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
- **28 Members**
- **9 Assistant**
- **9 Associate**
- **10 Senior**

### Publications
- **89 Unique Publications**
- **19 Inter-Program Collaboration** (24.4%)
- **15 Intra-Program Collaboration** (16.9%)

### Grants (Annual Direct Costs)
- **Non-Peer**
  - $0.8 M | 13 Projects
- **Other**
  - $2.6 M | 15 Projects
- **NCI**
  - $5.8 M | 35 Projects

<table>
<thead>
<tr>
<th>Year</th>
<th>Non-Peer</th>
<th>Peer</th>
<th>Current</th>
<th>R01/Equivalent Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>$6.5 M</td>
<td>$5.82 M</td>
<td>$9.42 M</td>
<td>16 (9 PIs)</td>
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<tr>
<td>2018</td>
<td>$8.868 M</td>
<td>$8.6 M</td>
<td>$6.6 M</td>
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### 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.**

- **Alan List, MD**
  - Chemical Biology & Molecular Medicine
- **John Cleveland, PhD**
  - Cancer Biology & Evolution
- **Sheng Wei, MD**
  - Immunology
CBE: Grant Highlight

- **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**

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CBE: Grant Highlight

- **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)

**CBE: Publication Highlight**

- 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

Bob Gillies, PhD

• 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

Philip Altrock, PhD

• 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

- Molecular Oncology
- Tumor Biology
- Cancer Physiology
- Evolutionary Biology
- Integrated Mathematical Oncology
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

Joel Brown, PhD
Evolutionary Biology

Kenneth Tsai, MD, PhD
Translational Research

Elsa R. Flores, PhD
Cancer Biology, CBE Program Leader

Sandy Anderson, PhD
Integrated Mathematical Oncology

Nikhil Kushalani, MD
Clinical Trials
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Cancer Biology & Evolution: 2018 Activities

- CBE Seminar Series
- CBE Educational Opportunities
- Innovation Funds
- CBE 2nd Annual Symposium
Cancer Biology & Evolution
Seminar Series - 2018

Cancer Biology and Evolution Program 2018 Seminars
2nd Monday, 12:00 pm - 1:00 pm (unless otherwise noted)

<table>
<thead>
<tr>
<th>DATE</th>
<th>CONFERENCE ROOM</th>
<th>SPEAKER</th>
<th>TITLE &amp; INSTITUTION</th>
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</thead>
<tbody>
<tr>
<td>January 8, 2018</td>
<td>Murphey</td>
<td>Florita Kuzrew, PhD</td>
<td>Moffitt Cancer Center</td>
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<td>February 12, 2018</td>
<td>Murphey</td>
<td>Hillary Geller, PhD</td>
<td>UConn, Stem Cell Lab</td>
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<td>March 12, 2018</td>
<td>Murphey</td>
<td>Andrey Manfey, PhD</td>
<td>Moffitt Cancer Center</td>
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<td>April 9, 2018</td>
<td>Murphey</td>
<td>Guenter Lynch, PhD</td>
<td>Moffitt Cancer Center</td>
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<td>April 14, 2018</td>
<td>Murphey</td>
<td>Linus Wua, PhD</td>
<td>Moffitt Cancer Center</td>
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<td>June 11, 2018</td>
<td>Murphey</td>
<td>ALL</td>
<td>2018 Symposium &amp; Poster Session</td>
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<td>July 9, 2018</td>
<td>Murphey</td>
<td>Lukas Edward Dowe, PhD</td>
<td>Harvard Medical College</td>
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<td>August 13, 2018</td>
<td>Murphey</td>
<td>Joshua Mundell, PhD, MD</td>
<td>UT Southwestern Medical School</td>
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<td>September 10, 2018</td>
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<td>Rong Li, PhD</td>
<td>Moffitt Cancer Center</td>
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<td>October 8, 2018</td>
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<td>Alejandro Castaneda, MD</td>
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<td>November 13, 2018</td>
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<td>Joel Brown, PhD</td>
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<tr>
<td>December 10, 2018</td>
<td>Murphey</td>
<td>Charles Chilcoat, PhD</td>
<td>Moffitt Cancer Center</td>
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CBE: Collaboration Highlight

- 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

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.”
- 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

- 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

LUAD
Projects 1, 2, 4

LUSC
Projects 1, 2, 4

SCLC
Projects 1, 3, 4

Nrf2
Nrf1
P Death Kinase
P53
Bcl-2
Bax
GSK3
Fork

Elsa R. Flores, PhD
PI and Project Leader
CBE

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

John Cleveland, PhD
Project Leader
CBE

Gina DeNicola, PhD
Project Leader
CBE

Paulo Rodrigues, PhD
Project Leader
Immunology
Cancer Biology & Evolution

2nd Annual Symposium

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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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

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.

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CBE: Clinical Trials

<table>
<thead>
<tr>
<th>Accrual (FY18)</th>
<th>Treatment</th>
<th>Supportive Care</th>
<th>Prevention</th>
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<tr>
<td>Cancer Biology &amp; Evolution</td>
<td>7</td>
<td>0</td>
<td>0</td>
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</table>

- 3 open adaptive therapy trials
  - A Pilot Study of Adaptive Abiraterone Therapy for Metastatic Castratoin 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?