

Cancer Biology & Evolution Program

Elsa R. Flores, PhD
Leader

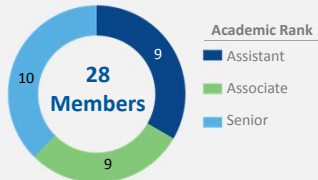


Agenda

- 2018 Publication and Grants
- Program Structure
- 2018 Activities
- Plans for 2019
- Questions

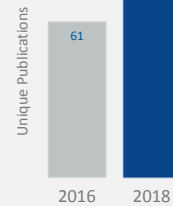
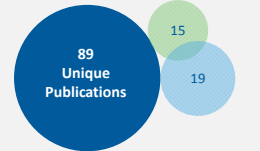
Cancer Biology & Evolution

Membership

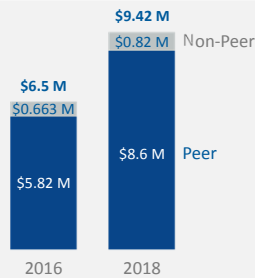
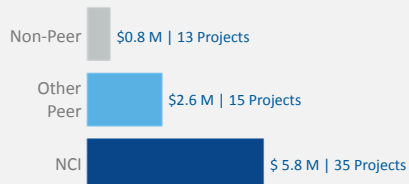


Peer Review Funded PIs
18

Publications



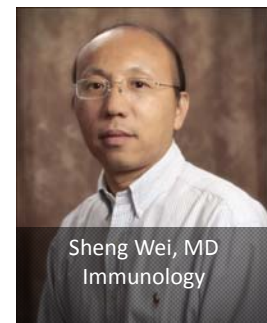
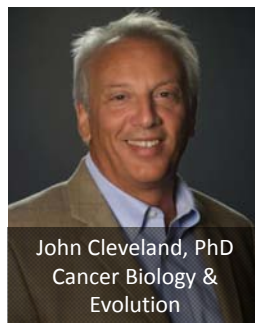
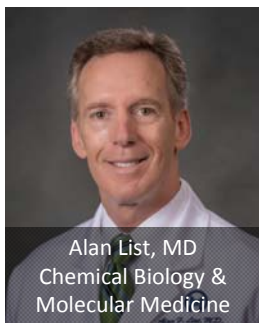
Grants (Annual Direct Costs)



Current
R01/Equivalent Projects
16 (9 PIs)

Annual Direct Costs
\$6.6M

CBE: Grant Highlight

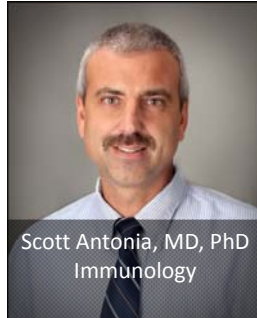


- Awarded **Leukemia & Lymphoma Society SCOR grant**
- Title: Regulation and Targeting of Inflammatory Circuits in Myelodysplastic Syndromes
- \$5,000,000 total costs over 5 years
- Brings together diverse investigators working towards the development of new diagnostics tools, treatments, or preventative strategies for blood-based cancers.

CBE: Grant Highlight



Sandy Anderson, PhD
Cancer Biology &
Evolution



Scott Antonia, MD, PhD
Immunology



Bob Gatenby, MD
Cancer Biology &
Evolution

- **NCI U01**
- Title: Eco-Evolutionary Dynamics of NSCLC to Immunotherapy: Response & Resistance
- \$3,236,925 total costs over 5 years
- Study will develop models to improve results from immunotherapy based on the understanding of the evolutionary (cellular and molecular) and ecological (tissue) dynamics that govern response and resistance of NSCLC to immunotherapy

CBE: Grant Highlight



Gina DeNicola, PhD

- Awarded her first career **R01 – 1%**
- **Automatically converted to R37 MERIT Award**
- \$2,300,000 over 7 years
- Title: Investigation of NRF2-Dependent Metabolic Liabilities

Aims:

1. Examine the whether cysteine dioxygenase (CDO1) antagonizes the NRF2-regulated antioxidant response by depleting cysteine
2. Examine the selective toxicity of CDO1 expression to cells with NRF2 activity due to toxic byproduct production
3. Examine whether CDO1 loss promotes lung tumorigenesis using our genetically engineered KEAP1 and NRF2 mutant mouse lung tumor models and patient tumor samples

CBE: Grant Highlight

- Cancer Biology Graduate student (Gillies lab)
- Awarded an **NCI F99/K00**
- Title: *“Understanding metabolic vulnerabilities in cancer and the impact the tumor microenvironment has on cancer progression”*
- Dual-phase transition award (graduate student to postdoc)
- 1st Moffitt student to receive award (grant flows through USF)



Shonagh Russell, PhD

CBE: Publication Highlight



Jianguo Tao, MD, PhD



John Cleveland, PhD

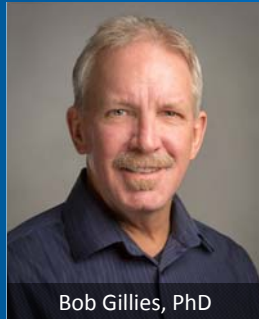
JCI The Journal of Clinical Investigation

PLK1 stabilizes a MYC-dependent kinase network in aggressive B cell lymphomas

Yuan Ren,¹ Chengfeng Bi,² Xiaohong Zhao,¹ Tint Lwin,¹ Cheng Wang,² Ji Yuan,² Ariosto S. Silva,³ Bijal D. Shah,⁴ Bin Fang,⁵ Tao Li,¹ John M. Koomen,⁵ Huijuan Jiang,^{1,6} Julio C. Chavez,⁴ Lan V. Pham,⁷ Praneeth R. Sudalagunta,³ Lixin Wan,⁸ Xuefeng Wang,⁹ William S. Dalton,⁴ Lynn C. Moscinski,¹ Kenneth H. Shain,⁴ Julie Vose,¹⁰ John L. Cleveland,¹¹ Eduardo M. Sotomayor,¹² Kai Fu,² and Jianguo Tao^{1,4}

- Concordant activation of MYC and BCL-2 oncoproteins in double-hit lymphoma (DHL) results in aggressive disease that is refractory to treatment
- By integrating activity-based proteomic profiling and drug screens, polo-like kinase-1 (PLK1) was identified as an essential regulator of the MYC-dependent kinome in DHL
- Inhibition of PLK1 triggered degradation of MYC and of the antiapoptotic protein MCL-1, and PLK1 inhibitors showed synergy with BCL-2 antagonists in blocking DHL cell growth, survival, and tumorigenicity, supporting clinical targeting of PLK1 in DHL

CBE: Publication Highlight



ARTICLE

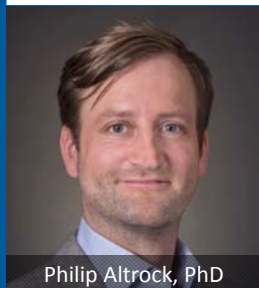
DOI: 10.1038/s41467-018-05261-x OPEN

Systems analysis of intracellular pH vulnerabilities for cancer therapy

Erez Persi^{1,2}, Miquel Duran-Frigola³, Mehdi Damaghi^{4,5}, William R. Roush⁶, Patrick Aloy^{3,7}, John L. Cleveland⁸, Robert J. Gillies⁴ & Eytan Ruppin⁹

- Team developed a computational methodology that explores how intracellular pH (pHi) can modulate metabolism
- Experimental testing of novel strategy reveals that it is particularly effective against aggressive phenotypes
- Study suggests essential roles of pHi in cancer metabolism and provides a conceptual and computational framework for exploring pHi roles in other biomedical domains

CBE: Publication Highlight



JCOTM | CLINICAL CANCER INFORMATICS
An American Society of Clinical Oncology[®] Journal

original reports

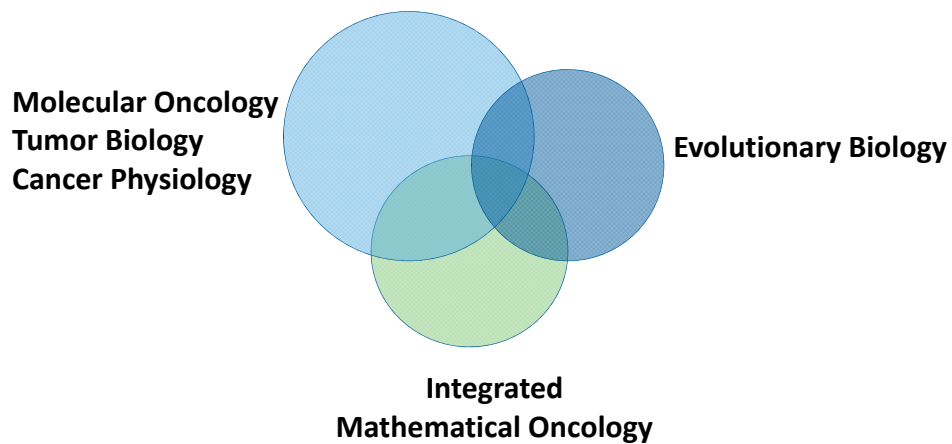
Computational Model of Progression to Multiple Myeloma Identifies Optimum Screening Strategies

- Dr. Altrock and colleagues identified patients who are at a higher risk of developing multiple myeloma early in order to improve patient outcomes
- Found that screening individuals with a high lifetime risk of developing a precursor condition can reduce the prevalence and specific mortality of symptomatic multiple myeloma
- Found prevalence of multiple myeloma could be reduced by 19 percent in individuals who begin screening at age 55 and have follow-up screening every 6 years
- A similar reduction in prevalence was also found when screening begins at age 65 with follow-up every 2 years

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CBE Program Structure



Cancer Biology & Evolution

Proposed Aims

Goal

Investigate and define the complex multi-scale dynamics that govern the biology and therapeutic responses of cancer, and to deliver new agents and strategies for the prevention and treatment of refractory or relapsed malignancies.

Original Aims:

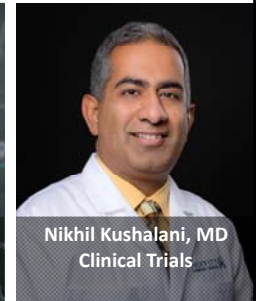
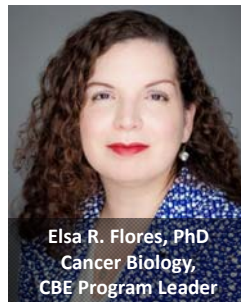
1. Empirically & mathematically define the dynamics operational in cancer and therapy
2. Exploit evolution by natural selection as the first principle operational in cancer
3. Translate evolutionary dynamics into personalized, modeled therapies

Proposed Aims:

1. Define networks operational in cancer development & progression
2. Develop animal & mathematical models of human cancer development & progression and therapeutic resistance
3. Translate basic discoveries into personalized, modeled therapies

Cancer Biology & Evolution

Steering Committee

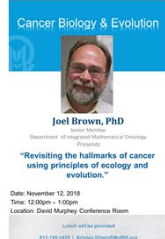
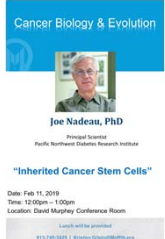




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Cancer Biology & Evolution: 2018 Activities

- CBE Seminar Series
- CBE Educational Opportunities
- Innovation Funds
- CBE 2nd Annual Symposium

 <p>Joel Brown, PhD Associate Professor Department of Integrated Mathematical Oncology Perkins</p> <p><i>"Revisiting the hallmarks of cancer using principles of ecology and evolution."</i></p> <p>Date: November 12, 2018 Time: 12:00pm - 1:00pm Location: David Murphy Conference Room Lunch will be provided 813.740.3400 Krisen.Grunwald@uth.tmc.edu</p>	 <p>Joe Nadeau, PhD Principal Scientist Pacific Northwest National Research Institute</p> <p><i>"Inherited Cancer Stem Cells"</i></p> <p>Date: Feb 11, 2019 Time: 12:00pm - 1:00pm Location: David Murphy Conference Room Lunch will be provided 813.740.3400 Krisen.Grunwald@uth.tmc.edu</p>
 <p>Charles Chalfant, PhD Associate Professor and Co-Director Microbiology and Molecular Biology UTMSD</p> <p><i>"The Role of RNA Splicing in Cancer Cell Signaling"</i></p> <p>Date: December 10, 2018 Time: 12:00pm - 1:00pm Location: David Murphy Conference Room Lunch will be provided 813.740.3400 Krisen.Grunwald@uth.tmc.edu</p>	 <p>Celeste Simon, PhD Scientific Director, Mammary Tumor Research Institute Arthur A. Sabatini, M.D., Professor, Department of Cell and Developmental Biology University of Pennsylvania Perelman School of Medicine</p> <p><i>"Hypoxia, Metabolism, and Tumor Progression"</i></p> <p>Date: Jan 14, 2019 Time: 12:00pm - 1:00pm Location: David Murphy Conference Room Lunch will be provided 813.740.3400 Krisen.Grunwald@uth.tmc.edu</p>

Cancer Biology & Evolution

Seminar Series - 2018



Cancer Biology and Evolution Program 2018 Seminars


2nd Monday, 12:00pm-1:00pm (unless otherwise noted)

DATE	CONFERENCE ROOM	SPEAKER	TITLE & INSTITUTION
January 8, 2018	Murphey	Florian Karreth, PhD	Moffitt Cancer Center
February 12, 2018	Murphey	Hilary Collier, PhD Host: Dr. Flores	Associate Professor, UCLA
March 12, 2018	Murphey	Andriy Marusyk, PhD	Assistant Member, Department of Cancer Physiology
April 9, 2018	Murphey	Connor Lynch, PhD	Associate Member, Department of Tumor Biology Moffitt Cancer Center
May 14, 2018	Murphey	Lixin Wan, PhD	Moffitt Cancer Center
June 11, 2018	Murphey	ALL	2018 Symposium & Poster Session
July 9, 2018	Murphey	Lukas Edward Dow, PhD Host: Dr. Karreth	Assistant Professor, Meyer Cancer Center Weill Cornell Medical College
August 13, 2018	Murphey	Joshua Mendell, MD, PhD Host: Dr. Karreth	Professor, Department of Molecular Biology UT-Southwestern
September 10, 2018	Murphey	Rong Li, PhD Host: Dr. Marusyk	Professor, Cell Biology and Chemical & Biomolecular Engineering Johns Hopkins School of Medicine and Whiting School of Engineering
October 8, 2018	Murphey	Alejandro Sweet-Cordero, MD Host: Dr. Flores	Associate Professor, UCSF
November 12, 2018	Murphey	Joel Brown, PhD	Senior Member, Department of Integrated Mathematical Oncology Moffitt Cancer Center
December 10, 2018	Murphey	Charles Chalfant, PhD	Professor, USF Cell Biology, Microbiology, and Molecular Biology Chair

CBE: Collaboration Highlight

Cancer Biology & Evolution

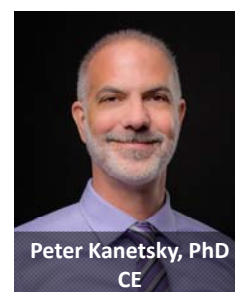
Douglas E. Brash, PhD
Depts. Therapeutic Radiology and Dermatology
Yale Comprehensive Cancer Center
Yale School of Medicine



"Skin cancer from the ground-state up"

Date: October 9, 2017
Time: 12:00 noon to 1:00 p.m.
Location: SRB, David Murphey Conference Room

Lunch will be provided
(813) 745-2329 | Laurie.Burns@Moffitt.org



- NIH/NCI multi-PI R01 – "Applying genomic dosimeters of UV damage to predicting skin cancer risk."
- Received 8% and will be funded

CBE: Collaboration / Faculty Recruitment Highlight

SPECIAL SEMINAR

Donald A. Adam Melanoma & Skin Cancer
Center of Excellence

**"Melanin biochemistry causes UV-like
DNA damage and melanoma therapy
resistance"**

Presented by faculty candidate:

SANJAY PREMI, PhD.

Associate Research Scientist

from the lab of

Douglas E Brash, PhD

Department of Therapeutic

Radiology

Yale School of Medicine

Yale University



Wednesday, December 20

1:30pm – 2:30pm

SRB David Murphey Conference Room

Contact: Joyce Lampasona 813-745-2007

Sanjay Premi, PhD

- **Former Postdoc of Doug Brash, PhD – Yale School of Medicine**
 - Developed novel drug combinations to induce synthetic lethality in RAS/RAF mutated, drug resistant melanoma
 - Identified tumor suppressive functions of Hematopoietic Stem Cell Regulatory Gene "Latexin" in malignant melanoma
 - Designed a Next-Gen-Sequencing (NGS) assay for genome-wide detection of DNA damage at 1bp resolution."
- **Science, 2015 – "Photochemistry. Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure"**
- **Assistant Member, CBE**
- **Starts March 4, 2019**

Cancer Biology & Evolution

Educational Opportunities

- **T32 Resubmission 01/2019 - "Integrated Program in Cancer and Data Science"**
 - to train the next generation of scientists proficient in experimental and quantitative biology
 - includes 30 faculty – primarily in CBE but also includes other programs and cuts across 2 Divisions



PI- Doug Cress, PhD
CBE Member
Sr. Member, Molecular Oncology
Division, Basic Science



Co-PI- Elsa R. Flores, PhD
CBE Program Leader
Chair, Molecular Oncology
Division, Basic Science



Co-PI- Brooke Fridley, PhD
CE Member
Chair, Biostatistics & Bioinformatics
Division, Quantitative Sciences

- IMO workshop, IMO PhD program, Oxford PhD students, Dartmouth undergraduate students, HIP-IMO, USF – Evolutionary Biology PhD program
- Postdoc coffee hour with the CBE seminar speakers

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Innovation Funds - \$50,000 per award

- *“Investigation of CircularRNAs in Melanoma”*



Florian Karreth, PhD
CBE Member
Assistant Member, Molecular Oncology

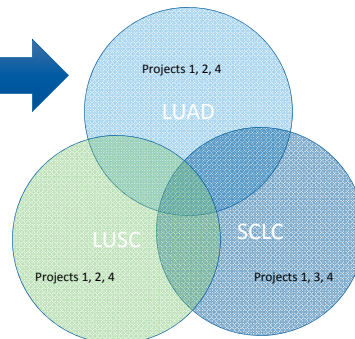
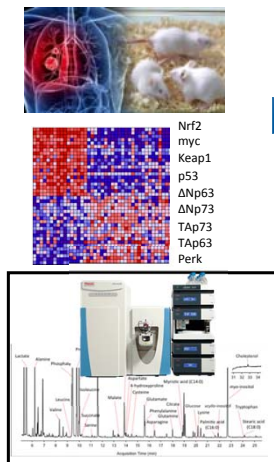
- *“Deciphering the roles of the p53 family members in cellular metabolism”*



Gina DeNicola, PhD
CBE Member
Assistant Member, Cancer Physiology

Cancer Biology & Evolution

Innovation Funds – P01 Application – Metabolic Vulnerabilities in Lung Cancer



Elsa R. Flores, PhD
PI and Project Leader
CBE



Eric Haura, MD
Co-PI and Project Co-I
CBMM



John Cleveland, PhD
Project Leader
CBE



Gina DeNicola, PhD
Project Leader
CBE



Paulo Rodriguez, PhD
Project Leader
Immunology



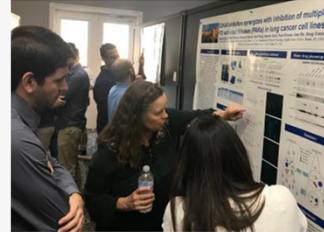
Cancer Biology & Evolution

2nd Annual Symposium

Cancer Biology and Evolution Symposium 2018

Cancer Biology and Evolution Symposium 2018

Join the CBE Program for our 2nd Annual Symposium featuring a poster session and a day full of great presentations.



Breakfast and lunch will be provided for attendees.

June 11, 2018

Couch Auditorium and SRB Atrium

Please RSVP if attending

813-745-3425 | Kristen.Gilpin@Moffitt.org

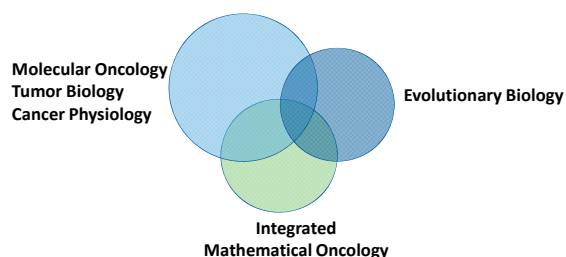
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Cancer Biology & Evolution

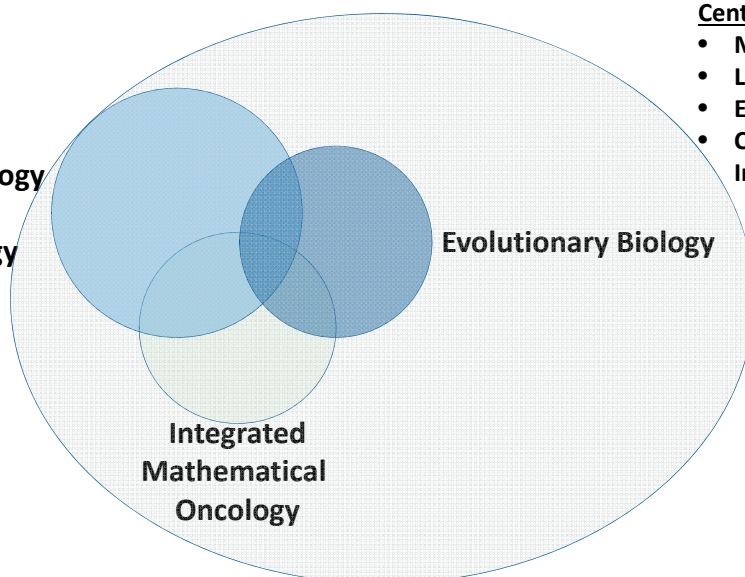
Plans for 2019

- 3rd Annual CBE Symposium – *October, 2019*
- CBE Seminar Series 2019
- Quarterly Scientific Think Tanks centered around specific disease sites using interdisciplinary approaches – *1st Quarter - Summer, 2019*
- Organization of CBE steering committee drawing from the different disciplines of the program



CBE Program Structure & Accomplishments

Molecular Oncology
Tumor Biology
Cancer Physiology



Centers of Excellence

- Melanoma & Skin Cancer
- Lung Cancer
- Evolutionary Therapy
- Cancer Infection & Immunization Research



Clinical Trials
P01 Application
Multi-PI Grants

CBE: Clinical Trials Highlight - Evolutionary Therapy



New Center of Excellence



Directors

Sandy Anderson, PhD

Bob Gatenby, MD

- **Goal:**
To deliberately embrace the dynamics driving drug resistance and to develop treatment strategies that can exploit these dynamics
- Will establish interdisciplinary clinical-trial collaborations, novel theoretical frameworks, and technological infrastructure to leverage massive amounts of data to meet the demands of dynamically personalized therapy
- Clinical trial led by Drs. Gatenby & Jingsong Zhang using the current drug abiraterone on an intermittent schedule in prostate cancer
 - To date, showing **four times** the treatment effect with **40%** the amount of drug.

CBE: Clinical Trials

Accrual (FY18)	Treatment	Supportive Care	Prevention
Cancer Biology & Evolution	7	0	0

• 3 open adaptive therapy trials

- A Pilot Study of Adaptive Abiraterone Therapy for Metastatic Castration Resistant Prostate Cancer (J. Zhang)
- Pilot Study of Adaptive BRAF-MEK Inhibitor Therapy for Advanced BRAF Mutant Melanoma (Eroglu)
- Sequential Maintenance with Thoracic Radiotherapy and Durvalumab (MEDI4736) monotherapy or Durvalumab (MEDI 4736) Combinations (Tremelimumab or Olaparib) in Patients with Extensive Stage-Small Cell Lung Cancer after First Line Platinum Based Chemotherapy (Chung)

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Cancer Biology & Evolution: *Questions*

- Does the program's proposed steering committee represent the research areas and clinical activities of the program?
- Do the new proposed aims encompass the breadth of research in the program?