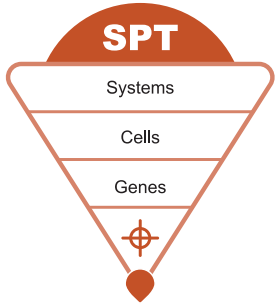
UCI 趙 Chao Family Comprehensive Cancer Center

Systems, Pathways & Targets (SPT)

ANGELA FLEISCHMAN, MD, PHD
JOHN LOWENGRUB, PHD
ROBERTO TINOCO, PHD

EAB 2025
MARCH 14, 2025

Objective & Specific Aims (Proposed for Renewal 2026)



OBJECTIVE

To identify critical mechanisms governing cancer initiation, progression and drug resistance that can be exploited for the development of novel treatments and diagnostics

AIMS

1 Cancer Pathway Targets

Identify key targets in signaling networks, developmental pathways, and metabolic programs that are relevant to cancer initiation, progression, and therapeutic resistance

2 Single-Cell Cancer Dynamics

Support multidisciplinary teams to study how heterogeneity at the single cell level and cell-cell interactions influence cancer progression and therapeutic resistance

3 Accelerate Therapy Translation

Enable clinical-basic science researcher multidisciplinary teams, via the DOTs, to accelerate the translation of preclinical research with a focus on multi-agent targeted therapy

Program Leadership

Angela Fleischman, MD, PhD
Co-Leader

EXPERTISE

- Associate Professor of Medicine, and Biological Chemistry
- Research Interests: Hematopoiesis, Myeloproliferative Neoplasm, role of inflammation in the development of hematologic malignancy

ROLES

- Support cancer cell biology research and collaboration
- Promote DOT interactions and clinical research
- CRTEC Liaison

John Lowengrub, PhD
Co-Leader

EXPERTISE

- Chancellor's Professor of Mathematics, and Biomedical Engineering
- Research Interests: Cancer Systems Biology, mathematical modeling, and emergent behavior (CRC, GBM, CML, PDAC, skin)

ROLES

- Support cancer systems biology research and facilitate collaborations
- Lead U54/P01 and R25 cancer systems biology grants

Roberto Tinoco, PhD
Assistant Program Leader

EXPERTISE

- Associate Professor, Molecular Biology and Biochemistry
- Research Interests: Cancer Immunology, T cells, Melanoma, Viral Immunology. Cellular and molecular mechanisms of T cell exhaustion and immune system dysfunction in cancer

ROLES

- Support cancer immunology research and facilitate collaborations
- Assist program co-leaders and acquire skills to lead and manage programmatic activities
- PED Liaison

SHARED RESPONSIBILITY

- Lead quarterly SPT meetings
- Connect SPT members with SPT collaborators and other CFCCC research programs
- Evaluate cancer relevance in SPT member new grants
- Review and assess new SPT member applications
- Identify SPT speakers for Scientific Retreat and other events
- Support COE Liaison

Response to Review

2021 NIH Merit Rating

OUTSTANDING TO EXCELLENT

STRENGTHS (2021 NIH Summary Statement)

> "The program excels in basic sciences and systems biology, achieving a multi-PI U54 grant, advancing clinical trials, building a strong metabolism group, recruiting talented early-career faculty, and providing excellent training"

CRITIQUE	RESPONSE
Clinical Integration: Strengthen collaboration with Alpha Clinics, DOTs, and COE to improve trial enrollment, increase accruals, and support clinical trialists	• One DOT meeting per quarter is dedicated to pre-clinical science presentations/discussions • Interventional clinical trial accruals increased 57% (from 67 in 2023 to 105 in 2024) • Recruited Miguel Villalona Calero, MD with Phase 1 clinical trial expertise • 9 SPT member awarded CFCCC pilot award for early-phase clinical trial (2021 – 2024) • 5 SPT members participated in Cancer Clinical Trial bootcamp (2023 – 2024)
Catchment Area Alignment: Align research and trials with catchment priority cancers and leverage molecular profiling for precision therapeutic trials	• UC Minority Patient-Derived Xenograft (PDX) Development and Trial Center (UCaMP) to Reduce Cancer Health Disparities (Dayyani) • Ph-like ALL studies (Pannunzio)
Collaboration Outcomes: Target collaborative efforts to improve inter- and intra- programmatic publications, quantify biorepository use, molecular profiling, and human relevance in publication	• Working groups: metabolism and developing tumor immunology emerging from retreat breakout session • Encourage applications to the CFCCC pilot award program supported by Anti-Cancer Challenge • Foster incorporation of human samples into basic science studies by highlighting ETR and heme malignancy biorepository at SPT events and CFCCC retreat • Strategically invite investigators who are seeking collaborators at SPT quarterly meeting and CFCCC annual retreat • Encourage use of GRT Hub for molecular profiling
Translational Vignettes: Provide specific future plans and detailed vignettes showcasing translation	• Examples of translationally relevant projects at different phases of translation will be presented in vignettes

Program Metrics CY2024

MEMBERSHIP

100 Members ▲

27 Departments ▲

7 Schools ▲

Member Highlight

Baker, PhD

Awarded NCI R01 for cell competition in development and homeostasis

Buisson, PhD

Awarded NCI R37 for molecular mechanisms of APOBEC-induced mutagenesis

Halbrook, PhD

Awarded NCI R37 for targeting metabolic cross talk in pancreatic cancer

Lara-Gonzalez, PhD

Awarded NIH MIRA R35 for developmental regulation of the cell cycle machinery

PUBLICATIONS

226 Total Publications

17% Intra-Program

24% Inter-Program ▲

58% Inter-Institutional

26% High Impact

FUNDING 2/28/2025

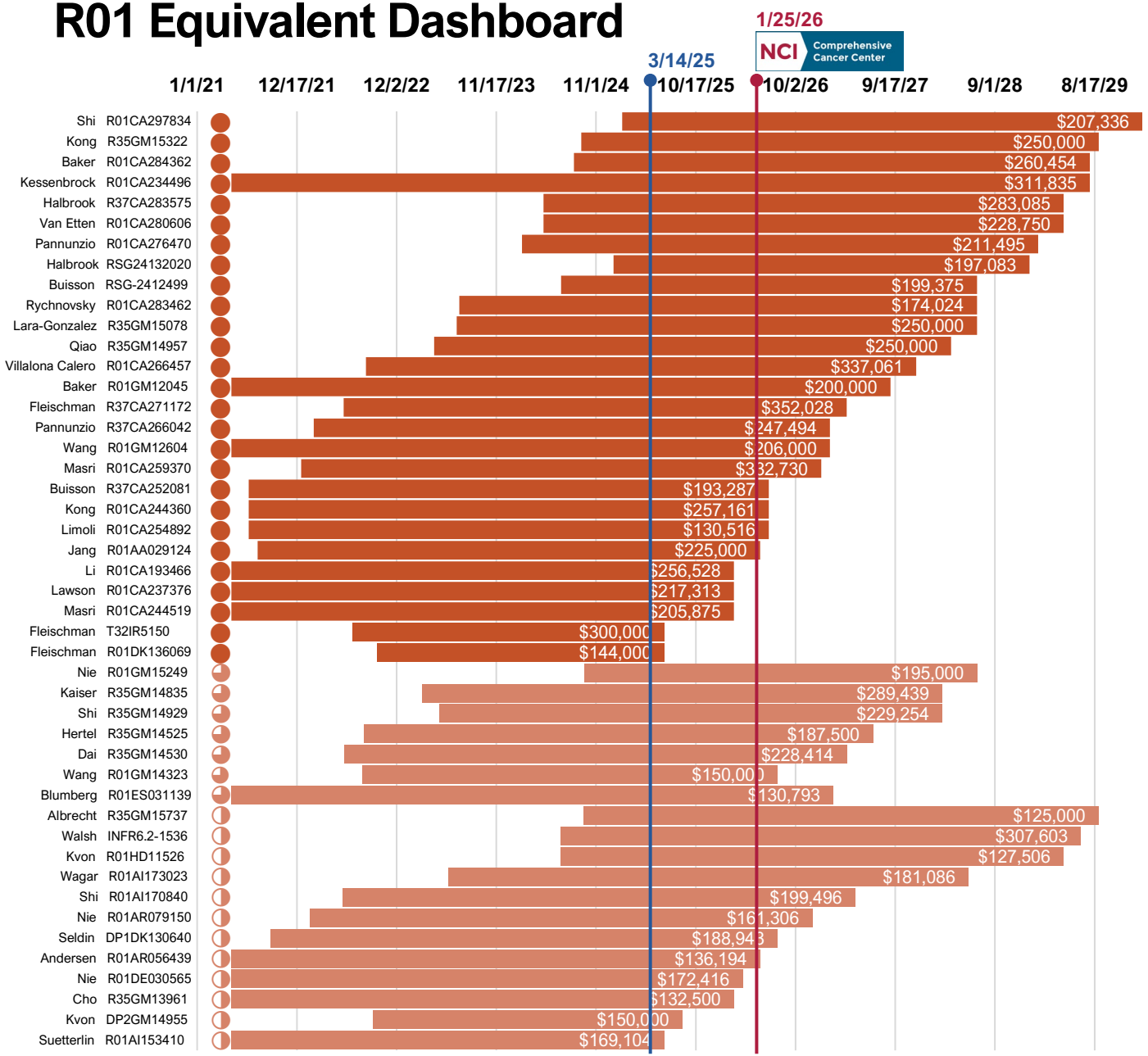
88 Funded Projects

	DIRECT COSTS
NCI ▲	$5,076,521
Other NIH ▲	$5,923,612
Other Peer-Reviewed ▲	$4,591,462
Total Peer-Reviewed ▲	**$15,591,595**

CLINICAL TRIALS

	OPEN TO ACCRUAL	ACCRUAL
Treatment Trials	71	105 ▲
Interventional Trials (including treatment)	74	105 ▲
Non-Interventional Clinical Studies	3	19

R01 Equivalent Dashboard



Cancer Relevance

Full Projects 28 PIs 19

100%

- Funded by NIH-recognized peer-reviewed funding agencies that exclusively fund cancer research
- DoD grants directed at specific cancers
- “Cancer” in RCDC
- Cancer terms in title, abstract, etc
- Applicability to cancer is clearly described in the abstract and public health statement
- All the grant is cancer related

Partial Projects 19 PIs 14

75%

- Cancer terms in title, abstract, etc.
- Cancer terms are not in title, abstract, etc. but the grant has significant cancer-related components
- Only minor components of the grant are not directly linked to cancer

50%

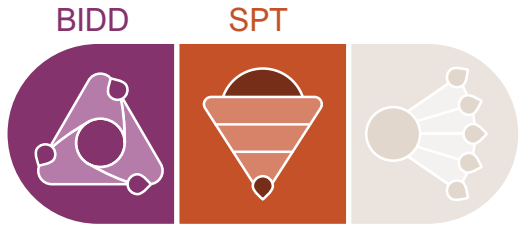
- Cancer terms are not in title, abstract, etc. but the subject on which grant focuses is used for cancer research, diagnosis or treatment
- Grant funds study of disease or risk factors that can lead to cancer

Inter-Programmatic Activity & Collaboration

Interprogrammatic Working Group on Cancer Metabolism led to new collaborations and grant applications

Interprogrammatic Working Group on Cancer Immunology emerged from SPT-led breakout session at the 2024 CFCCC Scientific Retreat

Hereditary Cancer Clinics improve adherence to NCCN germline testing guidelines for pancreatic cancer. Lee FC (**BIDD**), Dayyani F (**SPT**), Zell (**CC**), Valerin JB (**SPT**), J Natl Compr Canc Netw, 2024, PMC11462954



Circadian control of immunosuppression impacts immune checkpoint therapy efficacy. Masri (**SPT**), Eng (**BIDD**), Pannunzio (**SPT**)

Cancer immunology, cross talk between CD8+ T cells and Tregs inhibits efficacy of PD-1 immunotherapy. Nie (**SPT**), Marangoni (**SPT**) Ganesan (**BIDD**)

Cancer Systems Biology P01–Tipping Points in Cancer. Cancer initiation is driven by combinations of rare events, both non-genetic and genetic. MPIs: Lowengrub (contact, **SPT**), Lander (**SPT**), Lawson (**SPT**). Additional project leaders: Van Etten (**SPT**), Kessenbrock (**SPT**), Ganesan (**BIDD**)

Diet studies received CFCCC pilot award, led to publication and R01 submission. Fleischman (**SPT**), Odegaard (**CC**), Whiteson (**SPT**)

Extending letermovir prophylaxis in haplo-SCT patients. Jeyakumar (**SPT**), Kongtim (**CC**), Ciurea (**SPT**), Haematologica, 2024, PMC11532715

Study of **hematologic immune markers** in soft tissue sarcoma radiotherapy. Chow (**SPT**), Limoli (**SPT**), Harris (**CC**), Frontiers in Oncology, 2024, PMC11484061

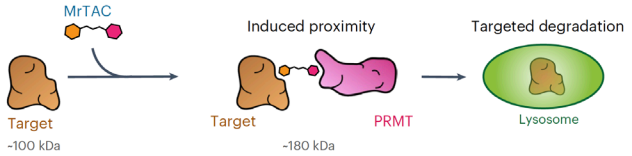
SPT

Novel modality for targeted protein degradation in lysosomes

Targeting the undruggable proteome

Targeted protein degradation (TPD)

Proximity-inducing compounds reshape cell activity, eliminate pathogentic proteins previously considered undruggable



Albrecht Lab

- Discovered arginine methylation is a natural modification of protein degradation in lysosomes, using CRC as a model system. (Franco et al, 2023)
- Exploited discovery to develop a small molecule (methylarginine targeting chimera, MrTAC), that induces proximity of a methyltransferase with a target protein to induce lysosomal degradation of cancer-driving proteins (Seabrook et al, 2024)
- Proof of concept using Halo-Tag PRMT1 and MYC, BRD4 as target proteins
- New route to TPD and therapeutics using the lysosome to eliminate intracellular proteins

CATCHMENT AREA RELEVANCE

Investigators

Albrecht, PhD

Trader, PhD

CFCCC Investments

SHARED RESOURCE

PROGRAMS

Outcomes

PUBLICATION
Franco, Sci. Advances, 2023
Seabrook, Nature Chem Biol, 2024

PATENT Application

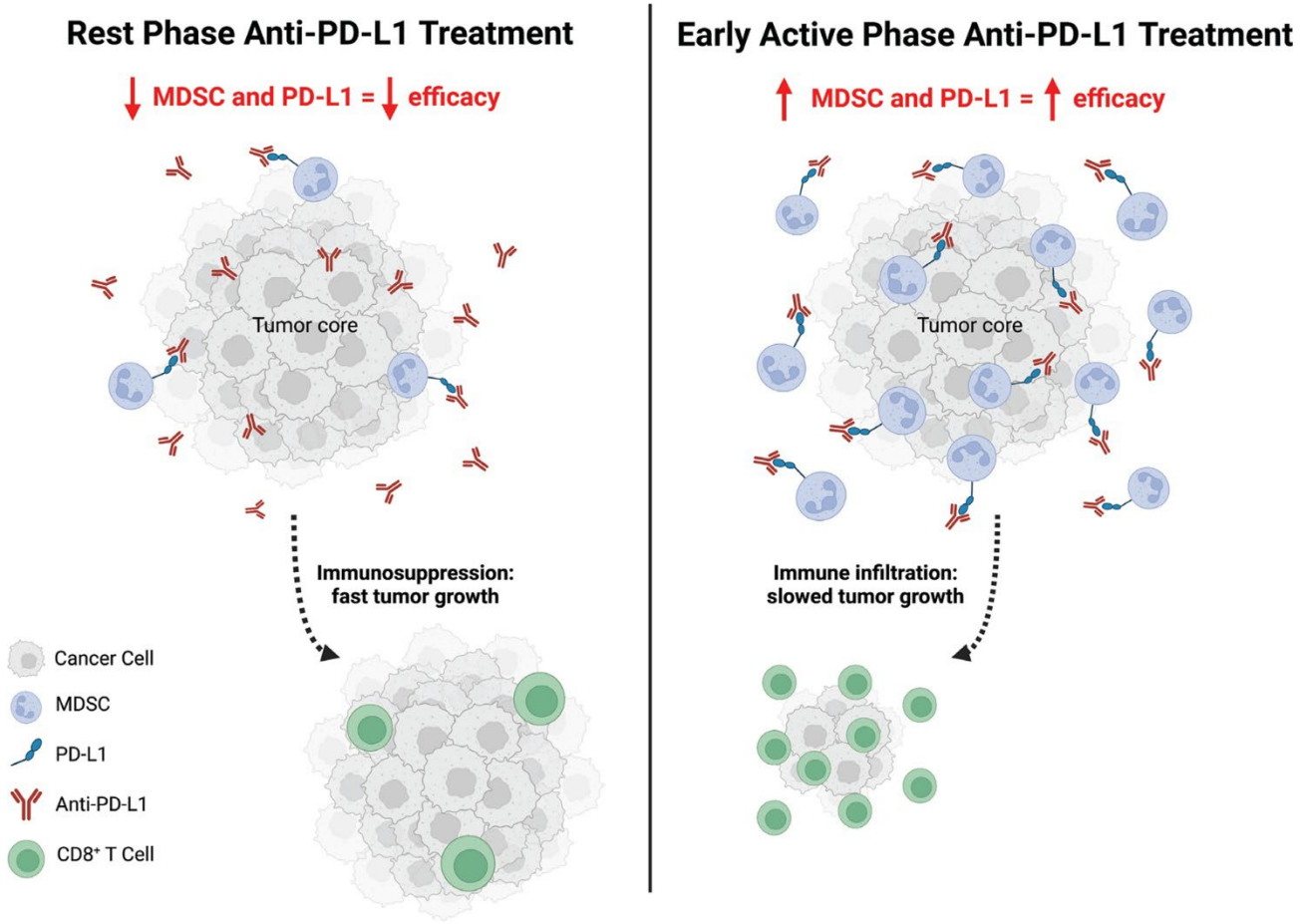
GRANTS
UC Drug Discovery Consortium (Ono Pharmaceuticals)
Cystinosis Foundation
R35GN157370 MIRA
Sloan Research Fellowship

IMPACT | New route to eliminate undruggable proteins in cancer and other human diseases

SPT

Circadian regulation of tumor immune suppression and ICB response

Cancer immunology experts uncover key tumor therapy-evasion mechanisms



CATCHMENT AREA RELEVANCE

Investigators


Kessenbrock, PhD


Lawson, PhD


Marangoni, PhD


Marazzi, PhD


Masri, PhD


Seldin, PhD

CFCCC Investments

SHARED RESOURCE

DOT

FUNDING
2024

PROGRAMS

Outcomes

PUBLICATION

Fortin, Nature Immunology, 2024
PMC11374317

GRANTS R01CA244519
R01CA259370

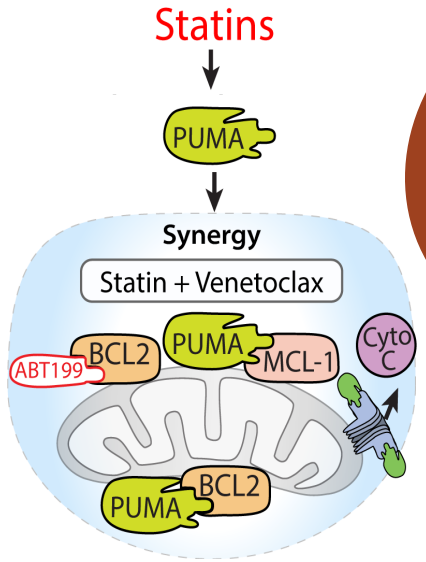
IMPACT The findings could lead to more effective treatment strategies for colorectal cancer and potentially other cancer types, improving patient outcomes by optimizing the timing of immunotherapy delivery

SPT

Statins augment BH3 mimetics in hematologic malignancies

Leveraging UCI science for translation into IITs

Identifying mevalonate pathway dependency in cancer



Phase 1 study complete: Pitavastatin + venetoclax in AML and CLL

NCT04512105

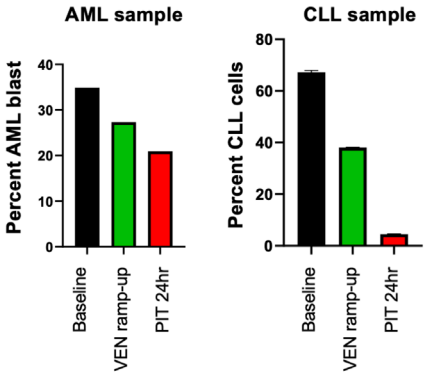


Figure 4: % AML blasts ($CD45^{lo}CD33+$) or CLL cells (CD19+CD5+) was assessed by flow cytometry using PBMCs from trial subjects. Blood samples were collected at **diagnosis** (baseline), after **venetoclax** ramp-up, and 24hr after the first dose of **pitavastatin** at dose level 1 (2 mg).

Planning Phase 2 study: AML with 17p deletion or other TP53 aberration

CATCHMENT AREA RELEVANCE

Investigators


Brem, PhD


Fruman, PhD


Fleischman, MD, PhD


Jeyakumar, MD


O'Brien, MD

CFCCC Investments

SHARED RESOURCE

DOT

FUNDING
2018
2019
2023

PROGRAMS

Outcomes

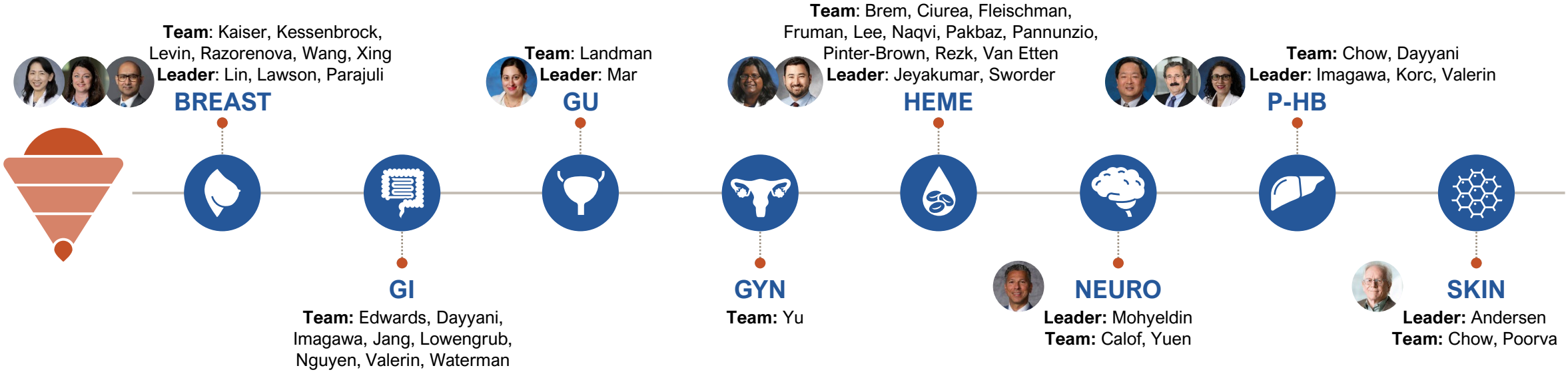
PUBLICATION

Brem, Blood Neoplasia, Vol 1, Issue 4, 2024

GRANTS
NCI R21CA209341
LLS Translational Research Program
DOD Impact Award
ACS Discovery Boost Grant

IMPACT | Addition of statins may enhance anti-apoptotic therapies in multiple hematologic malignancies, offering a low toxicity, low-cost approach to improve outcomes

Disease-Oriented Team Interactions



NEW EXTRAMURAL FUNDING

- R01CA266457 Phase 1 Evaluation of Enhanced NK cells as Treatment Strategy in NSCLC Patients Refractory to PD-1/PD-L1 immune checkpoint inhibitors (Villalona)
- RSG-24-1320209 Deconvoluting the Metastatic Pancreatic Cancer Tumor Microenvironment (Halbrook)

SHARED RESOURCES USED

OBC · GRT HUB · ETR · BSR

CLINICAL TRIALS OPENED

- Brem – developed study now open through SWOG (NCT04799275) in lymphomas with MYC and BLC2 and/or BCL6 Rearrangements
- Brem – NCT04512105 Phase 1 study of addition of Pivatastatin to venetoclax in AML and CLL
- Fleischman – IND and IIT for N-Acetylcysteine in Myeloproliferative Neoplasms (NCT05123365)

Catchment Area Activities

Community Education on Blood Cancer

Partnered with LLS to develop a full day community blood health event in Spanish in Santa Ana (April 2024). Speaker: Valeria Rangel, Pannunzio Lab

Conquering Cancer Seminar Series

Monthly seminar series with 40+ participants per session including high school students, parents, and teachers

Community Liaison

SPT member Shawn Griffin paired with community liaison to meet quarterly. Community member gives guidance on most impactful next steps of project

Community Members Review Grants

Community members are active participants in grant reviews including ACS IRG and Anti-Cancer Challenge

Impact of Research on the Catchment Area

PRIORITY CANCER	GRANT	PRIORITY POPULATION
ALL	Ph-Like ALL to Determine Predictive Markers R37CA266042 (Pannunzio)	H/Lat — High-risk Hispanic/Latino populations. This disease disproportionately affects Hispanic/Latino populations (34% of Orange County)
Colorectal	Early onset of Colorectal Cancer R01CA244519 (Masri)	H/Lat — Younger Hispanic/Latino groups. Median age in Orange County is 39.5
Myeloid Neoplasms	Impact of e-cigarette exposure on subsequent expansion of hematopoietic stem cells with myeloid malignancy associated mutations TRDRP T321IR5150 (Fleischman)	AYA — Adolescents. 27.5% of Orange County high schoolers have used e-cigarettes compared to 13.4% nationally
Skin	P01 Cancer Systems Biology – Melanoma Lander (**SPT**), Ganesan (**BIDD**)	Melanoma incidence and mortality above national average, highest quartile in CA for whites and Hispanic/Latino groups

Contribution to Education, Training & Mentoring

High School Programs – COSMOS and Youth Science Fellowship

COSMOS - Annual high school course on tissue and tumor growth, led by Lowengrub and Felix Grun, PhD, (Mass Spectrometry Shared Resource Manager) featuring lectures, labs, and research projects. YSFP - 6-week summer program providing high school students with hands-on lab experience. 14 students were mentored by SPT members in 2024, and 69 students from 2021 – 2024

Maximizing Access to Research Careers (MARC)

Longitudinal laboratory experience for undergraduates with guidance on entering PhD programs, T34 funded

R25 short course in Cancer Systems Biology

Intensive 3-week course for ~20 trainees, exploring key cancer research challenges through systems biology, lectures, and hands-on experiences

Cancer Clinical Trial Bootcamp and NIH Bootcamp

16-week program for designing an investigator-initiated cancer clinical trial protocol. Between 2023 and 2024, 5 SPT members have participated, with 6 SPT members serving as mentors yearly

Bidirectional Value Added: CFCCC to SPT

INVESTMENTS

$2,227,962 Annual Investment (CY024)

Investment (2021-Present)

Recruitment/Retention	$2,503,452
Pilot Funding	$1,397,565
Salary support	$1,609,773
IIT support (Stern)	$397,162
SR subsidy and rebates	$43,095
Equipment	$238,202
Education & Training	$120,000
Other	$20,759
Total	**$6,330,008**

Selected New Faculty (2021-Present)

Halbrook, PhD

Villalona, MD

Yu, PhD

SHARED RESOURCES

Use by SPT Members

TMF	OBC	GRT HUB	MS
8%	35%	39%	N/A

ETR	IVFOI	BSR	BBSR
40%	2%	9%	0%

Resulting Publications (CY2024)

30 Total Publications with SRs

10 High Impact

HIGHLIGHTS

- Support for working groups, seminar series, R25 short courses, and annual program retreats
- Funding opportunities including CFCCC pilot award (basic and clinical research), bridge funding and limited submissions
- Provide shared resources enabling access to advanced technologies, expert support, and collaborative opportunities to accelerate research
- Programmatic activities and resources including DOTs, clinical trial bootcamp, and BEE Scene

Bidirectional Value Added: SPT to CFCCC

BY LEADERSHIP

FLEISCHMAN

- Associate Director, Medical Scientist Training Program
- Hematologic Malignancies Biorepository

LOWENGRUB

- Co-Director, CaSB@UCI
- Director, MCSB interdisciplinary grad program
- Associate Director, NSF-Simons Center for Multiscale Cell Fate Research

TINOCO

- UCI Scientist for a Day
- MARC PI (T34)
- Beyond Cancer Speaker (Hispanic Heritage Month)

TO ACTIVITY

Membership

40%
100 of 248

CFCCC members are members of **SPT**

Publications

45%
226 of 500

CFCCC publications include a **SPT** author

Funding

39%
90 of 228

CFCCC peer-reviewed grants include **SPT** PI

$15.8M
of $37.97M

CFCCC peer-reviewed grants annual direct costs include **SPT** PI

HIGHLIGHTS

- Initiative to bring Systems Biology to Cancer Biology P01 (recommended for funding)
- Facilitated development of Immunology Working Group
- Contribution to Experimental Tissue Resource with heme biobank with frozen viable samples
- Leadership roles in educational programs integrating cancer-relevant curriculum to engage students
- Conquering Cancer Seminar Series and Beyond Cancer Speaker Series

Future Plans

AIMS

1 Cancer Pathway Targets

- Support logistics for Cancer Metabolism and Immunology working groups
- Quarterly retreat to foster and support new collaborative teams
- Fund discovery-based pilot grants to identify novel cancer targets

2 Single-Cell Cancer Dynamics

- P01 Systems Biology “Tipping Points in Cancer” aims to investigate cell-cell interactions in space and time at single cell resolution
- Encourage members to collaborate with the GRT Hub on developing and utilizing new single cell technologies including spatial
- In partnership with CRTEC, NIH Bootcamp for early-career faculty and T32 Alumni Seminar Series
- Develop workshop for program project grants (in partnership with CRTEC)

3 Therapy Translation

- Encourage creation of additional focus groups involving basic scientists and clinicians to create IITs
- Quarterly DOT meeting focusing on basic science presentations
- Encourage participation in Cancer Clinical Trials Bootcamp with CRTEC
- Promote bidirectional community engagement

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Questions?

www.cancer.uci.edu