agency and title of the grant, and abstract or other brief description of the goal and aims of the research and nature of genomics experimental workflow. Please follow-up by letting us know if your application was successful or if we can assist with the resubmission.

Budgeting for GRT Hub genomics iLab has a complete list of the rates for work in the GRT Hub; however, these rates do not necessarily include supplies, so you are advised when starting a new series of experiments to confer with the GRT Hub staff to accurately project both the cost of reagents and the recharge rate from the Hub covering the Hub's expenses in service contracts and staff time. Also, please check with your specific center regarding any supplements related to membership in the Cancer Center or Skin P30 and with the Manager for any volume related discounts.

Budgeting for computational staff time, computing cycles, hardware and software resources. NIH now appropriately stresses budgeting for data analysis including expert time compensation and computational resources. Staff can advise on the extent of these types of resources likely to be required and the suitability of HPC3 to support.

Publications

As the experimental workflow is reduced to and progresses into the data collection phase, it will be important to rigorously collect data and evaluate in real time to ensure that the expected data types are going to actually fulfill SOPs the needs for addressing the hypothesis or discovery mission. Upon completion of the experiment with appropriate records of the work, the staff can, on a recharge basis, assist with drafting parts of the experimental design, data collection, and analysis, and graphical displays, in which they were involved or before which they can be provided with complete documentation to facilitate the draft description. It is appropriate when there are creative contributions by the staff to include them in authorship on publications. This benefits the staff obviously, but in also your own efforts when you cite them as experts involved in your next grant application or letter of support from the GRT Hub.

Publications

When our services have provided data that will be used in a manuscript, we would appreciate acknowledgement of the shared instrumentation grants and support from the Chao Comprehensive Cancer Center at UCI, Complexity, Cooperation and Community in Cancer and the Skin Biology Resource-Based Center at UCI.

The following publications have acknowledged these services and support:

Publications
Sergei Butenko, Raji R. Nagalla, Christian F. Guerrero-Juarez, Francesco Palomba, Li-Mor David, Ronald Q. Nguyen, Denise Gay, Axel A. Almet, Michelle A. Digman, Qing Nie, Philip O. Scumpia, Maksim V. Plikus & Wendy F. Liu. Hydrogel crosslinking modulates macrophages, fibroblasts, and their communication, during wound healing. (2024) nature 2024 August 09. doi.org/10.1038.
Melanie T. Hacopian, Sarai S. Finks, and Kathleen K. Treseder. Drought mediates the response of soil fungal communities post-wildfire in a Californian grassland and coastal sage scrubland. (2024) elsevier 2024 June 30. j.soilbio.2024.109511.
Subrata Sabui, Selvaraj Anthonymuthu, Kalidas Ramamoorthy, Jonathan Skupsky, Tara Sinta Kartika Jennings, Farah Rahmatpanah, James M Fleckenstein, and Hamid M Said. Effect of knocking out mouse Slc44a4 on colonic uptake of the microbiota-generated thiamine pyrophosphate and colon physiology. (2024) ajpgi 2024 May 7. ajpgi.00065.2024
Childs, J.E., Morabito, S., Das, S., Santelli, C., Pham, V., Kusche, K., Vera, V.A., Reese, F., Campbell, R.R., Matheos, D.P., Swarup, V., and Wood. M.A. Relapse to cocaine seeking is regulated by medial habenula NR4A2/NURR1 in mice. (2024) Cell Rep. 2024 Mar 26;43(3):113956.
Chea, S., Kreger, J., Lopez-Burks, M.E., Laclean, A.L., Lander, A.D., and Calof, A.L. Gastrulation-stage gene expression in Nipbl+/- mouse embryos foreshadows the development of syndromic birth defects. (2024) Sci Adv. 2024 Mar 22; 10(12): eadl4239.
Chen, Z., Snetkova, V., Bower, G., Jacinto, S., Clock, B., Dizehchi, A., Barozzi, I., Mannion, B.J., Alcaina-Caro, A., Lopez-Rioz, J., Dickel, D.E., Visel, Z., Pennacchio, L.A., and Kvon, E.Z. Increased enhancer-promoter interactions during developmental enhancer activation in mammals. (2024) Nat Genet. 2024 Mar 20. doi: 10.1038/s41588-024-01681-2
Kastenschmidt, J.M., Schroers-Martin, J.G., Sworder, B.J., Sureshcandra, S., Khodadoust, M.S., Liu, C.L., Olsen, M., Kurtz, D.M., Diehn, M., Wagar, L.E., and Alizadeh, A.A. A human lymphoma organoid model for evaluating and targeting the follicular lymphoma tumor immune microenvironment. (2024) Cell Stem Cell. 2024 Mar 7;31(3):410-420.e4.

How to Acknowledge the GRT Hub in your Publications

Publication Acknowledgement

UCI 趙 Chao Family Comprehensive Cancer Center

Thank You

www.cancer.uci.edu

UCI 趙 Chao Family Comprehensive Cancer Center

Mass Spectrometry Shared Resource (MS)

Felix Grün, PhD
Director, MSF, Chemistry

Mission and Leadership

MISSION

Support researchers with expertise and services in mass spectrometric analysis of proteins, oligo nucleotides, metabolites and drugs

To fulfill this mission, **MS**:

- Consists of three facilities/labs that provide specialized expertise and high-end instrumentation
- Provides consultation on project goals, choice of analytical pipelines, instrument selection, method development
- Provides access to instruments (walk-up open access or staff operated)
- Provides staff services and user training as appropriate
- Provides data analysis and interpretation from self-guided to intensive collaborative projects
- Assists with publications and grant submissions

LEADERSHIP

Felix Grün, PhD

Director, MSF
Chemistry

Lan Huang, PhD

Director, HMSF
Physiology & Biophysics

Cholsoon Jang, PhD

Nutrient Metabolism &
Disease Lab

Services

High-end Mass Spectrometry Facility (HMSF)

https://sites.uci.edu/hmsf

High-end Orbitrap instruments

- ThermoSci Orbitrap Fusion Lumos Tribrid
- ThermoSci Orbitrap XL
- **Qualitative and quantitative profiling of whole proteomes**
- **Multiplexed, targeted, and label-free quantitative proteomics**
- **Characterization of post-translational modifications (PTMs)**
- **Protein interaction and structural analysis using cross-linking (XL-MS)**

Staff services:

- Staff operated (Clinton Yu, PhD)
- Per sample, project or longer term collaborative support
- Project seed funding

Nutrient Metabolism & Disease Lab (NMDL)

Project Services

- Orbitrap and triplequad LC-MS/MS instruments
- **Untargeted and targeted metabolomics/lipidomic analyses**
- **Stable isotope tracing experiments**
- **Focused on metabolic changes in health and disease**

Services:

- Data acquisition
- Bioinformatic analysis

Services

Mass Spec Facility (MSF, Chemistry)

https://ucimsf.ps.uci.edu

Walk-up Open Access for 20 instruments

- LC-MS and GC-MS for **polar and non-polar small molecule analysis** (low resolution)
- LC-MS/MS for **peptide/protein characterization**; sequencing; PTMs; (high resolution ± 3ppm)
- LC-MS/MS for **untargeted metabolomics/lipidomics**
- LC-MS/MS for **quantitative targeted metabolomics** (e.g. custom assays, PK/PD studies)
- MALDI for **proteomics and polymers**
- MALDI IMS for **spatial metabolomics/lipidomics**

Staff services (B. Katz, C. Dicksion, F. Grün):

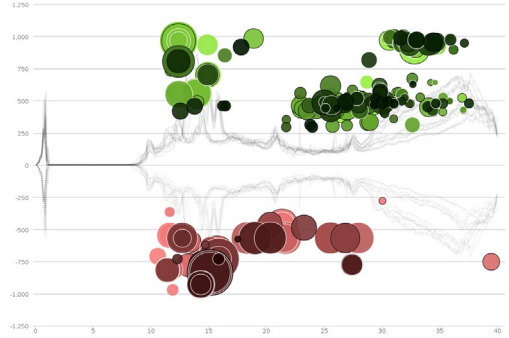
- **User/instrument training** (weekly)
- Molecular formulae (MF) validations
- Protein characterization (exact mass; sequencing; PTMs; conjugates)
- Oligonucleotide (exact mass; conjugate validation)
- Imaging Mass Spectrometry
- Data processing and software packages: onsite or via Server & Remote Desktop

Pricing/Service time

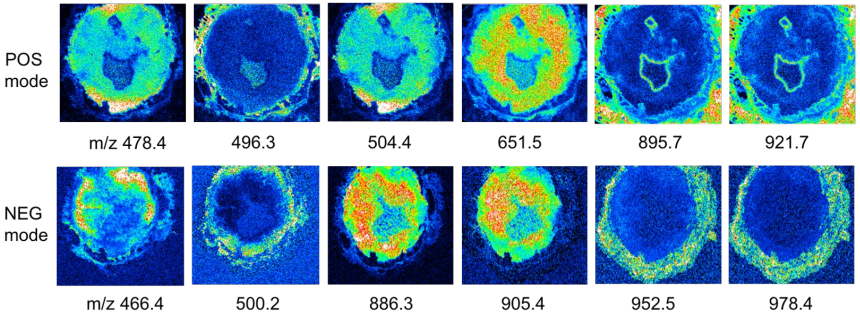
- Low cost ($3-20 per sample)
- High-throughput: results from 5 mins to 2-3 day
- **Open 24/7**

Example Service

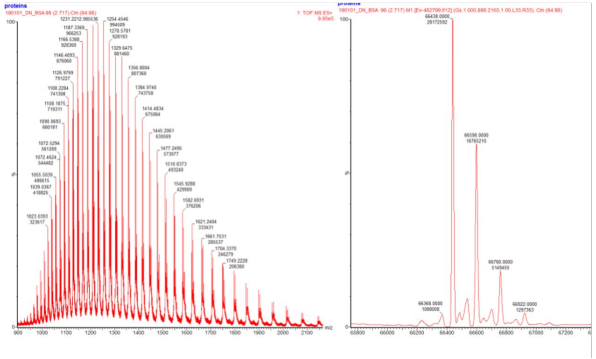
Untargeted Metabolomics: Biomarkers



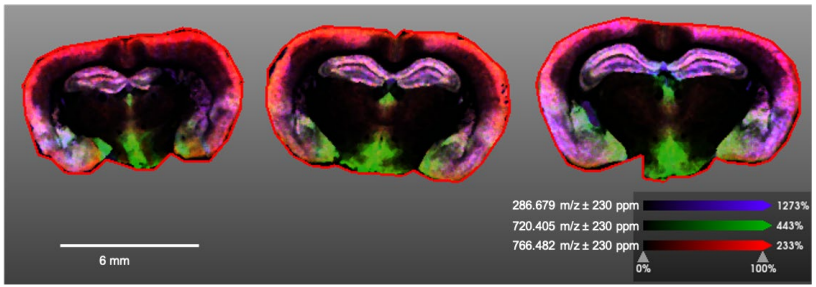
Tumor Imaging: Spatial Metabolite Profiling



Protein Characterization



AD Brain Lipid Imaging



NIH S10 award: Shimadzu iMScope

UCI 趙 Chao Family Comprehensive Cancer Center

Thank You

www.cancer.uci.edu

UCI 趙 Chao Family Comprehensive Cancer Center

In Vivo Functional Onco-Imaging (IVFOI)

Gultekin Gulsen, PhD | *Co-Director*
Zhuoli Zhang, MD, PhD | *Co-Director*
Farouk Nouizi, PhD | *Manager*

Mission and Leadership

MISSION

Enhance and support basic and clinical cancer researchers by providing the necessary expertise, imaging instrumentation, and image analysis techniques

To fulfill this mission, **IVFOI**:

- Provides high-quality image acquisition and data analysis services for translational clinical studies
- Establishes several multi-modality imaging systems to support innovating imaging studies
- Develops several cutting-edge technologies for quantitatively accurate high-resolution small animal imaging and translates them to clinical settings

LEADERSHIP

Gultekin Gulsen, PhD
Co-Director

Zhuoli Zhang, PhD
Co-Director

Farouk Nouizi
Manager

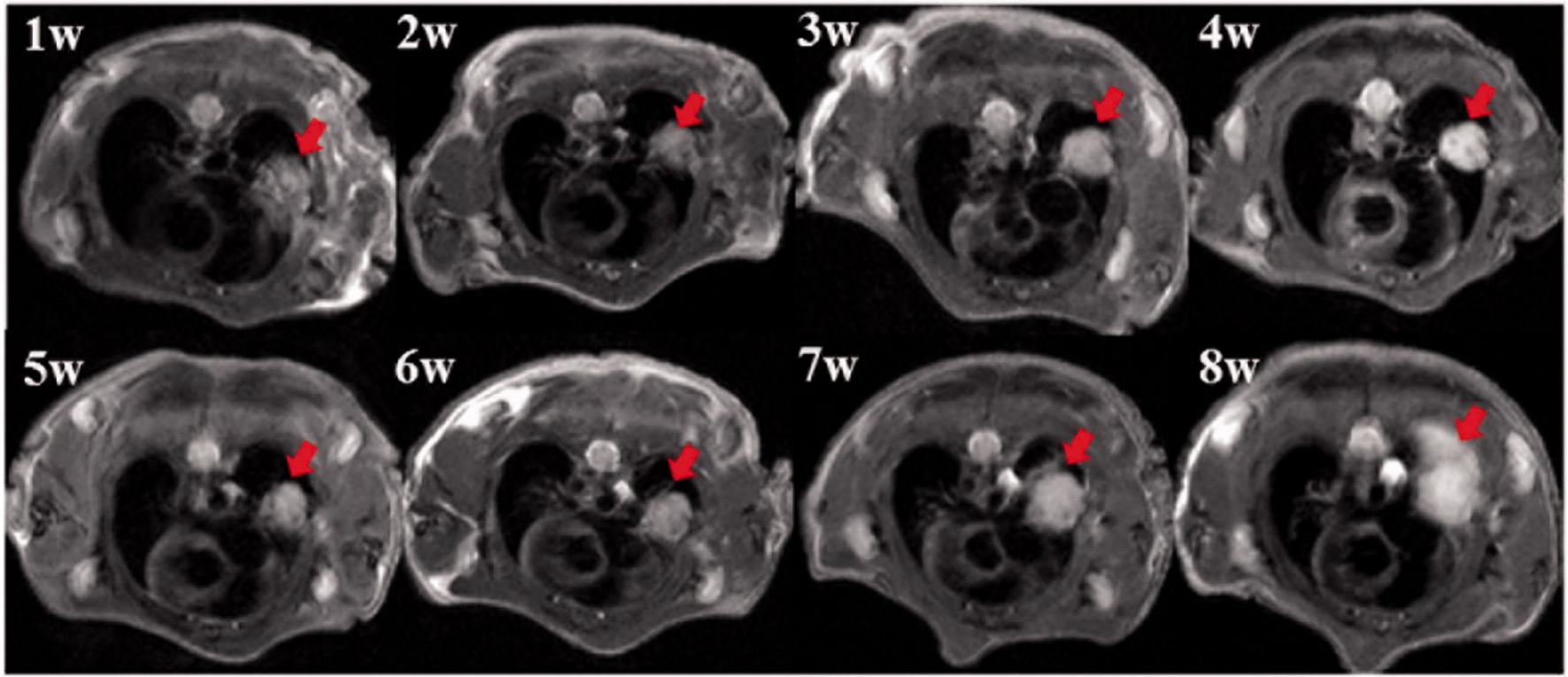
In-Vivo Functional Onco-Imaging (IVFOI)

Support Preclinical and Clinical Imaging Activities

- Design
- Protocol
- Execution
- Data Analysis
- Translational

In-Vivo Functional Onco-Imaging (IVFOI)

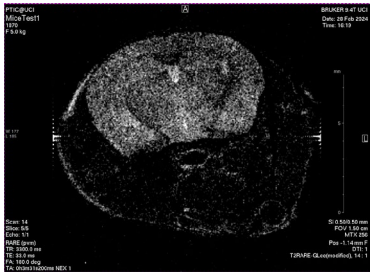
Measure Tumor Volume with Time?



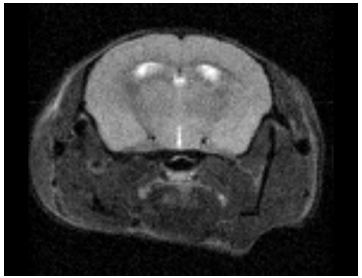
Key Equipment & Technologies

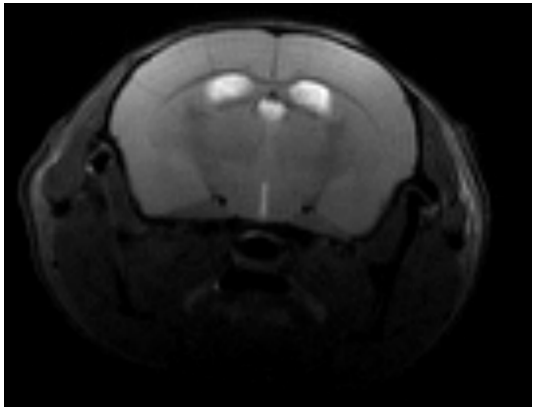
Bruker 9T MRI

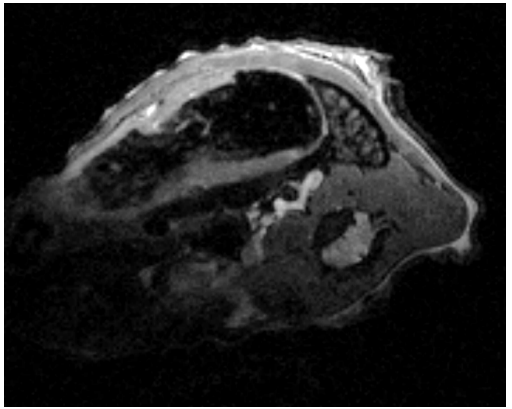
Feb 2024



Jun 2024

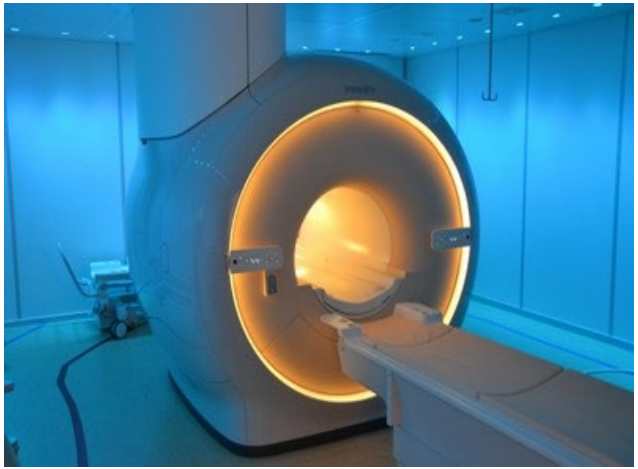


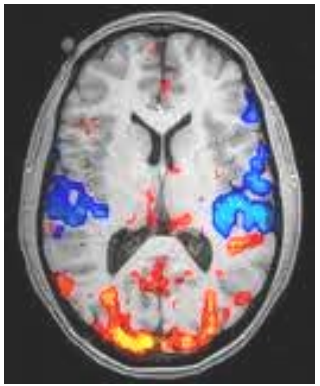


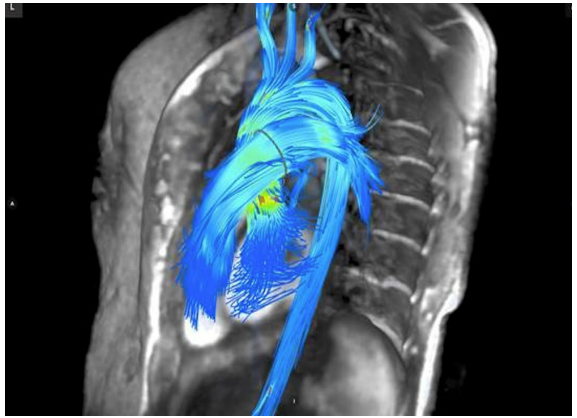


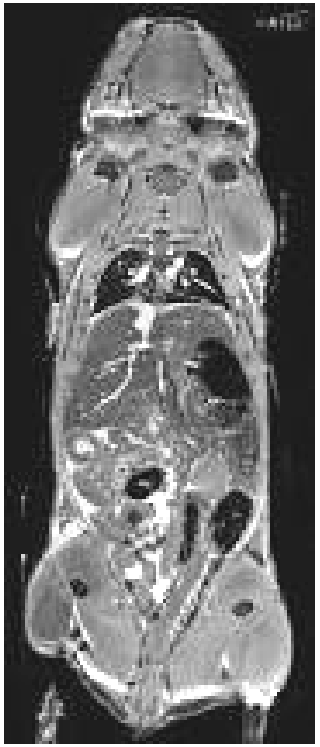
Key Equipment & Technologies

Phillips Achieva 3T MRI

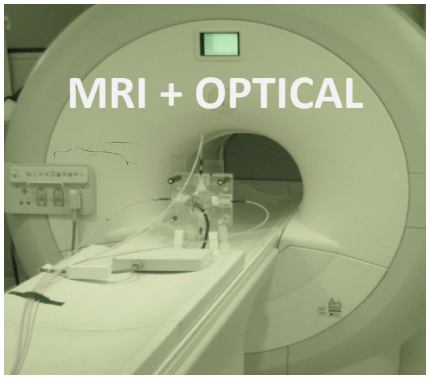




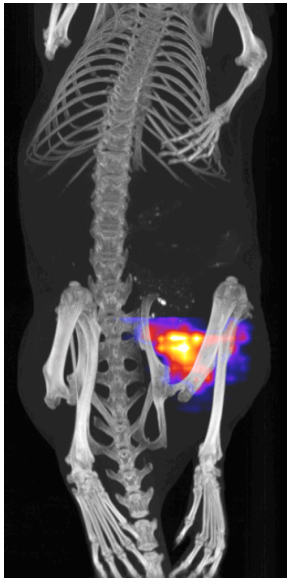




Key Equipment & Technologies



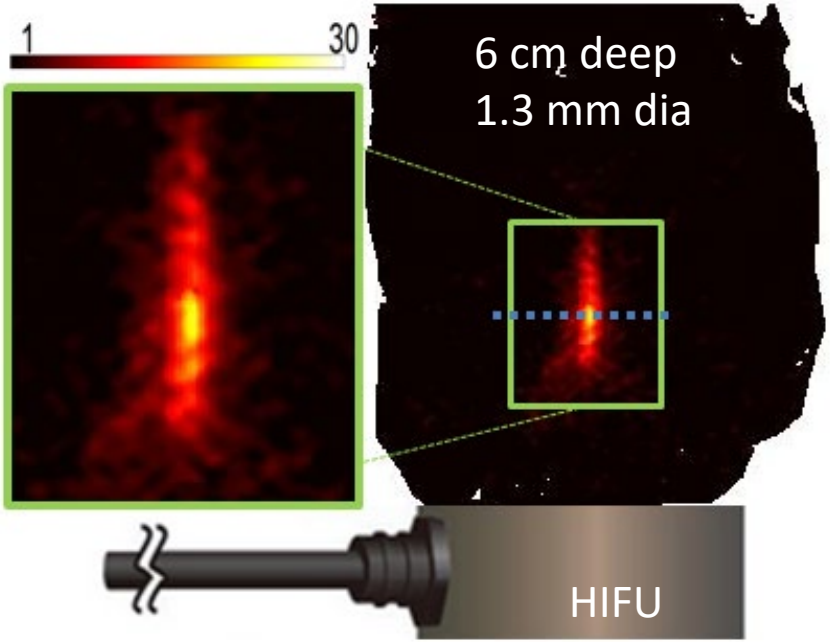
Xray + PET+OPTICAL



- Infrared Fluorescent Protein
- Smart Targeting Probes
  such as MMP, VGEF targeting

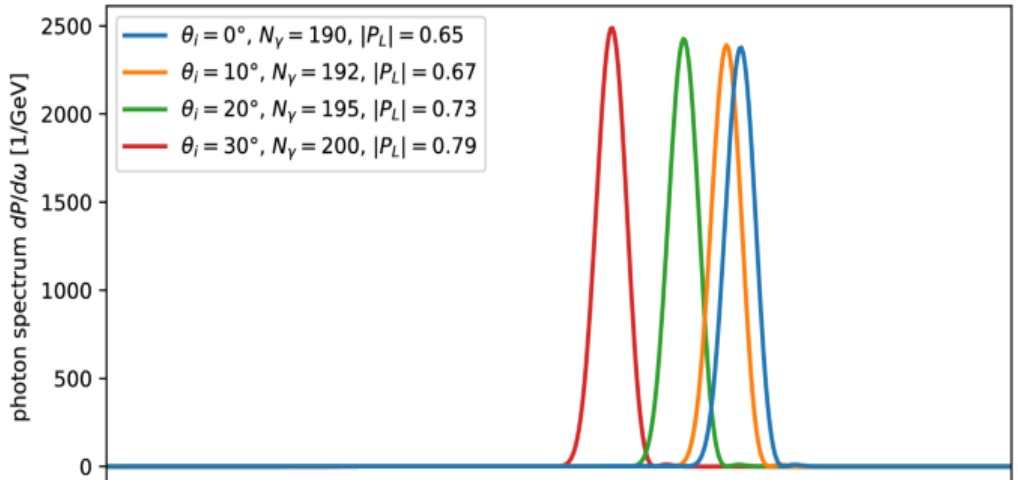
Near Future Plans

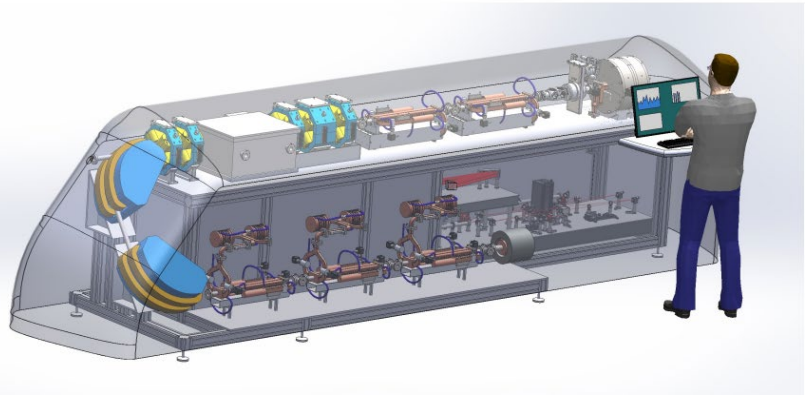
MRI Compatible High Intensity Focused Ultrasound



Commercial MR Compatible HIFU system for small animals

LUMITRON Tunable Monoenergetic X-ray Source (TMXS)





Chris Barty, PhD (BIDD)

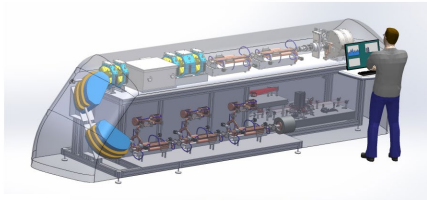
Lumitron

UCI Chao Family Comprehensive Cancer Center

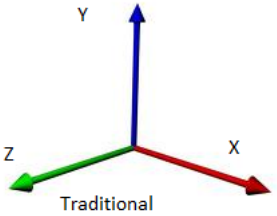
LUMITRON Tunable Monoenergetic X-ray Source (TMXS)

4T1 Breast Cancer
Tumor Model

X-ray Beam
(Ultra Low Dose)



- Designing an interface
- Performing Simulations
- Contributing to UCI site design
- Waiting for the beam-time



xyz translation stage (2D Planar Imaging)
+
rotation state (3D Tomographic Imaging)

Chris Barty, PhD (BIDD) | **Lumitron**

UCI 趙 Chao Family Comprehensive Cancer Center

Thank You

www.cancer.uci.edu

UCI 趙 Chao Family Comprehensive Cancer Center

Experimental Tissue Resource (ETR)

Robert Edwards, MD, PhD | *Co-Director*
Wendy Cozen, DO MPH | *Co-Director*
Delia Tifrea, PhD, MBA | *Manager*

Mission and Leadership

MISSION

ETR supports the research mission across UC Irvine and the campus research community

- **HS# 2012-8716**
  Honest broker status → Facilitates and track usage of tissue for research
- **Support**
  1. Chao Family Comprehensive Cancer Center grant
  2. Pathology Department
  3. Approved recharge rates

LEADERSHIP

Robert Edwards, MD, PhD
Co-Director

Wendy Cozen, DO, MPH
Co-Director

Delia Tifrea, PhD, MBA
Manager

Services

- **Tissue and Correlative Clinical Data Procurement and Distribution**
  - Fresh; archival bio-banked flash-frozen; archival formalin-fixed, paraffin-embedded (FFPE) tissues
  - Virtual biorepository portal for FFPE specimens
  - Customized request of clinical data annotation
  - Cryopreserved viable blood and marrow cell samples

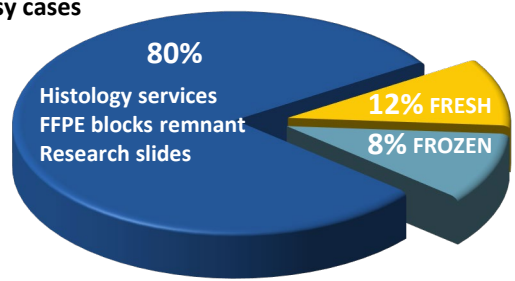
- **Tissue Histology, Immunohistochemistry (IHC), and Digital Pathology services**
  - Routine histology services: embedding, cutting FFPE and frozen, staining, cytochemical stains, automated IHC staining, and IHC optimization.
  - Ventana DP200 high-speed digital slide scanners
  - Custom and standard TMA

- **Interpretive Histopathology and Mouse Pathology Services**
  - Necropsy, histopathology consultations, consultation on orthotopic and patient-derived xenograft (PDX) tumor models and experimental design

- **Archival FFPE blocks and slides remnants since 1989**

343,635 surgical cases

2,365 autopsy cases



- **Cancer related projects/year 63%**

- **Total individual requests/year 1620**
- **Patients -Human tissue RO/year 1200**
- **Animal tissue projects RN/year 200**
- **Fresh tissue –34 projects/year –> 320tissue/year**

More information regarding all services can be found at: https://cancer.uci.edu/experimental-tissue-resource

Key Equipment & Technologies

- **Routine histology services:** Leica Peloris Tissue processor, microtome, Leica CM3050 Cryostat, Ventana Discovery automatic stainer






- -80°C and LN2 freezers
- Freezerworks SUMIT biobanking inventory program
- Ventana DP200 high-speed digital slide scanner
- TMA Grand Master- 3DHISTECH

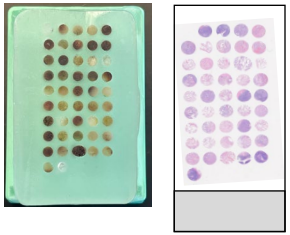

Feature technology

- **TMA Grand Master- 3DHISTECH**

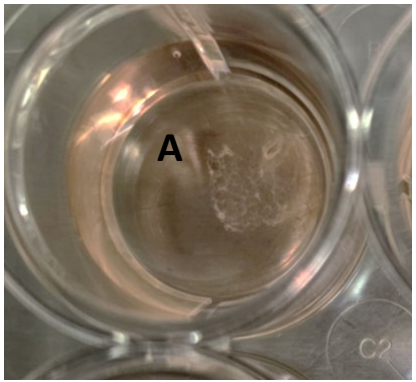
Available core/block (core diameter):

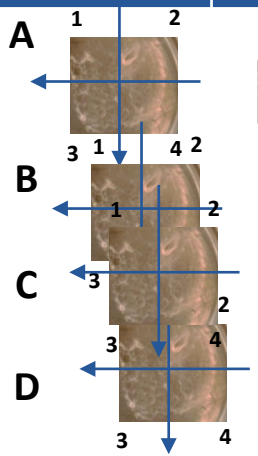
- ✓ 558 - (0.6 mm)
- ✓ 286 - (1 mm)
- ✓ 135 - (1.5 mm)
- ✓ 84 - (2 mm)

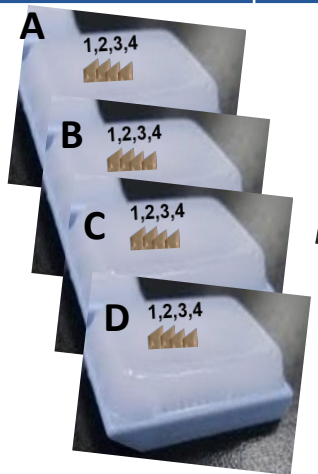
Feasible for proteomics ***nanoString***- GeoMx DSP

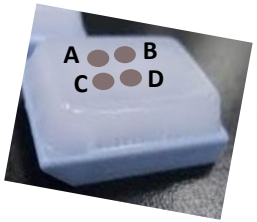


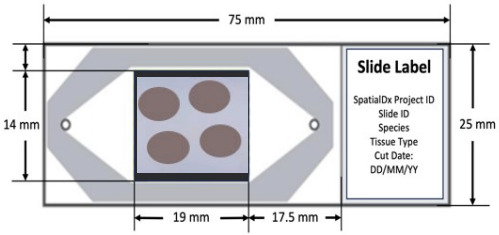
150 microns thick lung Tissue cultured	Formalin fixed cut in 4	Stacking	Paraffin embedding	Custom TMA	High-plex Single-Cell Spatial Omics











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Biostatistics Shared Resource (BSR)

Min Zhang, MD, PhD[2]
Director

Mission and Leadership

MISSION

BSR provides a centralized resource of biostatistical expertise for the experimental design and analysis of basic, translational, clinical, and population-based cancer research

To fulfill this mission, **BSR**:

- Initiates active participation during grant preparation in the areas of cancer etiology, genetics, detection, and prevention
- Partners on research design, qualitative, and quantitative protocol features
- Incorporates existing and develops new statistical methods
- Provides guidance on sample size requirements

LEADERSHIP

Min Zhang, MD, PhD[2]
Director

Wen-Pin Chen, MS
Manager

Services

- **Study Design, Data Analysis, and Interpretation**
  - Study design and sample size calculations
  - Data management and quality control
  - Data analysis, interim analyses, interpretation of findings, treatment of missing data

- **Develop & Maintain Statistical Quality Control Procedures**
  - Statistical review of research protocols and grant preparation
  - Evaluate protocols for clear statements of objectives, background and purpose
  - Elements for evaluation include drug information, staging criteria, eligibility criteria, stratification or randomization schemes, treatment plan, monitoring of toxicities and dosage modification, and criteria for evaluation and endpoint definitions

More information regarding all services can be found at: http://cancer.uci.edu/bsr

Services

- **Omics Data Analysis**
  - Genomic (SNP, WGS, WES) data analysis (including GWAS, PheWAS)
  - Transcriptomic (bulk/single cell RNA-seq) including eQTL
  - Epigenetics (ChIP-seq; ATAC-seq)
  - Single-cell multi-omics
  - Functional (pathway, GO)
  - Metabolomics

- **Consulting**
  - Bioinformatics
  - Database
  - Machine Learning
  - Statistical genetics and genomics

- **Research Computing**
  - HIPAA-compliant computational needs, cloud computing technologies
  - Setup and run computationally intensive jobs on Cloud
  - Programming assistance
  - Database design, creation and management

Training & Education

BigCARE 2024 Summer Workshop

bigcare.uci.edu

The Chao Family Comprehensive Cancer Center (CFCCC) of the University of California, Irvine is pleased to announce the annual NCI-funded workshop on "Big Data Training for Cancer Research" (BigCARE) on July 14-26, 2024. This intensive workshop will help cancer researchers develop skills for managing, visualizing, analyzing, and integrating various types of omics data in cancer studies. The workshop is open to oncologists, faculty, postdoctoral researchers, and graduate students. With supplemental funding from NIAID, we also welcome researchers in infectious & immune-mediated diseases. Individuals from underrepresented groups are especially encouraged to apply. The workshop will be held on-site at the University of California Irvine, in Irvine, CA. There is **no cost** for registration, tuition, food, and lodging! Travel scholarships would be available for a limited number of participants. We will continuously review applications weekly until all spots are taken. The latest application deadline is Friday, March 1, 2024. Please check our website for more information.

The BigCARE Team

When:
July 14-26, 2024

Where:
University of California, Irvine (UCI)

Website:
bigcare.uci.edu

Contact:
bigcare@uci.edu

NIH NATIONAL CANCER INSTITUTE | UCI Chao Family Comprehensive Cancer Center | UCI Program in Public Health | NIH National Institute of Allergy and Infectious Diseases

Selected 2024 Publications

CFCCC INVESTIGATOR(S)	PROGRAM	PUBLISHED JOURNAL	YEAR
Christine McLaren, PhD Fa-Chyi Lee, MD Farshid Dayyani, MD, PhD Jason Zell, DO, MPH Jennifer B Valerin, MD, PhD	CC BIDD SPT CC SPT	J Natl Compr Canc Netw	2024
Daniela Bota, MD, PhD	BIDD	Neuro-oncology	2024
Christine McLaren, PhD Xiaolin Zi, PhD	CC CC	Clin Transl Med.	2024
Argyrios Ziogas, PhD Gelareh Sadigh, MD	CC CC	Cancer	2024
Farshid Dayyani, MD, PhD Fa-Chyi Lee, MD	SPT BIDD	Oncologist	2024
Helen Ma, PhD Pankaj Gupta, MD Wendy Cozen, PhD	CC SPT CC	Blood Adv.	2024

Future Plans

Community Engagement / Catchment Area

- Continue to support the development of grant applications / manuscripts that focus on the catchment area and result from partnerships developed through CE efforts;
- Continue to provide consulting services on bioinformatics, biostatistics, database access, data integration;
- Expand new services on machine learning, statistical genetics and genomics, research computing to facilitate interdisciplinary collaborations in catchment area.

Enhancing Diversity, Equity and Inclusion

- Offer scholarships for underrepresented trainees to attend the NCI-funded big data workshop;
- Develop new machine learning methods to improve the analysis of data from minority populations.

Education and Training

- Organize annual NCI-funded summer workshop on “Big Data Training for Cancer Research”;
- Offer regular need-based workshops on basic statistical analysis, workflow for sequencing data analysis; FAIR computational workflows on the cloud;
- Organize regular seminar series to provide education opportunities for trainees.

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Biobehavioral Shared Resource (BBSR)

Michael A. Hoyt, PhD
Director

Mission and Leadership

MISSION

To support cancer center members and cancer researchers with expertise and services in planning, conducting, and disseminating translational biobehavioral research.

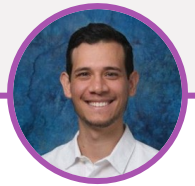
To fulfill this mission, **BBSR**:

- Assists in the conduct and communication of high quality biobehavioral research.
- Provides consultation on behavioral and/or quality-of-life patient-reported outcome measures, research design, data collection, interpretation of self-report data, manuscript preparation, and behavioral interventions.
- Participates in translational research in psychoneuroimmunology and examination of behavioral issues that enhance recruitment and development of behavioral and quality-of-life outcomes.
- Offers expertise on instrument selection and development, as well as consideration for data collection assessment intervals and strategies to obtain valid and reliable data.

LEADERSHIP

Michael A. Hoyt, PhD
Director

Michelle Fortier, PhD
Assistant Director



Jose Lechuga
Manager

Services

- Selection of Patient Reported Outcomes and Measures (PROs)
- Participant Recruitment and Retention Strategy Assistance
- Qualitative and Quantitative Data Collection and Management
- Intervention Design and Implementation
- Training and Education in biobehavioral research
- Consultation and support in best practices for the collection of biomarkers in behavioral studies
- Advanced (project-oriented special study design and analysis)

More information regarding all services can be found at: https://cancer.uci.edu/bbsr

Recent Scientific Highlights

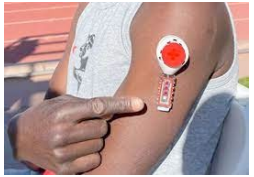
- Building an Oncofertility Questionnaire

- Empowering Interventions to Improve Lung Cancer Screening

- Addressing Financial and Social Needs Among Patients with Cancer

- Delivering a behavioral cancer intervention

- Stress & Well-being in Asian Americans with Advanced/Metastatic Cancer



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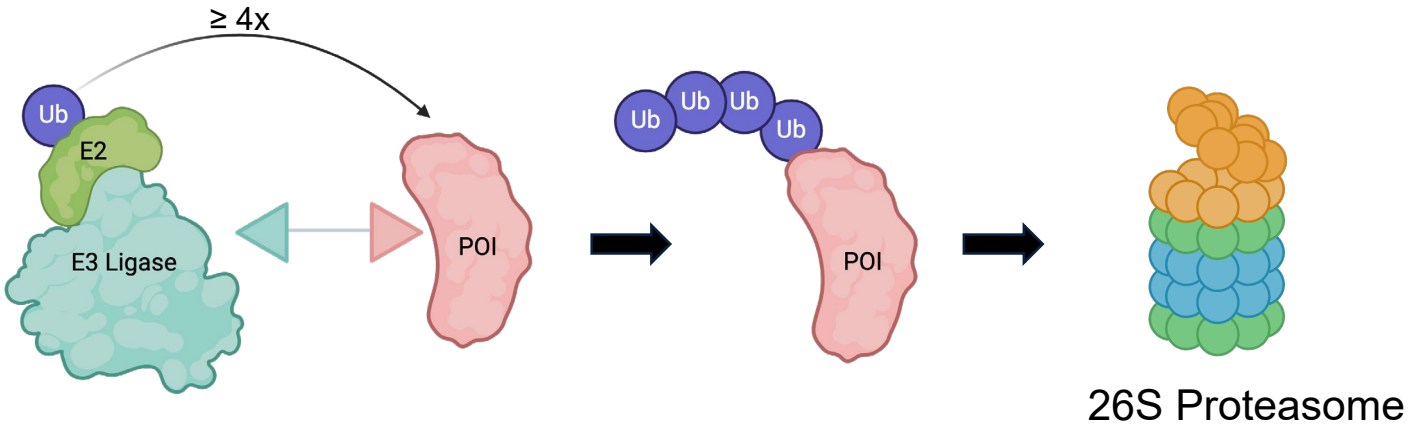
ByeTAC: Bypassing an E3 Ligase for Targeted Protein Degredation

Cody A. Loy
4th Year – Pharmaceutical Science PhD candidate
PI: Darci J. Trader, PhD

Bypassing an E3 Ligase

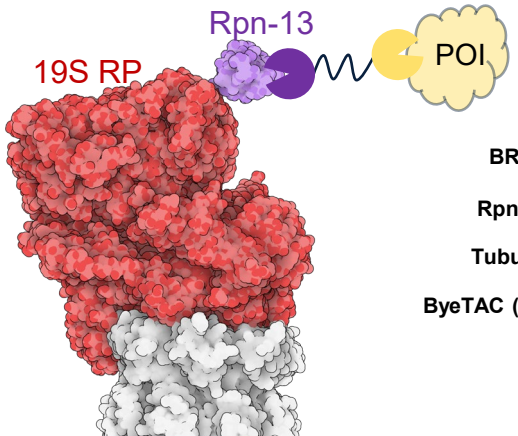
PROTACs

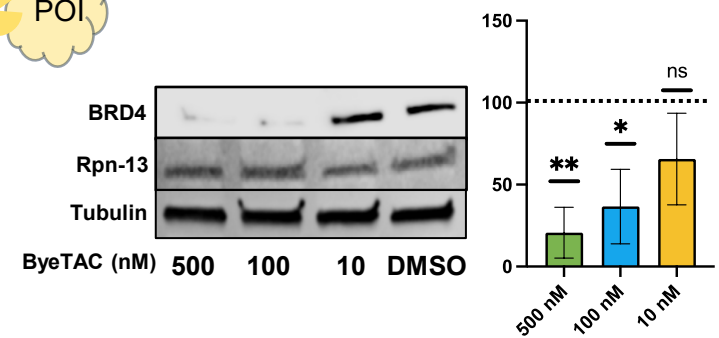


ByeTACs

Rpn-13

- Non-essential ubiquitin receptor
- Recruited in diseased states
- Attractive target for inhibition





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Relationship between cytokines, brain-derived neurotrophic factor, and cognitive impairment in adolescent and young adult cancer patients

Julia Trudeau
Graduate Student Researcher
UCI School of Pharmacy & Pharmaceutical Sciences

November 8, 2024

UCI School of Pharmacy & Pharmaceutical Sciences

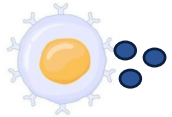
1 in 3 adolescent and young adults with cancer (AYAC, 15-39 yo) report cancer-related cognitive impairment (CRCI)

Negatively affects quality of life

Cancer

Chemotherapy

Inflammation



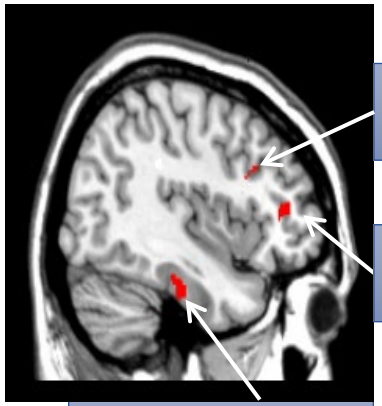
Pro-inflammatory cytokines
i.e. IL-6, IL-8, IFNγ, TNF-α

Anti-inflammatory cytokines
i.e. IL-4, IL-10

?

Brain-derived neurotrophic factor (BDNF)

CRCI



Structural changes in the brain in a 20 year old patient

Tan CJ et al. *Psychooncology*. 2020; 29(8):1355-1362.
Ng DQ et al. *Scientific Reports*. 2023;13(1):16298.
Chan A et al. *Cancer Medicine*. 2023;12(4):4821-4831.

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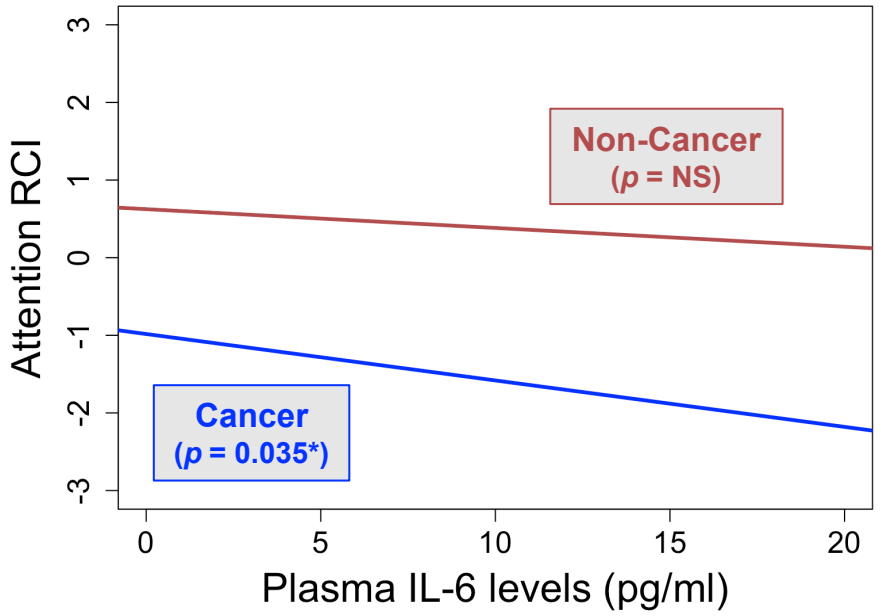
Objective:
Evaluate the associations between cytokines, BDNF, and cognition in AYAC compared to non-cancer controls from a longitudinal study

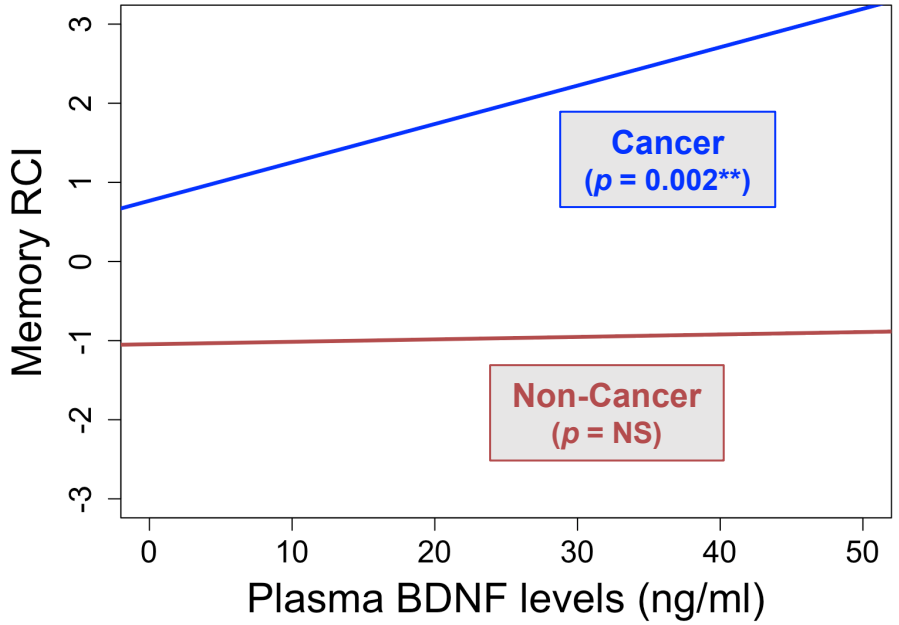
Mechanistic insight

Predictive biomarkers

Higher IL-6 associated with **worse cognition** in **AYAC** but not in **controls**



Lower BDNF associated with **worse cognition** in **AYAC** but not in **controls**



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Feasibility Study on the Effect of a Methionine-Reduced Diet on Serum Levels in Patients with Solid Tumors

Zhaohui Liao Arter, MD[1], Cholsoon Jang PhD[2], Christine Hui, MPH[1], Peter Kaiser PhD[2] , Farshid Dayyani MD, PhD[1]

Methionine-Reduced Diet Trial

Background

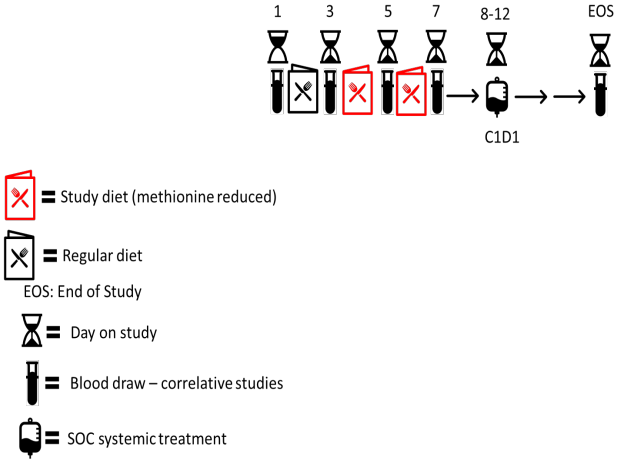
- Many solid tumors like carcinomas, sarcomas rely on high levels of methionine for growth.
- Methionine restriction has shown tumor growth inhibition and improved chemotherapy and radiation therapy response in animal models.

Trial Design

- **Type:** Single-center, open-label, Phase 0 feasibility study.
- **Objective:** Assess adherence to a methionine-reduced diet and its impact on plasma methionine levels in patients with solid tumors.

Study Objectives

- **Primary Endpoint:** Percentage of patients completing the prescribed diet.
- **Secondary Endpoint:** Adverse events (AE) by CTCAE v5.5, serum methionine levels, metabolomic and immunologic plasma markers levels.



Treatment Plan:

- Day 1-2: Regular diet with baseline blood draw on Day 1.
- Day 3-6: Methionine-reduced diet for 4 days.
- Day 3: Blood draw before starting diet.
- Day 5: Blood draw after 48 hours on diet.
- Day 7: Optional blood draw after 96 hours.
- Day 8-12: Standard of care (SOC) cancer treatment begins.
- Final Blood Draw: Between Days 21-28 after SOC initiation.

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Targeting of Mitochondrial Protein Magmas Enhances Sensitivity to GBM Treatment

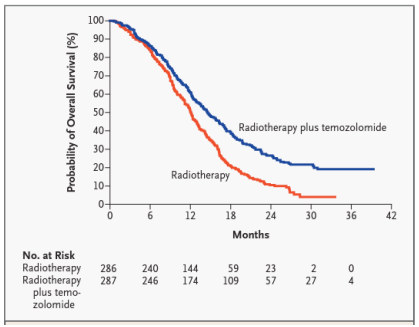
Scientific Retreat | November 8, 2024

Javier Lepe
PI: Daniela Bota, MD, PhD

Targeting of Mitochondrial Protein Magma Enhances Sensitivity to GBM Treatment

Highly aggressive malignant Brain cancer
Incidence 3 in 100,000 people in the U.S.

Median survival: 14.6 months



Radiation

Surgery

Standard of Care

Chemotherapy (TMZ)

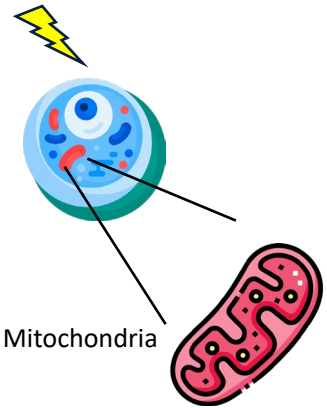
Tumor Treating Fields (DeNovo)

*Clinical trials for new treatments fail to meet their primary endpoints

Stupp R. et. al. 2005 N Engl J Med

Targeting of Mitochondrial Protein Magma Enhances Sensitivity to GBM Treatment

Radiation / Chemotherapy



Resistance mechanisms
DNA damage repair
Glioma stem cells
Tumor heterogeneity
Mitochondrial reprogramming*

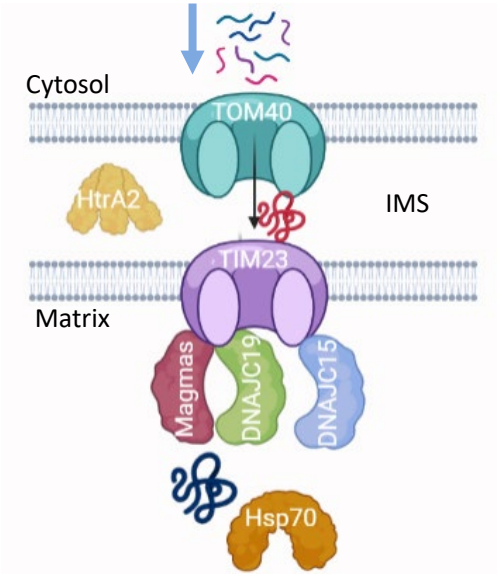
Research Focus

Role of MAGMAS in treatment resistance

MAGMAS - ~13kDa Mitochondrial Protein
Highly expressed in GBM
Regulates protein trafficking in the mitochondria
Inhibition with BT9 and KD sensitizes cells to treatments

Protein Trafficking Pathway

Precursor proteins



Mature proteins

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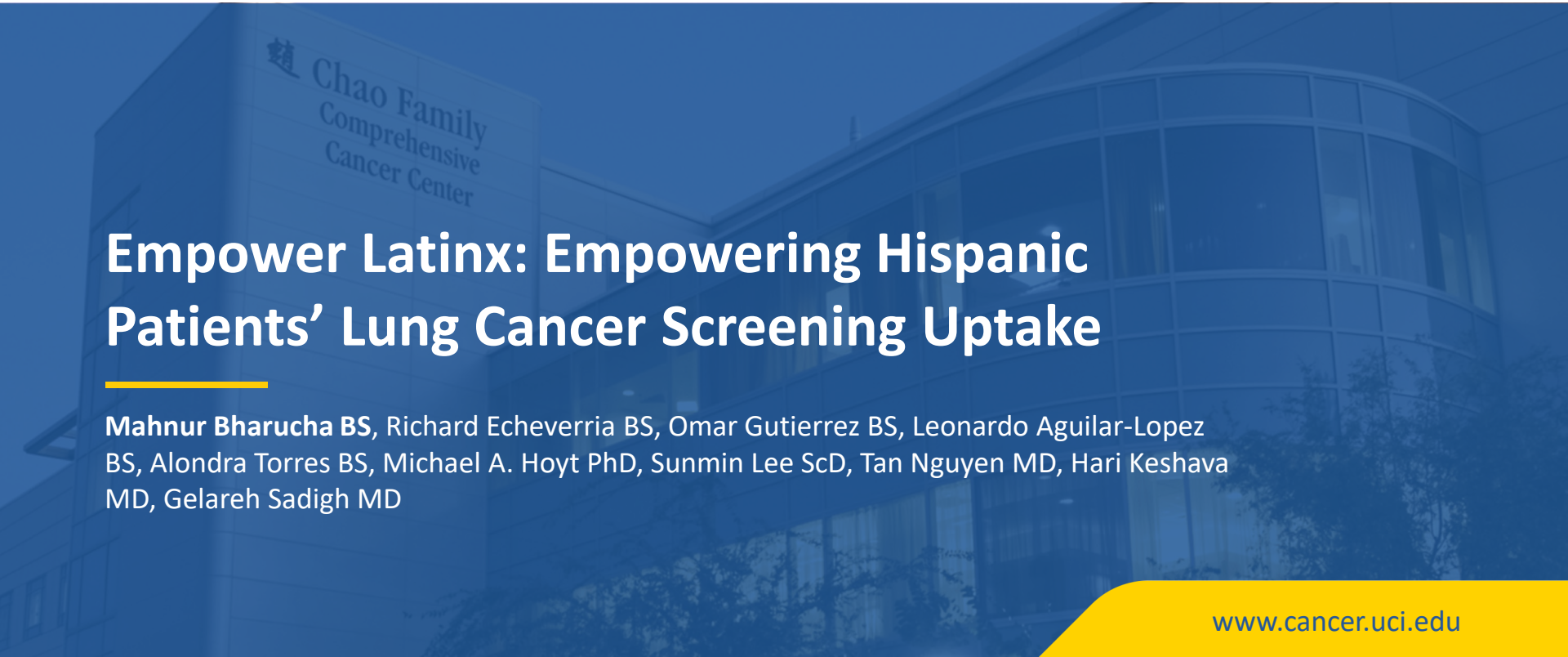
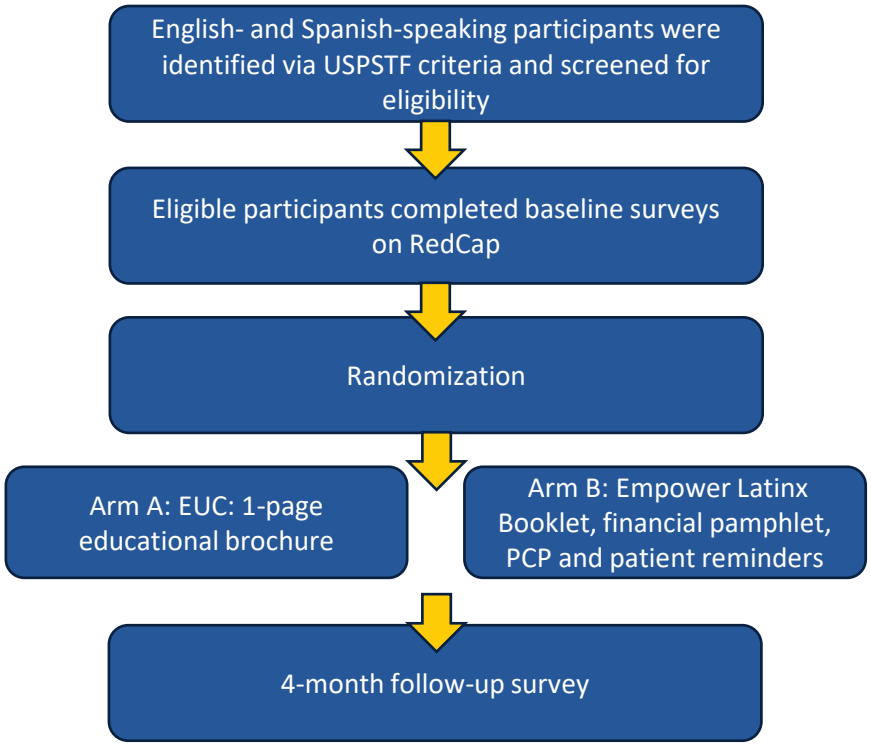


Empower Latinx: Empowering Hispanic Patients' Lung Cancer Screening Uptake

Mahnur Bharucha BS, Richard Echeverria BS, Omar Gutierrez BS, Leonardo Aguilar-Lopez BS, Alondra Torres BS, Michael A. Hoyt PhD, Sunmin Lee ScD, Tan Nguyen MD, Hari Keshava MD, Gelareh Sadigh MD

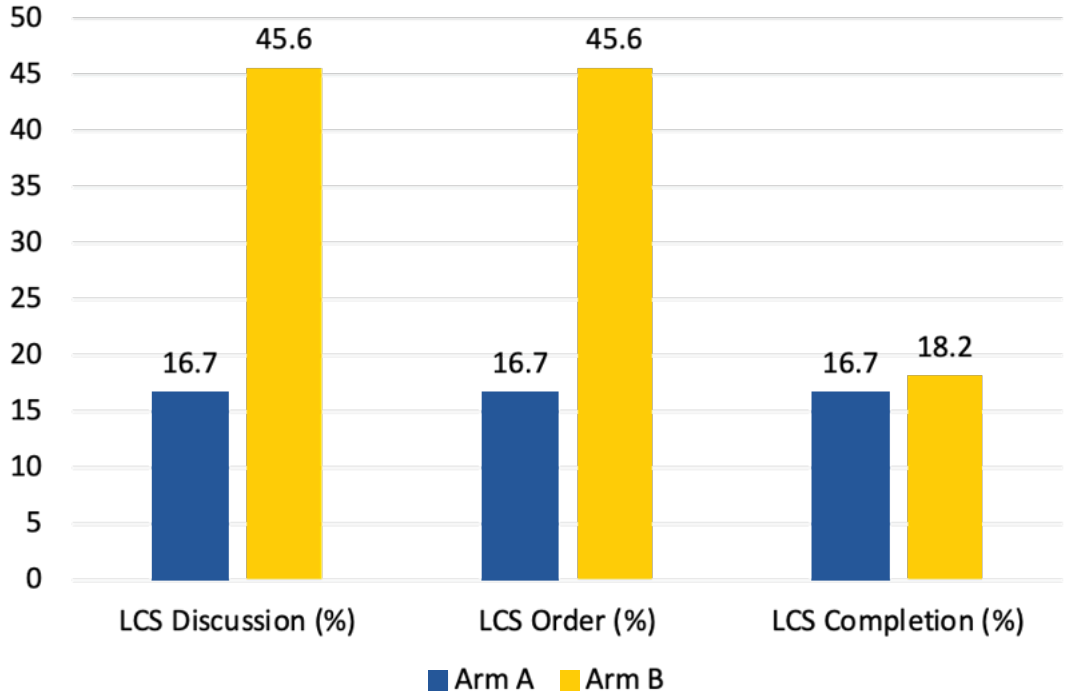
Background & Study Design

- Lung cancer is the leading cause of cancer-related deaths in the U.S.
- Screening rates in the U.S. are critically low (5.8% of all eligible patients)
- Screening rates in California are even lower (0.7%)
- Hispanic patients are 16% less likely to be diagnosed early and 30% more likely not to receive any treatment compared to white patients.



Current Results

Demographics (n=23)	Values
Average Age (years)	59.9
Male (%)	47.8
Spanish Speaking (%)	26.0
Insurance	Values
Medicaid (%)	60.9
Medicare (%)	30.4
Private Insurance (%)	8.7
LCS Barriers	**Percentage (%)**
Lack of knowledge	43.5
Cost	39.1
Anticipated Expenses	39.1



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A Phase 1 Study of the Combination of Pitavastin (Pita) with Gemcitabine and nab-paclitaxel in patients with Unresectable Pancreatic Adenocarcinoma (uPDAC)

Jennifer Valerin[1,2], David Fruman[2,3], Sophie Hasson[1], Tanvi Chichili, Farshid Dayyani[1,2], Christopher Halbrook[2,3]

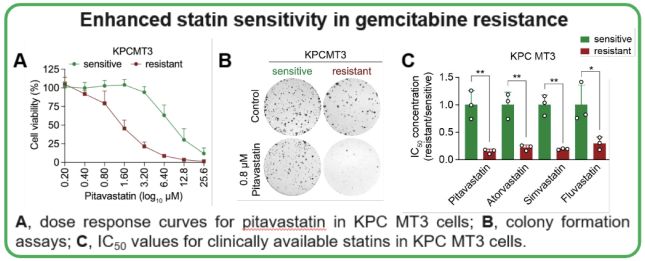
1. Department of Medicine - Division of Hematology/Oncology, University of California Irvine
2. Chao Family Comprehensive Cancer Center, University of California Irvine
3. Department of Molecular Biology and Biochemistry, University of California Irvine

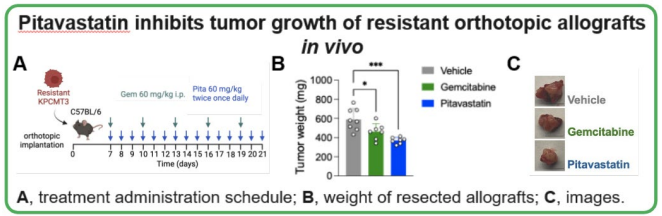
Background

- Pancreatic cancer remains one of deadliest major cancers driven by lack of response and acquisition of resistance to current treatments
- Current SOC for uPDAC: gemcitabine and nab-paclitaxel combination shows synergy and safety over single agent chemo: (PMID: 24131140) improved PFS, OS and RR

Role of HMG-CoA inhibitors in PDAC:

- Preclinical observation: acquired gemcitabine resistance in pancreatic cancer cells required metabolic rewiring





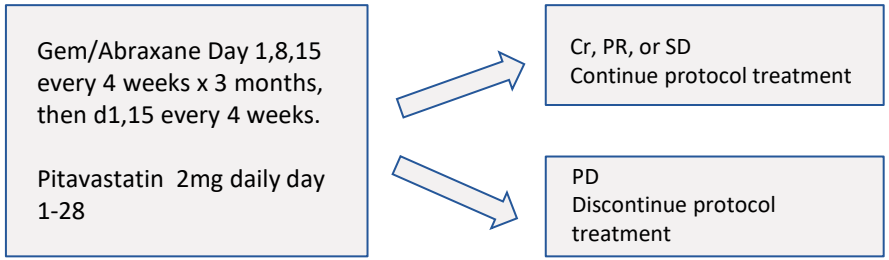
- Inhibition of HMG-CoA reductase reduces synthesis of isoprenoids which bind to Ras protein involved cell growth, proliferation, differentiation, and cancer development signaling pathways (PMID 25220658)
- In vitro, inhibition of tumor spheroid growth, induction of apoptosis and necrosis (PMID 29180851)

Gemcitabine and Pitavastatin combo in pre-clinical studies:

- In vitro, synergistically suppressed proliferation of MIA PaCa-2 cells through sub-G1 and S phase cell cycle arrest, activation of apoptosis/necrosis, and activation of cellular metabolism and autophagy (PMID 32606957)
- In vivo, inhibited tumor growth in Mia PaCa-2 xenografts (PMID 32606957)

Hypothesis

- The combination of Pitavastatin (HMG-CoA reductase inhibitor) with Gemcitabine and nab-paclitaxel is feasible and tolerable and via sub-G1 and S phase cell cycle arrest, activation of apoptosis/necrosis and other crucial cytotoxic mechanisms, might improve outcomes in uPDAC.



Abbreviations:
uPDAC: unresctable Pancreatic Adenocarcinoma, SOC: Standard of Care, DL: Dose Levels,
Pita: Pitavastatin, RP2D: Recommended phase II dose

Trial Design

- Single center, prospective, open label, non-randomized phase 1B trial (3+3 design)

Main Eligibility
- 1L + uPDAC
- ECOG 0-2
- appropriate organ function

Treatment
- Gemcitabine and nab-paclitaxel: Day 1,8,15 every 4 weeks x 3 months, then d1,15 every 4 weeks.
- Pitavastatin: Day 1-28 every 4 weeks.
    - DL -1: Pita 1 mg
    - DL 0: Pita 2 mg
    - DL +1: Pita 4 mg

Primary objective
- Primary endpoint: RP2D of Pitavastatin in combination with Gemcitabine and nab-paclitaxel in treatment of uPDAC.

Secondary objectives
- PFS, OS, ORR (in patients with measurable disease)

Total number of pts to be enrolled:
- min= 8, max= 12 (includes number of anticipated screen failures)

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