Program Co-Leader, Chemical Biology & Molecular Medicine

- Recruited to Moffitt in 2007 after residency
- Lung cancer focus with special emphasis on identifying new molecular targets for treatment of treatment naïve & resistant lung cancer
- Director for Clinical Research in Thoracic Oncology Dept
- Peer-Reviewed Funding
  - DOD grant defining the impact of HDAC inhibitors on tumor immunogenicity, T cell functionality & PD-1 blockade response in NSCLC patients (PI)
  - FL Biomedical grant targeting immunosuppressive cancer-associated fibroblasts & immune checkpoints in NSCLC (PI)
- Has served as PI of over 50 clinical trials (19 IITs)
- Over 70 publications

Chemical Biology & Molecular Medicine

Jhanelle E. Gray, MD
Eric B. Haura, MD
Program Co-Leaders

Jhanelle E. Gray, MD

- Translational/Early Phase Clinical Trialist focused on Novel Therapeutics

- Passions:
  - Personalized clinical cancer research utilizing novel approaches that lead to transformative cancer research innovations
  - Bridging bench to bedside
  - Mentoring
  - Contributing to the reduction in cancer burden.

- Expertise: Building team science collaborations to formulate, design and execute scientifically driven, rationale trial designs.

Agenda

- Program Overview
- Recruitment
- Revised Specific Aims
- Clinical Translation
- Future Directions

Agenda

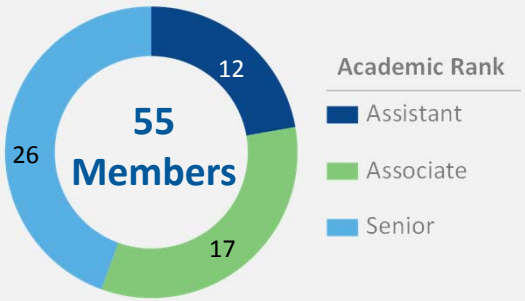
- Program Overview
- Recruitment
- Revised Specific Aims
- Clinical Translation
- Future Directions

External Advisory Council Report 2018

- **Revise CBMM aims** to capture the role of the program in prioritizing research directions
- Add additional **Multi-investigator grants** (P01, SPORE)
- Recognize and **highlight** examples of **clinical translation**

Chemical Biology & Molecular Medicine

Membership

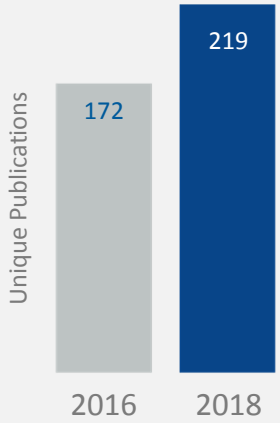


Peer Review Funded PIs
26

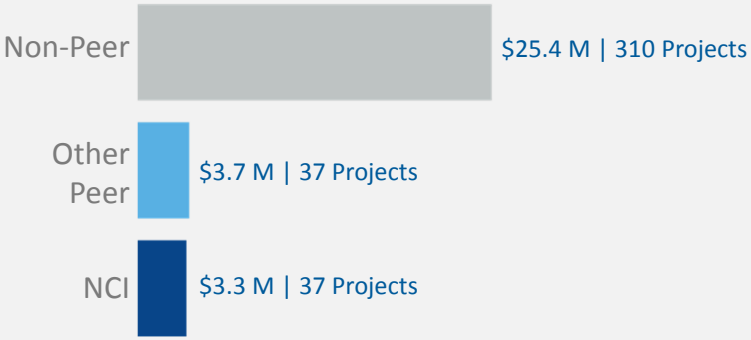
Clinical Trial PIs
23

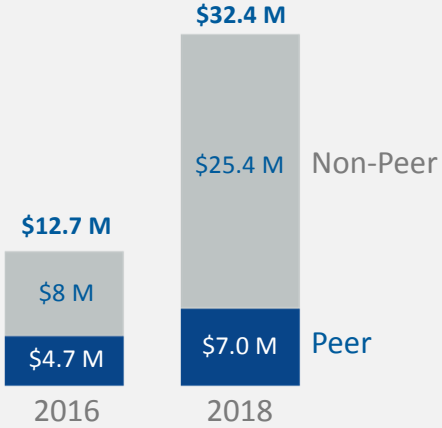
Collaborative Scientists
4

Publications



Grants (Annual Direct Costs)





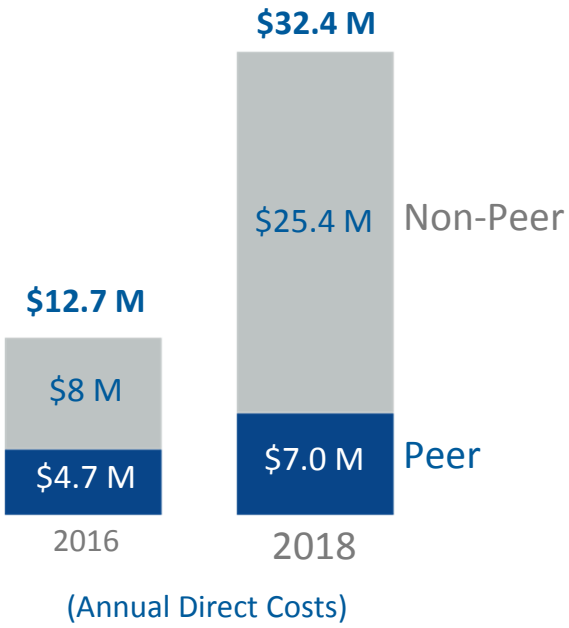
Current

R01/Equivalent Projects
23 (14 PIs)

Annual Direct Costs
$6.4M

2016 – Application | 2018 – Calendar Year

CBMM Program Grants

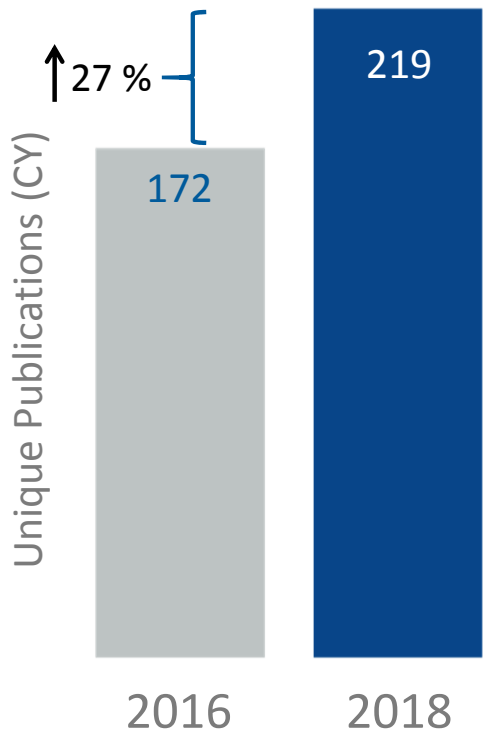


FY 2018:
Fold increase since 2016

All	Peer reviewed
~2.6	~1.5

Multi-I Grants	PI	Submission
Thoracic SPORE	Haura	2018
Myeloma SPORE	Sullivan	2019
Thoracic P01	Haura	2019
UM1	Sullivan	2019
U01 (Multiscale Modeling)	Shain	2019

CBMM Program Publications



Impact Factor

2016 Average	2018 Average	Fold increase
5.45	9.1	1.65

Select Journals (2018)	#	Authors
Lancet Onco/Haem	3	Smalley, List, Komrokji
Nat Commun	1	Sebti
JCO	2	Strosberg, Lancet
CCR	4	Gray, Smalley, Padron, Fleming
Leukemia	2	List, Padron
Blood	2	Lancet, Tao

Agenda

- Program Overview
- Recruitment
- Revised Specific Aims
- Clinical Translation
- Future Directions

New Members - 9

Gastrointestinal Oncology

Rutika Mehta
Assistant Member

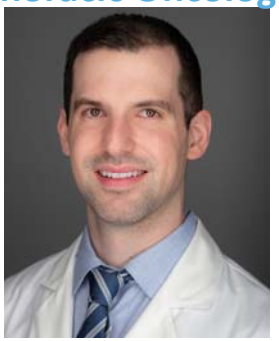
Genitourinary Oncology

Rohit Jain
Assistant Member

Neuro-Oncology

James Liu
Assistant Member

Thoracic Oncology



Andreas Saltos
Assistant Member

Drug Discovery

Derek Duckett
Senior Member

Patsy McDonald
Associate Member

Andrew Kuykendall
Assistant Member

Malignant Hematology

Chestasi Talati
Assistant Member

David Sallman
Assistant Member

Agenda

- Program Overview
- Recruitment
- **Revised Specific Aims**
- Clinical Translation
- Future Directions

Specific Aims Revisited

Original Specific Aims

1. Identify, validate, and characterize targets with therapeutic relevance in refractory and metastatic malignancies
2. Design small molecule chemical probes to modulate oncogenic targets and pathways
3. Develop and implement mechanism-based therapeutic trials

Revised Specific Aims

1. Identify and validate pathways and targets of cancer and therapy resistance
2. Characterize mechanisms of action and optimize existing drugs and lead compounds
3. Design and implement therapeutic trials with a precision medicine approach

Novel Mechanism to Thwart *Kras* –driven Tumors (Aim #1)

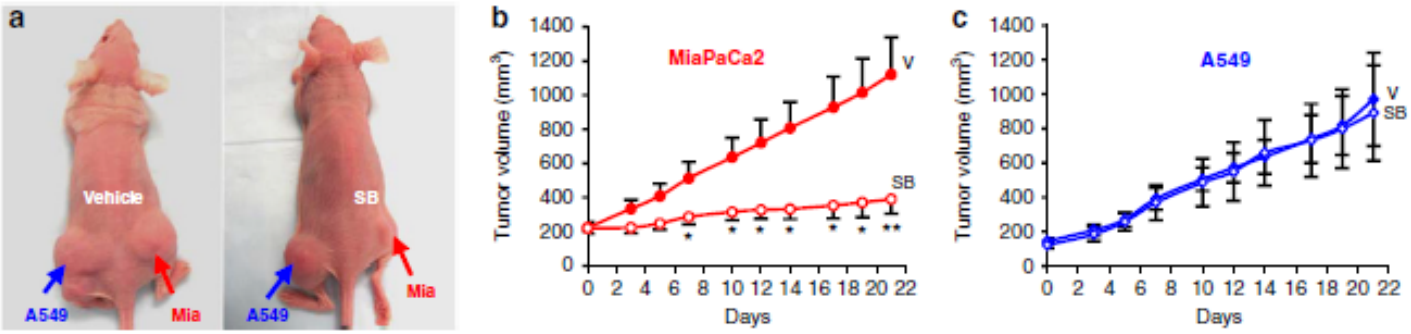
nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-07644-6 OPEN

GSK3 suppression upregulates β-catenin and c-Myc to abrogate KRas-dependent tumors

Aslamuzzaman Kazi[1], Shengyan Xiang[1], Hua Yang[1], Daniel Delitto[2], José Trevino[2], Rays H.Y. Jiang[3], Muhammad Ayaz[1], Harshani R. Lawrence[1], Perry Kennedy[1] & Saïd M. Sebti[1,4]



Said Sebti PhD

Work funded by
NCI R35
Outstanding Investigator Award

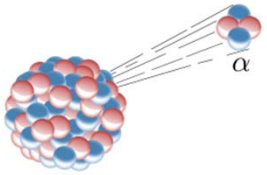
Targeted Alpha-Particle Therapy (TAT) - Melanocortin 1 receptor (MC1R) for Uveal Melanoma (Aims 2 → 3)

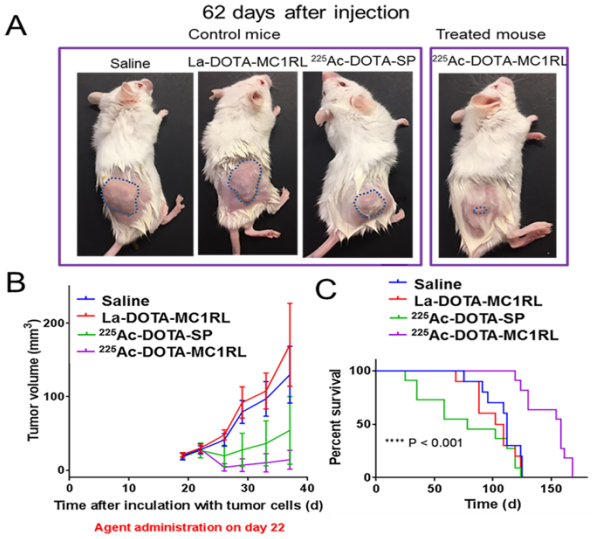
2011
- Specific MC1R-Ligand developed
- Morse group collaboration

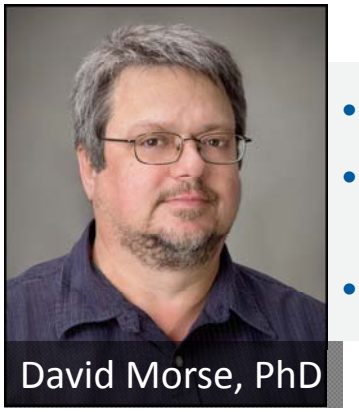
2013
- MC1R specific probe has *in vivo* detection of melanoma
- Morse, DL et al. *Mol Pharm*

2015-7
- ^{225}Ac-DOTA-MC1RL development and preclinical testing

2018-9
- ^{225}Ac-DOTA-MC1RL drug licensed
- Morse, DL et al. *J Nucl Med*






David Morse, PhD

- **Melanoma Research Alliance Grant**
- **First-in-human trial is in development**
- **Led by Dr Khushalani MCC- PI**

HSP90i Can Overcome BRAF Resistance in Melanoma (Aim 3)

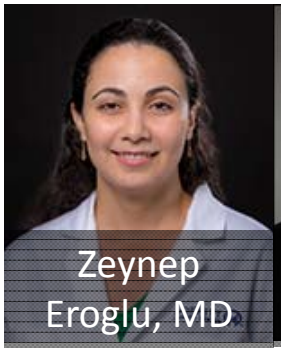
2011
- XL888 overcomes BRAFi resistance
- Smalley et al. *Clin Can Res*

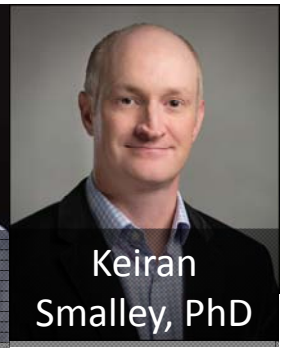
2014
- HSP90i blocks Pi3K signaling in *mBRAF* melanoma
- Smalley et al, *Mol Cel Prot*

2016-8
- Trial 1: BRAFi + HSP90i completed
- Eroglu & Smalley et al. *Clin Can Res*

2018-9
- Trial 2: HSP90i, BRAFi + MEKi
- Completed Accrual

	N: 20
ORR	15 (75%)
CR	3 (15%)
PR	12 (60%)
DCR	19 (95%)


Zeynep Eroglu, MD


Keiran Smalley, PhD

Subsequent Clinical Trial

mBRAF Stage III/IV Melanoma → Vemurafenib 720 mg BID, Cobimetinib 40 mg QD plus XL888 (30-90 mg BIW)

Primary Endpoint: MTD and RP2D
Serial tumor biopsy and blood collections

Agenda

- Program Overview
- Recruitment
- Revised Specific Aims
- **Clinical Translation**
- Future Directions

Investigator-initiated Clinical Trials Open During CY 2016-2018

IIT Type	CBMM
I. Drug discovered at MCC	**4**– e.g., Triciribine + carbo in ovarian ca (Sebti; Wenham PI)
II. Intervention developed or conceived in MCC lab	**25**– e.g., APR-246 + Azacitidine in *TP53m* MDS + AML (List (Mentor); Sallman PI/YIA) – Vorinostat + pembrolizumab (Gray/Beg DOD; Gray PI)
III. IIT developed with pharma, NCCN, UM1, etc.	**47** – e.g., Ixazomib + venetoclax (Nishiori UM1 PI)
Total	**76**

CBMM Investigator Initiated Trials

	Moffitt Sponsored INDs	Pharma Held INDs	IIT Accruals	Total Trial Accruals	Total Trials
2016	33	16	279	657	198
2017	43	11	334	787	215
2018	52	8	418	962	241

- MCC INDs have increased by ~57.6% (~1.57 fold increase).
- IITs accruals have increased by ~50 % (~1.5 fold increase)
- Total trial accruals have increased ~ 46% (~ 1.46 fold increase)

Agenda

- Program Overview
- Recruitment
- Revised Specific Aims
- Clinical Translation
- Future Directions

Future Directions

- **Revise CBMM aims** to capture the role of the program in prioritizing research directions
  - Recruitment new co-PL and Chair of Drug Discovery
  - Finalize revised aims
  - Revise and finalize goals

- Add additional **Multi-investigator grants** (P01, SPORE)
  - Strategically plan for larger grants and demonstrated successes of pilot grant funding
  - Build better connections with Phase I teams and collaboration with other Programs

- Recognize and **highlight** examples of **clinical translation**
  - Better showcase IITs and mentoring

- Build Engagement
  - Annual Retreats
  - Working groups with Faculty Chairs
  - CBMM Monthly Meetings & Seminars

Questions:

- In order to focus a “diffuse” program, are we on the right path with the aims?
- With such a large program, what is the best approach to setting realistic expectations from the reviewers?
- Do we need to reduce our membership?
- Are there unexplored strategies/best practices to building team science to foster larger, multi-I grants.

Immunology Program

Jose R Conejo-Garcia, MD, PhD
Frederick Locke, MD
Program Co-Leaders

Immunology Program

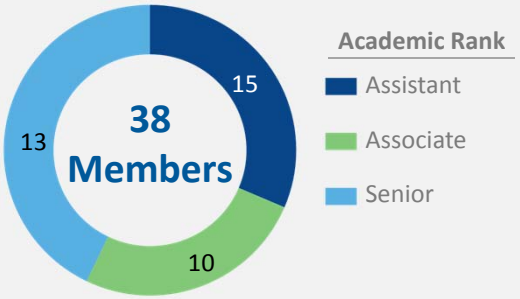
Goal

To define the basic mechanisms by which tumors evade rejection by the immune system and to develop new strategies to thwart them

Original Aims	Newly proposed Aims (based on EAC recommendation)
1. Advance and translate T-cell therapies for solid tumors and hematologic malignancies	1. To understand molecular and cellular mechanisms to exploit innate and adaptive immunity against cancer.
2. Define molecular and cellular mechanisms to exploit innate and adaptive immunity against cancer	2. To elucidate and target pathways governing effectiveness, resistance and toxicity in anti-cancer immunotherapy.
3. Prevent graft-versus-host disease (GVHD) while sparing graft-versus-leukemia responses after hematopoietic cell transplantation (HCT)	3. To develop and implement anti-cancer cellular therapies

Immunology

Membership



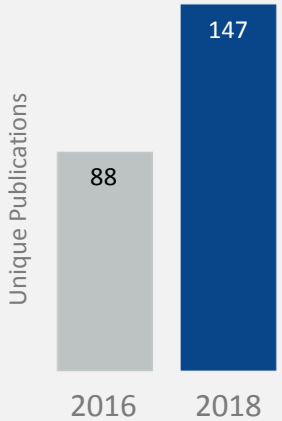
Peer Review Funded PIs

23

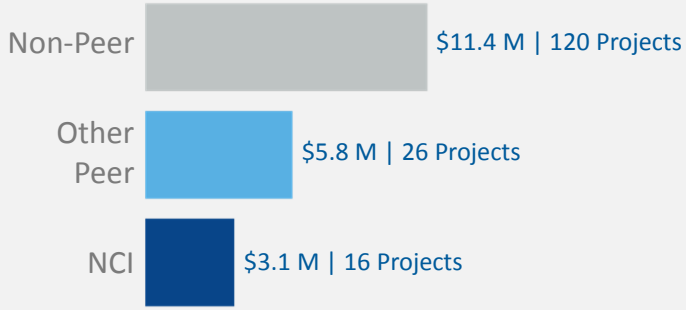
Clinical Trial PIs

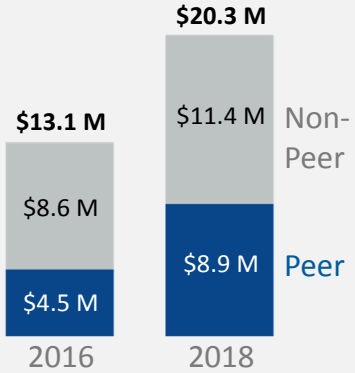
9

Publications



Grants (Annual Direct Costs)





Current

R01/Equivalent Projects

17 (12)

Annual Direct Costs

$6.8M

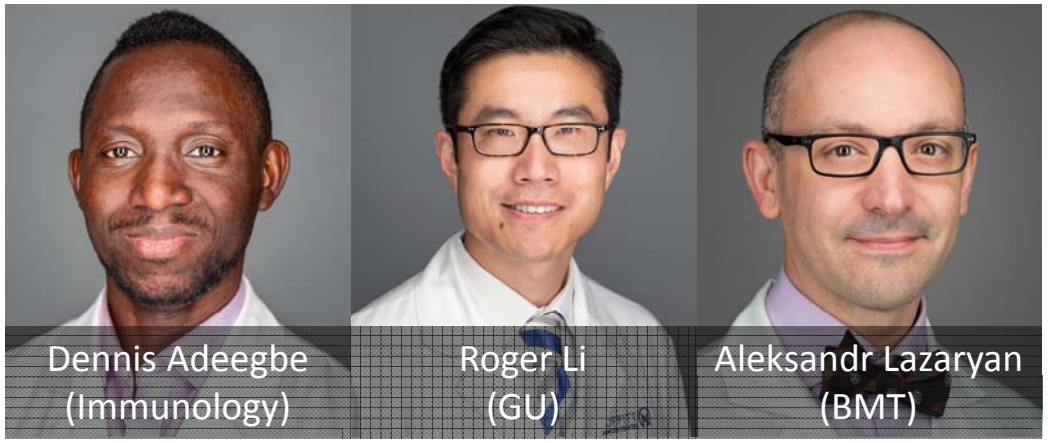
2016 – Application | 2018 – Calendar Year

Membership (n=38; 23 peer-reviewed funded)

- By Rank
  - Assistant Member 15
  - Associate Member 10
  - Senior Member 13

- By Degree
  - MD or MD/PhD 23
  - PhD 15

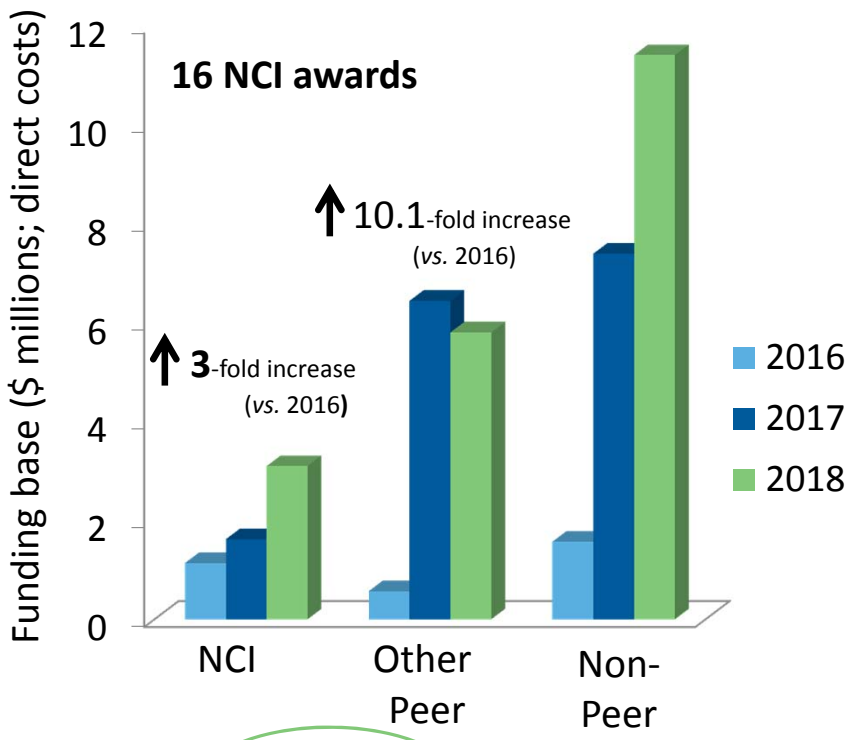
- 4 open recruitment opportunities
- New Members (Recruits)



EAC recommendation: Increase recruitment

- 3 interviews for NIH-funded investigators scheduled in 2019
- Recruitment of new BMT Chair & Malignant Hematology Vice-Chair (Future IMM Members)

Immunology Program Peer-Reviewed Funding (As of December 31, 2018)



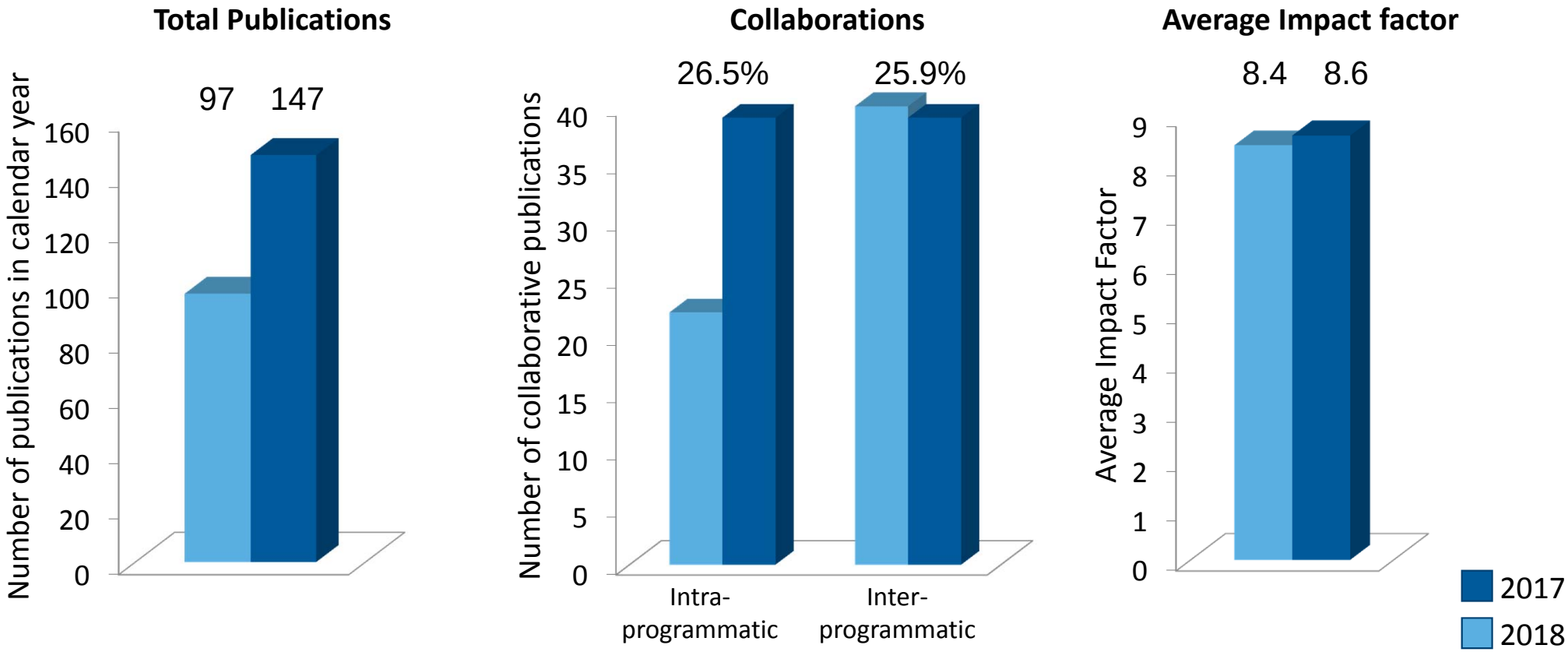
Direct costs: **$20.3 million** → ***1.5-fold*** increase *vs.* 2017

Actions to improve NCI funding (based on EAC recommendations):

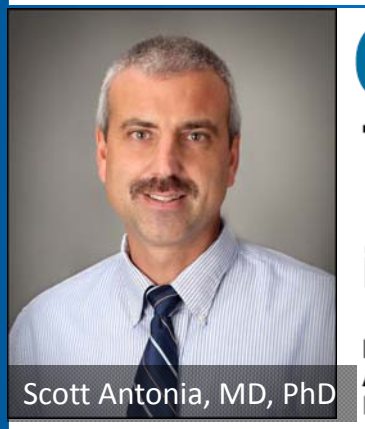
- Mentoring plans & committees for all Assistant Members (scores pending for 3 resubmissions)
- Pilot funding seeds the prospect of securing extramural funding (100K/year)
- New recruits focused on NIH-funded investigators (4 funded candidates scheduled for 2019 Q1)
- New pilot grant funding mechanism for collaborations between members of Cancer Epidemiology & Immunology (2 awards of up to $50K)
- New U54/U01 under preparation for the IOTN RFA (Moonshot) (7 IMM members involved)
- SPOREs (Myeloma submitted, Lung Cancer & Cutaneous pending)
- Not including new $10 million DoD Breast cancer award (4 IMM members included).

Immunology Program Publications

***NEJM* (2), *Cancer Cell* (2), *Lancet Oncology;* Additional collaborations in *Nature* (2), *Cell* (2), *NEJM* (2)**



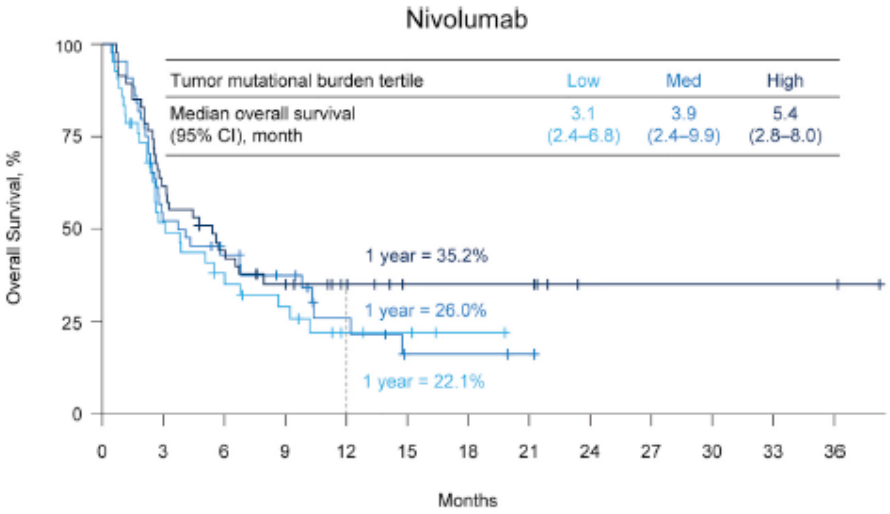
Scientific Highlight

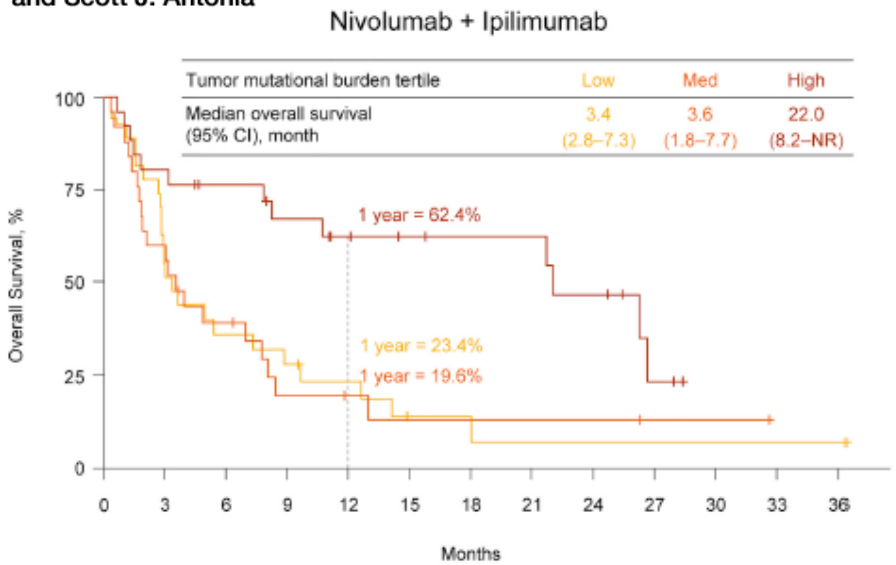

Scott Antonia, MD, PhD

Cancer Cell

Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer

Matthew D. Hellmann,[1,11,12,*] Margaret K. Callahan,[1,11] Mark M. Awad,[2] Emiliano Calvo,[3] Paolo A. Ascierto,[4] Akin Atmaca,[5] Naiyer A. Rizvi,[6] Fred R. Hirsch,[7] Giovanni Selvaggi,[8] Joseph D. Szustakowski,[9] Ariella Sasson,[9] Ryan Golhar,[9] Patrik Vitazka,[9] Han Chang,[9] William J. Geese,[9] and Scott J. Antonia[10]





Immunotherapy Clinical Trials

206 patients accrued onto interventional immunotherapeutic trials in 2018

- **Immunotherapy Working Group (IWG)**
  - Multi-disciplinary forum for industry sponsored CAR T, TILs and TCR studies
  - Platform to foster collaboration aimed at clinical translation
  - **EAC recommendation**: Sets institutional priorities for cellular immunotherapy trials

- **Immune Cell Therapy (ICE-T) Service**
  - Provides clinical care for patients on cellular or other high risk immunotherapies
  - IWG provides determines which trials would be eligible for the service

Moffitt Investigators are Designing & Testing New Cellular Immunotherapies

- New Cellular Immunotherapies*
  - APC lines for expansion of ACT: Marco Davila
  - CAR T for AML: Marco Davila (Atara)
  - gd T cells after Allogeneic Transplant: Marco Davila
  - CAR T for solid tumors: Daniel Abate-Daga
  - CER T cells for FSHR+ ovarian CA: Jose Conejo-Garcia/ Robert Wenham (ITUS)
  - DC vaccines for Breast cancer: Brian Czerniecki
  - DC vaccines for lymphoid cancers: Fred Locke
  - TILs for Sarcoma: John Mullinax
  - TILs for Bladder: Pilon Thomas
  - TILs for Lung cancer: Scott Antonia & Ben Creelan
  - TILs for Melanoma: Amod Sarnaik & Shari Pilon-Thomas
  - Tregs to prevent GVHD: Joseph Pidala
  - TLS for solid tumors: Jim Mulé
- Production Assistance for Cellular Therapy (PACT) projects: Linda Kelley
  - Cell Therapy for MIL Expansion for AML: Marco Davila
  - gd T Cell Purification and Expansion for AML: Marco Davila
  - Phase I Trial of Ex-vivo Expanded Unrelated Donor Regulatory T cells for Prevention of Graft-versus-Host Disease: Joseph Pidala

*Partial list of Moffitt translational investigators with grant funding to develop Cellular Immunotherapies

Cellular Immunotherapy Trials at Moffitt

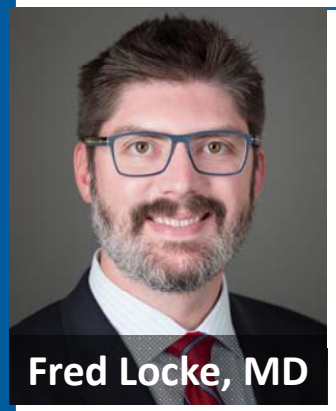
- Allogene Allo-CAR T for DLBCL
- Kite 107 CAR T for DLBCL 2nd line vs SOC
- Kite 112 CAR T for Front line DLBCL
- Kite 102 CAR T for MCL
- Kite 103 CAR T for ALL
- Kite 106 CAR T + atezo for DLBCL
- Kite 105 CAR T for Follicular Lymphoma
- Novartis CAR T + ibrutinib for r/r DLCBL
- Novartis CAR T for Follicular Lymphoma
- BB/Celgene BCMA P1 CAR T for Myeloma
- BB/Celgene BCMA P2 CAR T for Myeloma
- BB/Celgene BCMA P3 CAR T for Myeloma
- Kite BCMA CAR T for Myeloma
- CEYLAD NKG2D CAR T for AML/MDS

- Iovance TILs for GYN
- Iovance TILs for H&N
- Iovance TILs for Melanoma
- Adaptimmune A3/A6 TCR for Lung
- Adaptimmune NY-ESO-1 TCR Sarcoma
- Adaptimmune NY-ESO-1 TCR Myeloma
- Amgen DLL3 CAR T for SCLC
- Bellicum PSCA CAR T for Pancreatic CA
- Kite MAGE A3/A6 TCR for Solid tumors
- Kite HHV7 TCR for cervical/H&N

- CTEP Nivolumab for relapse post Allo
- CTEP BiTe + revlimid for lymphoma
- CTEP atezo after ACT

*Partial list of Moffitt Cellular Immunotherapy trials accruing or in start up

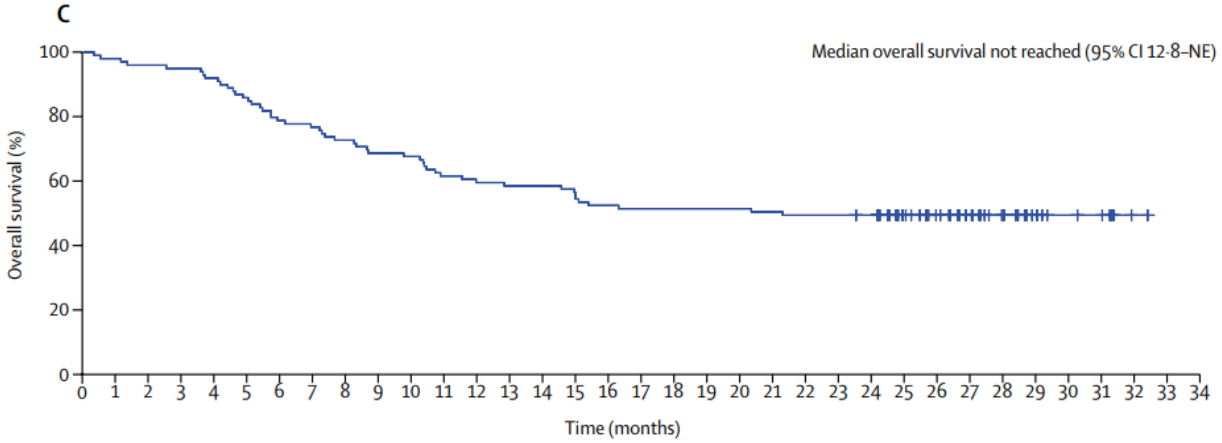
Scientific Highlight



THE LANCET
Oncology

Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial

Frederick L Locke, Armin Ghobadi, Caron A Jacobson, David B Miklos, Lazaros J Lekakis, Olalekan O Oluwole, Yi Lin, Ira Braunschweig, Brian T Hill, John M Timmerman, Abhinav Deol, Patrick M Reagan, Patrick Stiff, Ian W Flinn, Umar Farooq, Andre Goy, Peter A McSweeney, Javier Munoz, Tanya Siddiqi, Julio C Chavez, Alex F Herrera, Nancy L Bartlett, Jeffrey S Wiezorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu**



Questions

- Are we in the right track in terms of publications, clinical trials and impact?
- What other actions can we take to improve NCI funding?
- Are the new program specific aims appropriate?

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

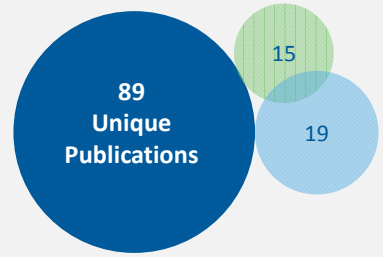
Membership

Academic Rank
- Assistant
- Associate
- Senior

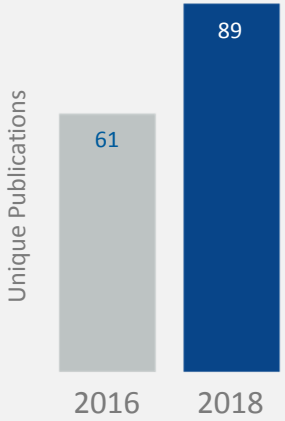
Peer Review Funded PIs

18

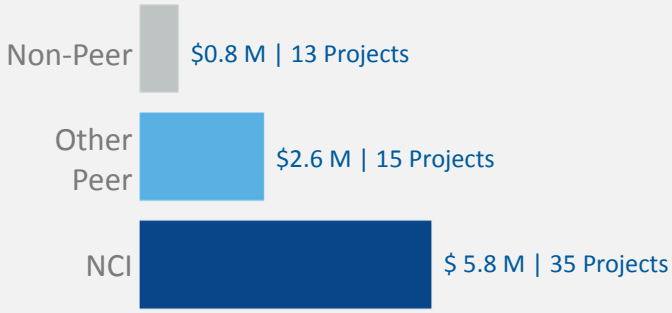
Publications

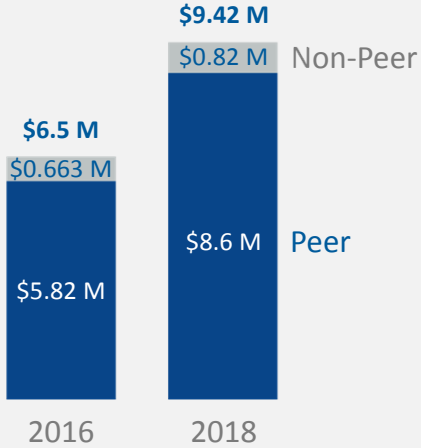


- Inter-Program Collaboration (24.4%)
- Intra-Program Collaboration (16.9%)



Grants (Annual Direct Costs)





Current

R01/Equivalent Projects

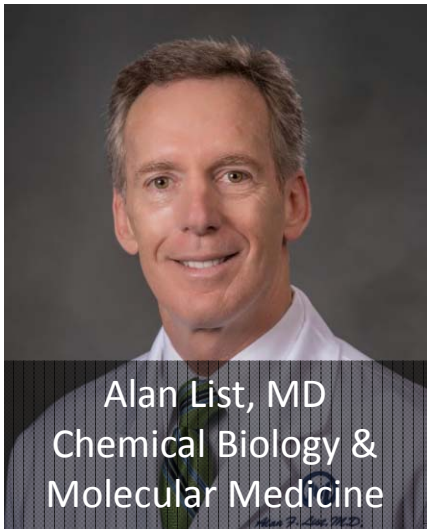
16 (9 PIs)

Annual Direct Costs

$6.6M

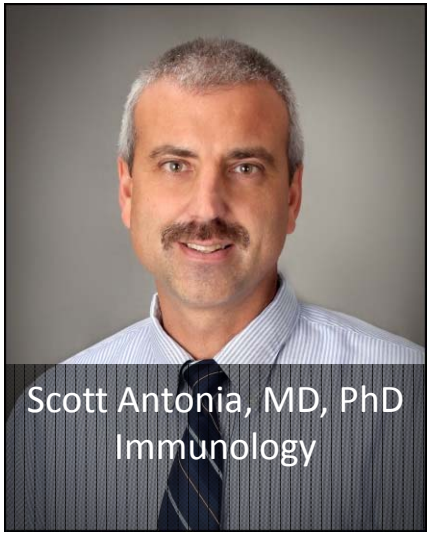
2016 – Application | 2018 – Calendar Year

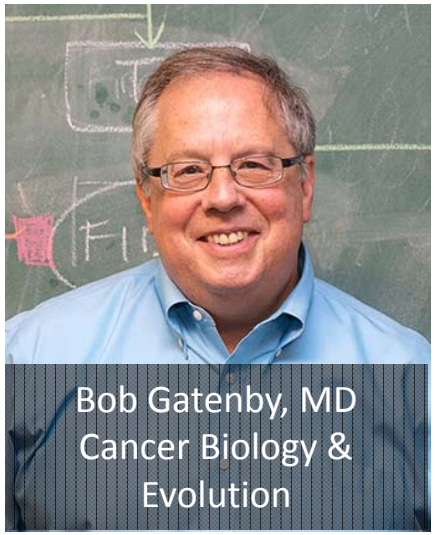
CBE: *Grant Highlight*



- 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.

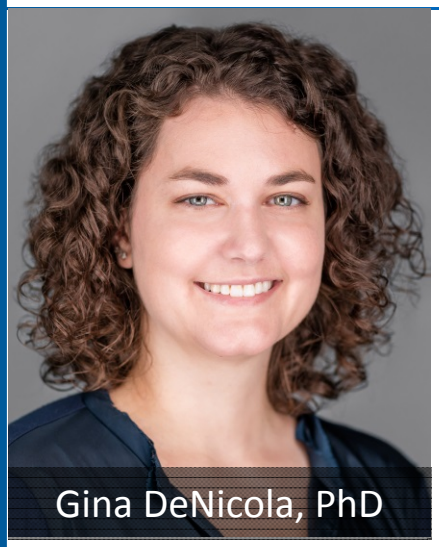
CBE: *Grant Highlight*





- **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

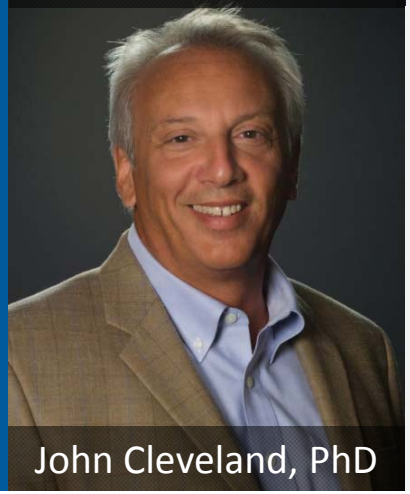
CBE: *Grant Highlight*

- 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

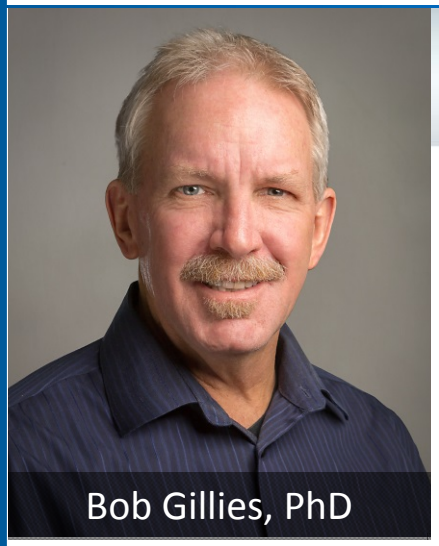
JCI The Journal of Clinical Investigation

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*



nature COMMUNICATIONS

ARTICLE

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

Systems analysis of intracellular pH vulnerabilities for cancer therapy

Erez Persi[1,2], Miquel Duran-Frigola[3], Mehdi Damaghi[4,5], William R. Roush[6], Patrick Aloy[3,7], John L. Cleveland[8], Robert J. Gillies[4] & Eytan Ruppin[9]

- 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

JCO™ | CLINICAL CANCER INFORMATICS
An American Society of Clinical Oncology® Journal

original reports

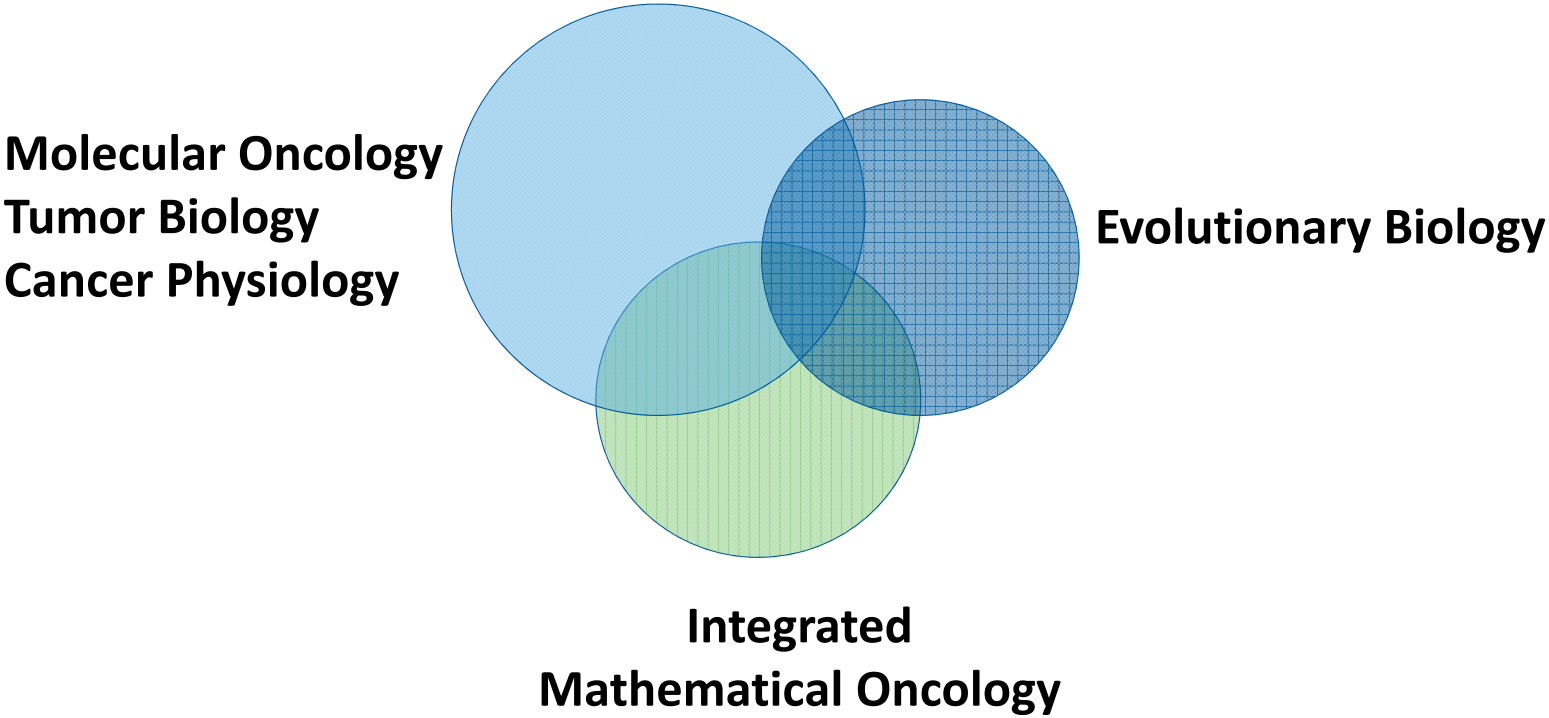
Computational Model of Progression to Multiple Myeloma Identifies Optimum Screening Strategies

- 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

Agenda

- 2018 Publications and Grants
- **Program Structure**
- 2018 Activities
- Plans for 2019
- Questions

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:

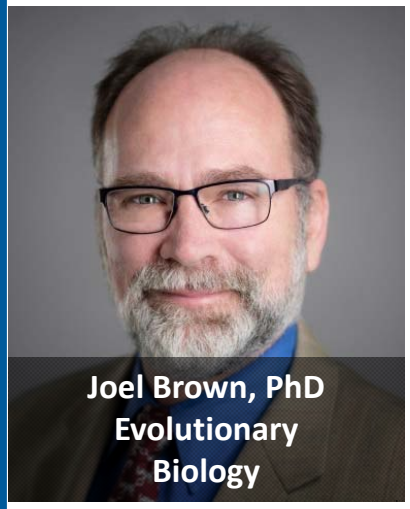
1. Empirically & mathematically define the dynamics operational in cancer and therapy
2. Exploit evolution by natural selection as the first principle operational in cancer
3. Translate evolutionary dynamics into personalized, modeled therapies

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

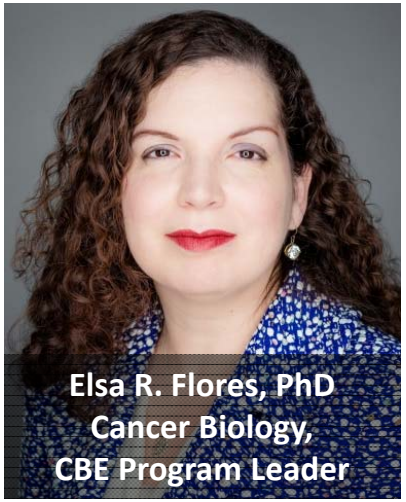
Cancer Biology & Evolution

Steering Committee

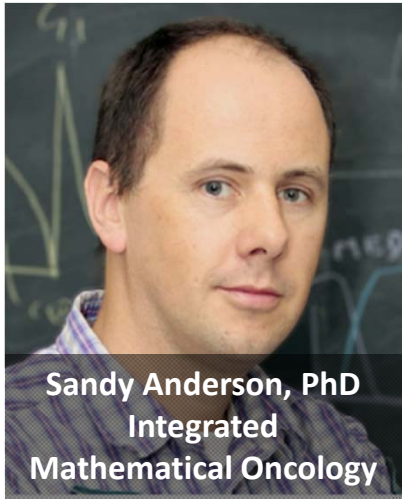


Joel Brown, PhD
Evolutionary Biology

Kenneth Tsai, MD, PhD
Translational Research



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



Sandy Anderson, PhD
Integrated Mathematical Oncology

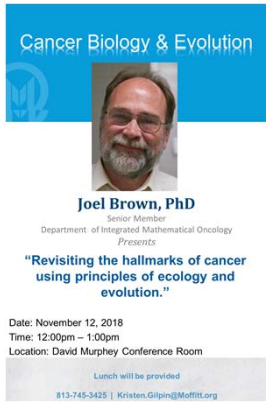
Nikhil Kushalani, MD
Clinical Trials

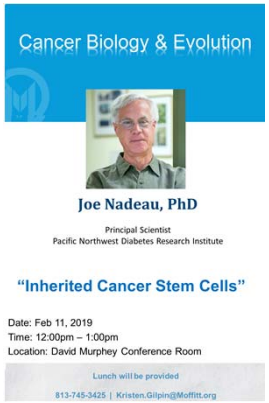
Agenda

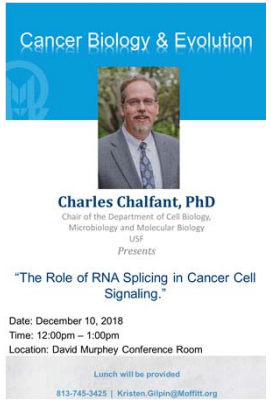
- 2018 Publications and Grants
- Program Structure
- **2018 Activities**
- Plans for 2019
- Questions

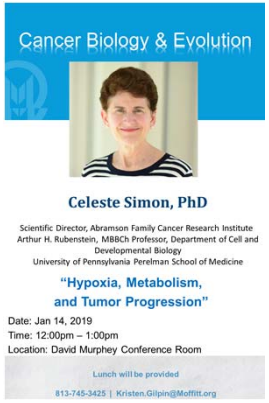
Cancer Biology & Evolution: *2018 Activities*

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









Cancer Biology & Evolution

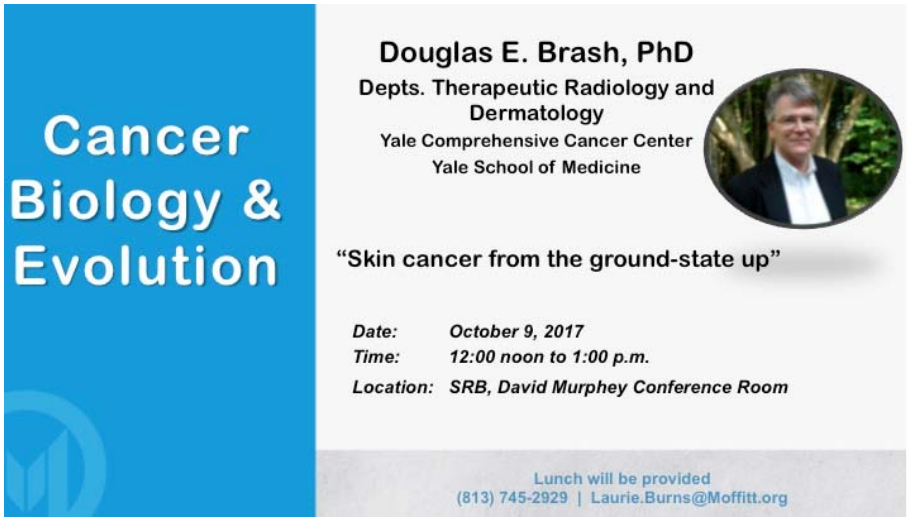
Seminar Series - 2018

MOFFITT CANCER CENTER

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 Coller, 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*



- 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**

Cancer Biology & Evolution

Innovation Funds - $50,000 per award

- *"Investigation of CircularRNAs in Melanoma"*

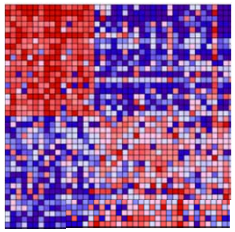
Florian Karreth, PhD
CBE Member
Assistant Member, Molecular Oncology

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

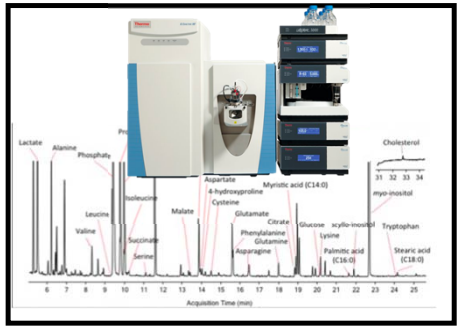
Gina DeNicola, PhD
CBE Member
Assistant Member, Cancer Physiology

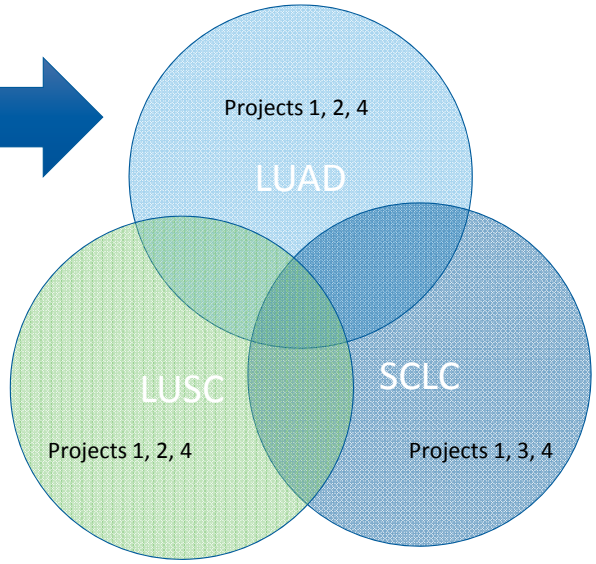
Cancer Biology & Evolution

Innovation Funds – P01 Application – Metabolic Vulnerabilities in Lung Cancer



Nrf2
myc
Keap1
p53
ΔNp63
ΔNp73
TAp73
TAp63
Perk





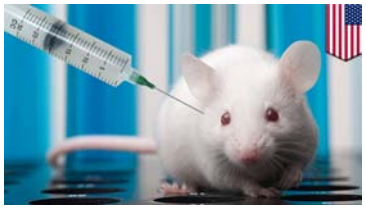
Elsa R. Flores, PhD
PI and Project Leader
CBE

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



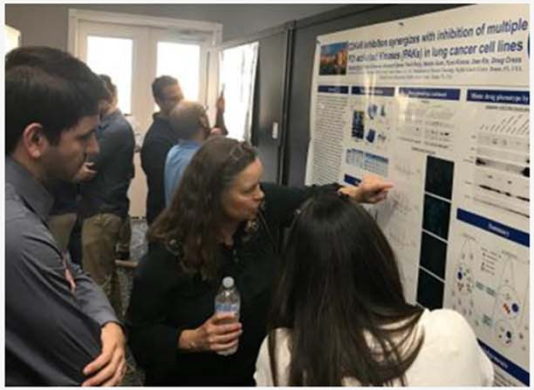
Cancer Biology & Evolution

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

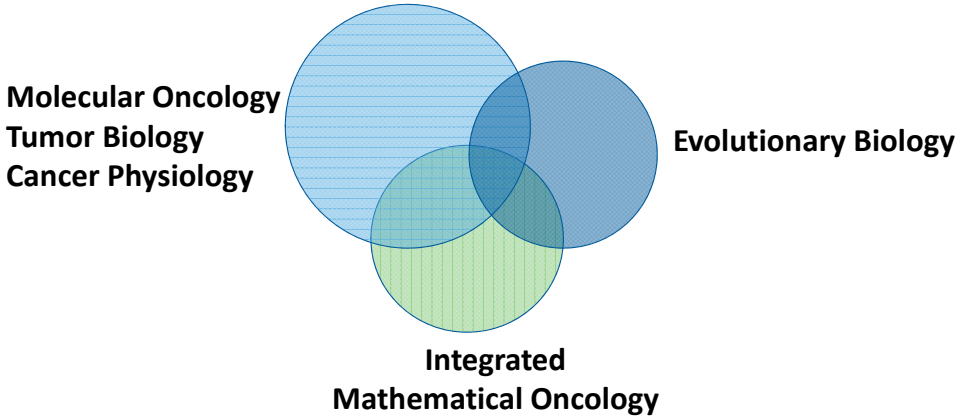
Agenda

- 2018 Publications and Grants
- Program Structure
- 2018 Activities
- **Plans for 2019**
- Questions

Cancer Biology & Evolution

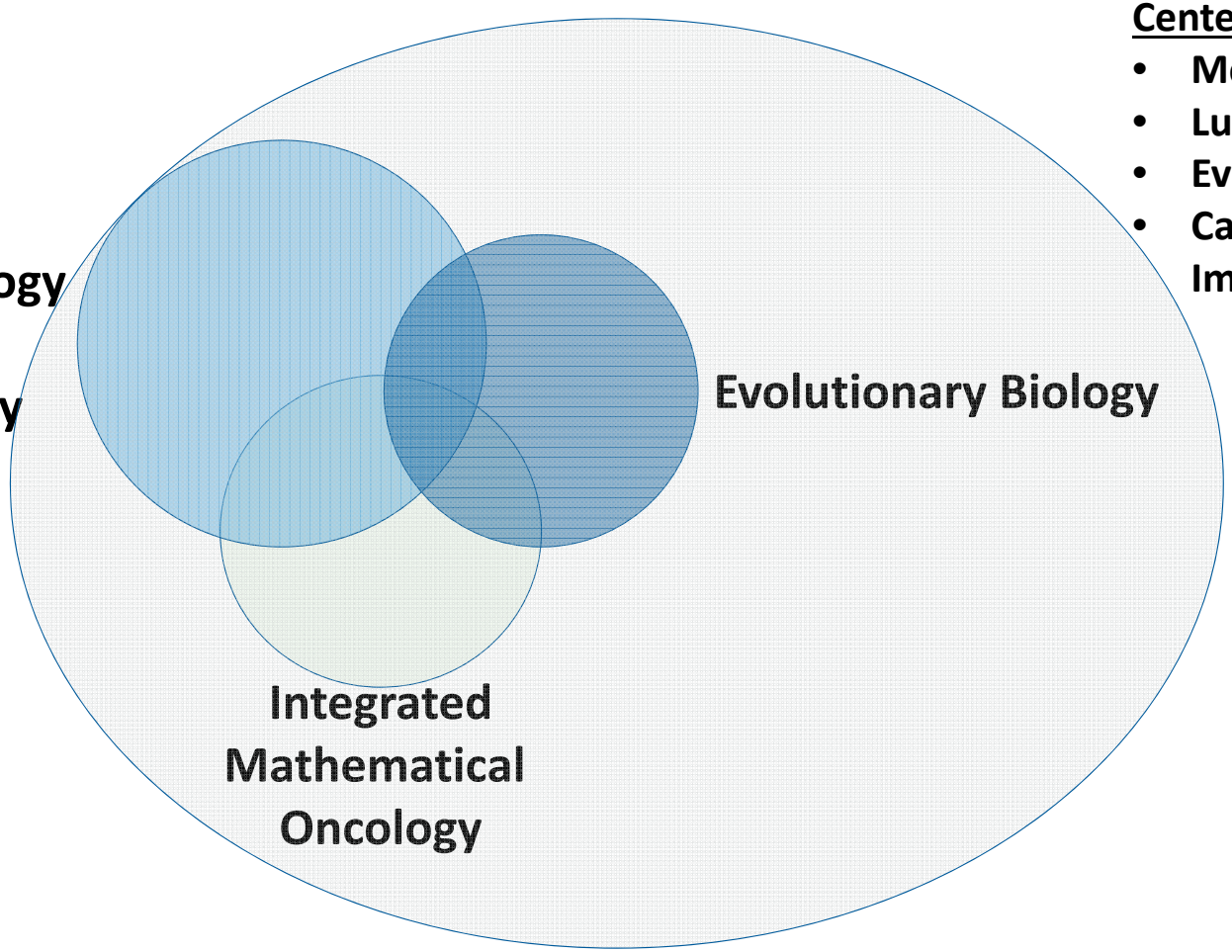
Plans for 2019

- 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

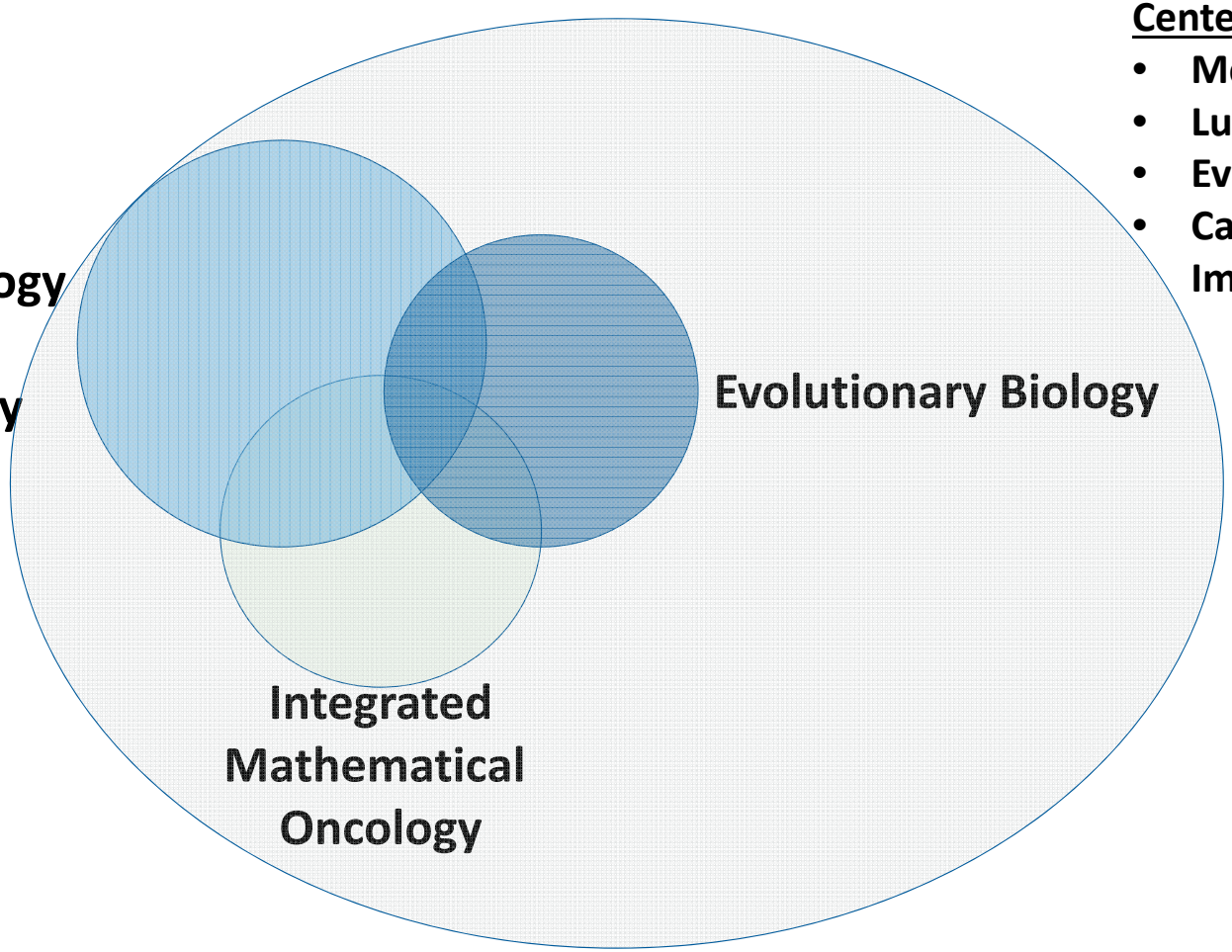


Centers of Excellence

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

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

- 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 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)

Agenda

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

Questions

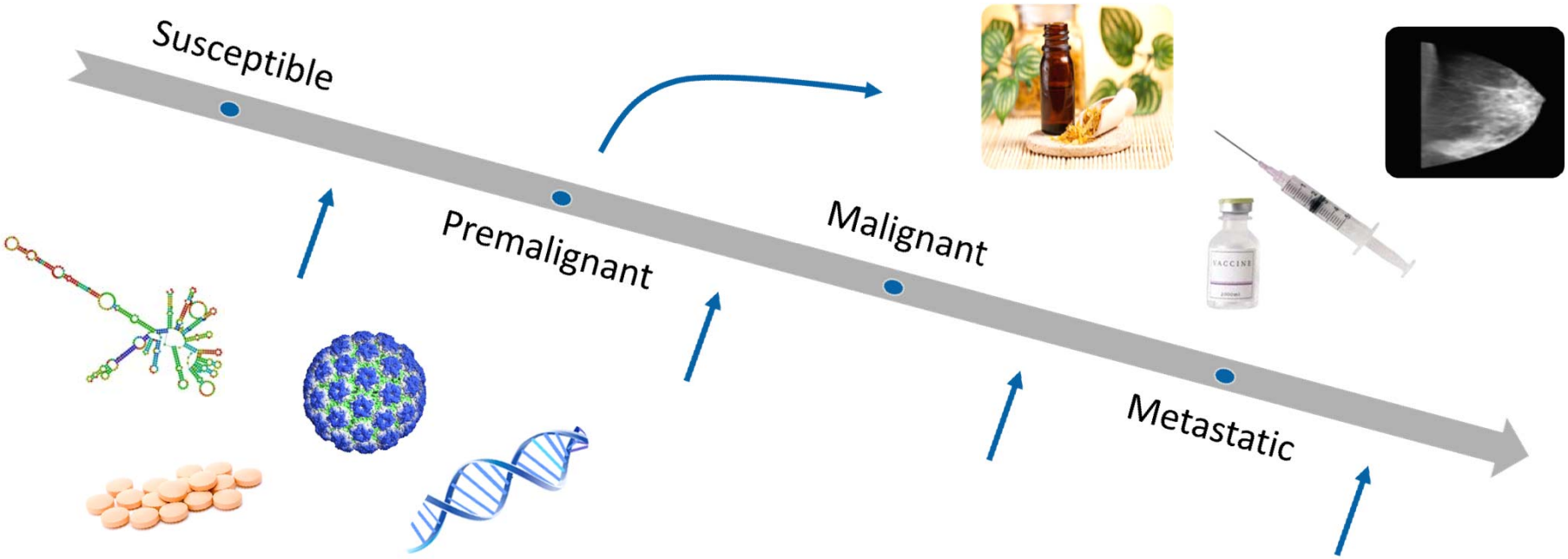
- Does the program's proposed steering committee represent the research areas and clinical activities of the program?
- Do the new proposed aims encompass the breadth of research in the program?

Cancer Epidemiology Program

Peter Kanetsky, PhD, MPH
Program Leader and Chair
Moffitt Distinguished Scholar

Program Goal

Reduce the cancer burden by identifying determinants of disease development, progression and outcome and by translating findings into successful prevention approaches and interventions



Program Appraisals

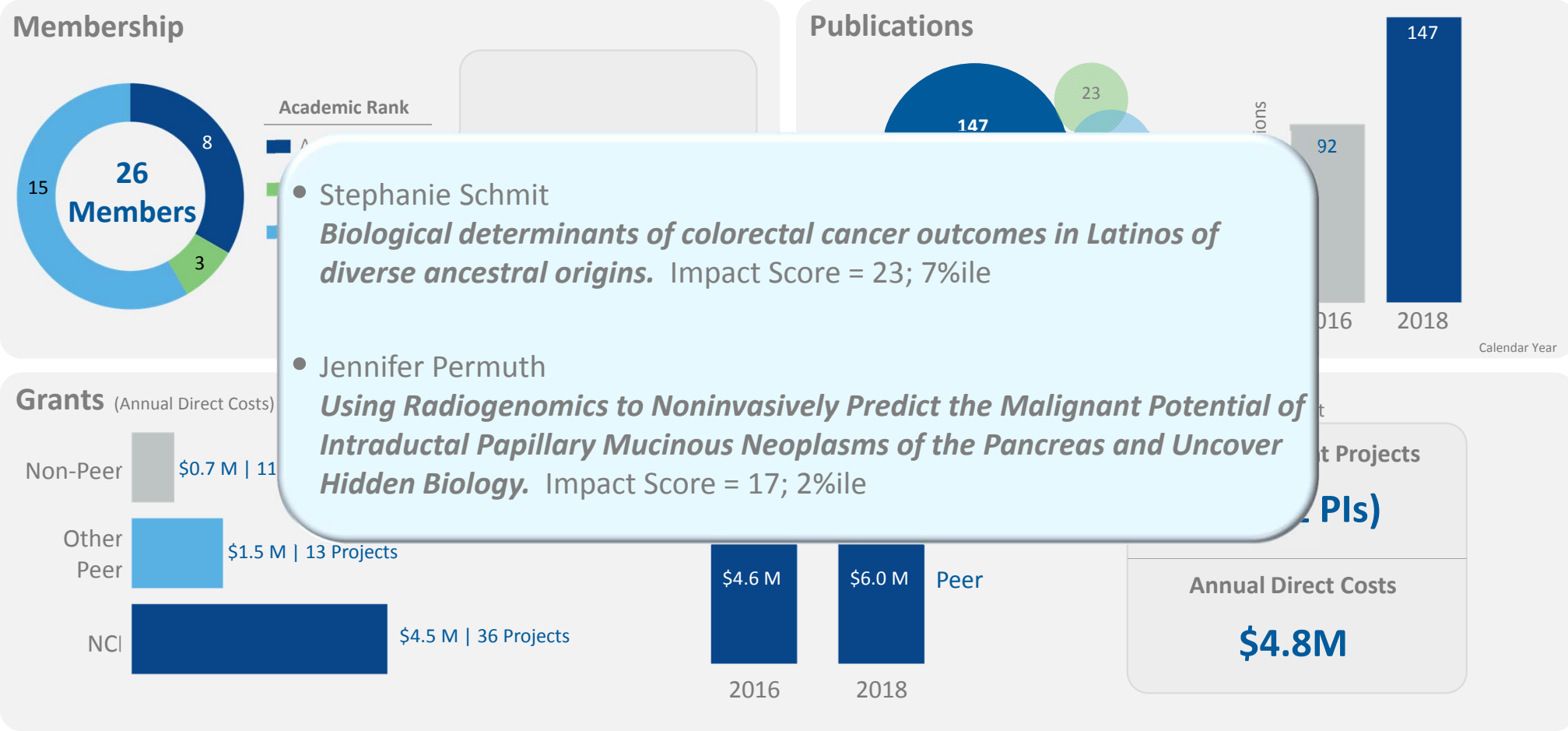
CCSG Renewal 2016

- Exceptional merit
- No major criticisms

EAC Meeting 2018

- Program recruitment
- Program co-Leader
- Publication statistics
- Aim 3
- Future directions

Cancer Epidemiology



- Stephanie Schmit
  Biological determinants of colorectal cancer outcomes in Latinos of diverse ancestral origins. Impact Score = 23; 7%ile

- Jennifer Permuth
  Using Radiogenomics to Noninvasively Predict the Malignant Potential of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Uncover Hidden Biology. Impact Score = 17; 2%ile

New Members

Anna Coghill, Assistant Member

- Infections and immunoepidemiology
- Epstein-Barr virus-related cancers
- Interest in HIV and cancer

Lauren Peres, Assistant Member

- Ovarian cancer disparities
- Interest in multiple myeloma
- R00 – Inflammation and ovarian cancer

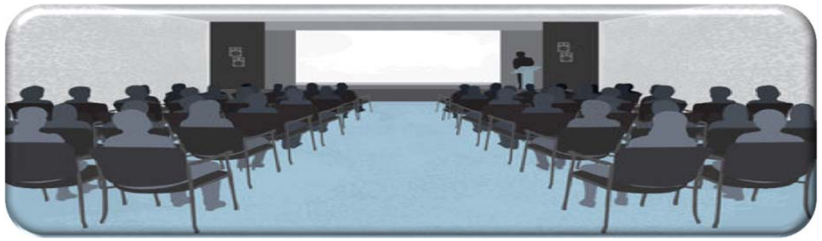
Manish Kohli, Senior Member

- Vice Chair, Genitourinary Oncology
- Director, DeBartolo Family Personalized Medicine Institute
- R01 – circulating biomarkers in prostate cancer

Ongoing Recruitment

Assistant Member

- Research in hematological malignancies
- Three candidate visits (January/February)



Program Co-Leader

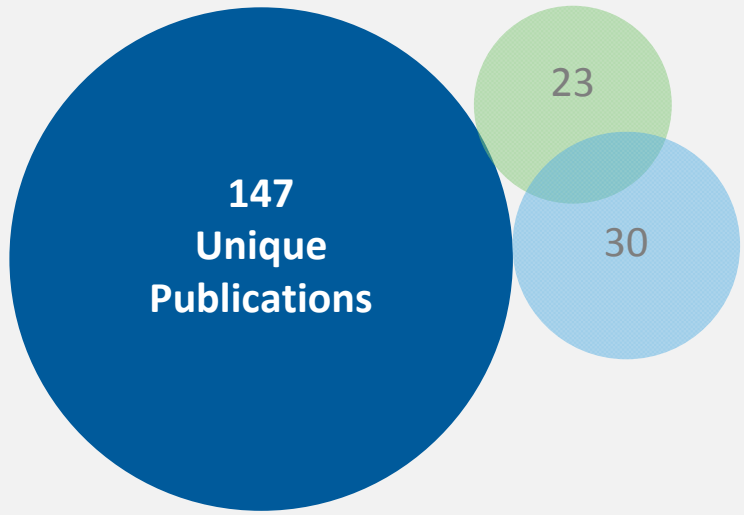
- Risk prediction or clinical epidemiology and large health records databases
- Recruitment initiated Jan 2019

9 established leaders

6 targeted individuals

Publication Metrics

- Mean IF = 5.5
- 14% with IF > 8
- Strategic discussions at meetings
- Monthly tracking
- Assistant members – ramp up time
- Senior members – consortia involvement



Inter-Program Collaboration (20.4%)

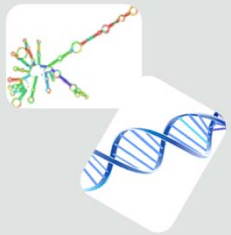
Intra-Program Collaboration (15.6%)

Program Aims

Aim ①

Examine the association of inherited susceptibility biomarkers with cancer risk and outcome

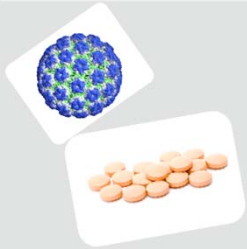
Identify inherited susceptibility biomarkers of cancer risk, progression, and outcome and explore underlying mechanisms



Aim ②

Identify and test whether acquired biomarkers can predict cancer risk and outcome

Identify and validate acquired biomarkers predicting cancer risk, progression, and outcome and explore underlying mechanisms



Aim ③

Discover and test the efficacy of promising approaches for the prevention and early detection of cancer

Discover and test the efficacy of promising approaches and novel interventions to reduce cancer burden across the continuum

Aim 3

Aim ③

Discover and test the efficacy of promising approaches and novel interventions to reduce cancer burden across the continuum

Scientific Progress

Stephanie Schmit

- Meta analysis
- 12,952 European cases & 48,383 controls
- 12,085 multi-ethnic cases & 22,083 controls
- 9 novel loci
- ~15% increase in familial risk
- Polygenic risk score identifies 4% of population with OR≥2

OXFORD

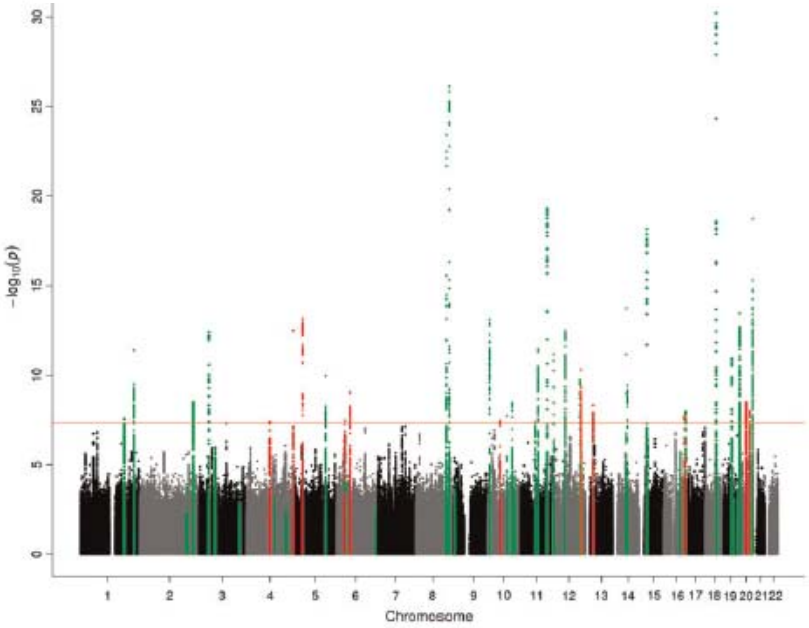
JNCI J Natl Cancer Inst (2019) 111(2): djy099

doi: 10.1093/jnci/djy099
Article

ARTICLE

Novel Common Genetic Susceptibility Loci for Colorectal Cancer

Stephanie L. Schmit*, Christopher K. Edlund*, Fredrick R. Schumacher*, Jian Gong*, Tabitha A. Harrison, Jeroen R. Huyghe, Chenxu Qu, Marilena Melas, David J. Van Den Berg, Hansong Wang, Stephanie Tring, Sarah J. Plummer, Demetrius Albanes, M. Henar Alonso, Christopher I. Amos, Kristen Anton, Aaron K. Aragaki, Volker Arndt, Elizabeth L. Barry, Sonja I. Berndt, Stéphane Bezieau, Stephanie Bien, Amanda Bloomer, Juergen Boehm, Marie-Christine Boutron-Ruault, Hermann Brenner, Stefanie Brezina, Daniel D. Buchanan, Katja Butterbach, Bette J. Caan, Peter T. Campbell, Christopher S. Carlson, Jose E. Castelao, Andrew T. Chan, Jenny Chang-Claude, Stephen J. Chanock, Iona Cheng, Ya-Wen Cheng, Lee Soo Chin, James M. Church, Timothy Church, Gerhard A. Coetzee, Michelle Cotterchio, Marcia Cruz Correa, Keith R. Curtis, David Duggan, Ulrike Peters†, Graham Casey†, Li Hsu†, David V. Conti†, Stephen B. Gruber†



Scientific Progress

Shelley Tworoger

- 200,000+ nurses in NHS I & II
- 1000+ cases of ovarian cancer
- Pre-diagnostic use of aspirin and NSAID associated with better survival
- Survival advantage also seen among "switchers" to analgesics post-diagnosis

THE LANCET Oncology

Articles

Pre-diagnosis and post-diagnosis use of common analgesics and ovarian cancer prognosis (NHS/NHSII): a cohort study

Melissa A Merritt, Megan S Rice, Mollie E Barnard, Susan E Hankinson, Ursula A Matulonis, Elizabeth M Poole*, Shelley S Tworoger*

www.thelancet.com/oncology Vol 19 August 2018

	Pooled analysis*		
	Events (n)	Participants (N)	HR (95% CI)
Pre-diagnosis aspirin use†			
Total	623	1022	..
Never	143 (23%)	250 (24%)	1·00 (reference)
Past	202 (32%)	342 (33%)	0·95 (0·75–1·22)
Recent	278 (45%)	430 (42%)	0·99 (0·79–1·25)
Post-diagnosis aspirin use†			
Total	491	940	..
Never (pre-diagnosis or post-diagnosis)	119 (24%)	231 (25%)	1·00 (reference)
Past‖	227 (46%)	395 (42%)	0·94 (0·73–1·21)
Recent	145 (30%)	314 (33%)	0·68 (0·52–0·89)
Pre-diagnosis NSAID use†			
Total	491	824	..
Never	191 (39%)	278 (34%)	1·00 (reference)
Past	144 (29%)	263 (32%)	0·83 (0·66–1·05)
Recent	156 (32%)	283 (34%)	0·94 (0·75–1·18)
Post-diagnosis NSAID use†			
Total	433	881	..
Never (pre-diagnosis or post-diagnosis)	174 (40%)	335 (38%)	1·00 (reference)
Past‖	160 (37%)	292 (33%)	0·93 (0·74–1·19)
Recent	99 (23%)	254 (29%)	0·67 (0·51–0·87)

Scientific Progress

Shelley Tworoger

- 200,000+ nurses in NHS I & II
- 1000+ cases of ovarian cancer
- Pre-diagnostic use of aspirin and NSAID associated with better survival
- Survival advantage also seen among “switchers” to analgesics post-diagnosis
- Use of NSAID increased risk
- Low-dose aspirin associated with decreased risk of ovarian cancer
- Risk reduction not observed for regular dose aspirin

Research

JAMA Oncology | Original Investigation

Association of Analgesic Use With Risk of Ovarian Cancer in the Nurses' Health Studies

Mollie E. Barnard, ScD; Elizabeth M. Poole, PhD; Gary C. Curhan, MD, ScD; A. Heather Eliassen, ScD; Bernard A. Rosner, PhD; Kathryn L. Terry, ScD; Shelley S. Tworoger, PhD

OXFORD

JNCI J Natl Cancer Inst (2019) 111(2): djy100

doi: 10.1093/jnci/djy100
Article

ARTICLE

Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium

Britton Trabert, Elizabeth M. Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L. Anderson, Theodore M. Brasky, Louise A. Brinton, Renee T. Fortner, Mia Gaudet, Patricia Hartge, Judith Hoffman-Bolton, Michael Jones, James V. Lacey Jr., Susanna C. Larsson, Gerardo G. Mackenzie, Leo J. Schouten, Dale P. Sandler, Katie O'Brien, Alpa V. Patel, Ulrike Peters, Anna Prizment, Kim Robien, V. Wendy Setiawan, Anthony Swerdlow, Piet A. van den Brandt, Elisabete Weiderpass, Lynne R. Wilkens, Alicja Wolk, Nicolas Wentzensen, Shelley S. Tworoger; on behalf of the Ovarian Cancer Cohort Consortium (OC3)

Scientific Progress

Matt Schabath

- Survey of 450 oncologist at 45 comprehensive cancer centers
- 149 (33%) completed
- 66% - important to know gender identity
- 40% - importance to know sexual orientation
- 70% - interested in LGBTQ education
- Significant decrease in confidence of health knowledge for both LBG and trans patients post survey
- Identifies need for development of curriculum & guidelines addressing LGBTQ cancer disparities

original report

National Survey of Oncologists at National Cancer Institute–Designated Comprehensive Cancer Centers: Attitudes, Knowledge, and Practice Behaviors About LGBTQ Patients With Cancer

Contents lists available at ScienceDirect

Patient Education and Counseling

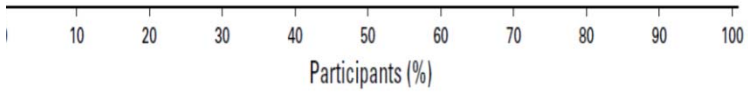
journal homepage: www.elsevier.com/locate/pateducou

Developing a web-based LGBT cultural competency training for oncologists: the COLORS training

Julia Seay[a,*], Amar Hicks[b], Merry Jennifer Markham[b], Matthew Schlumbrecht[a], Meghan Bowman[c], Jennifer Woodard[b], Austin Kollefrath[a], Daniela Diego[a], Gwendolyn P. Quin

[a] Sylvester Comprehensive Cance
[b] University of Florida Health Ca
[c] H. Lee Moffitt Cancer Center &
[d] New York University School of

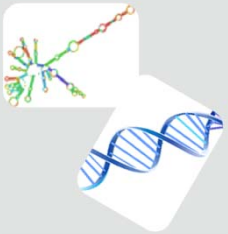
KNOWLEDGE ABOUT TRANS HEALTH NEEDS



Discussion

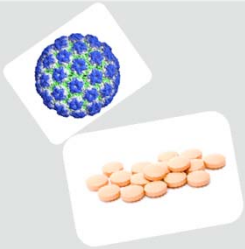
Aim ①

Identify inherited susceptibility biomarkers of cancer risk, progression, and outcome and explore underlying mechanisms



Aim ②

Identify and validate acquired biomarkers predicting cancer risk, progression, and outcome and explore underlying mechanisms



Aim ③

Discover and test the efficacy of promising approaches and novel interventions to reduce cancer burden across the continuum

Health Outcomes & Behavior

Thomas H. Brandon, PhD
Program Leader

Health Outcomes & Behavior

Goal

To contribute to the prevention, detection, and control of cancer through the study of health-related behaviors, health-related quality of life, health care practices, and cancer-related health disparities

Previous Aims

1. Develop & promote **prevention and early detection** of cancer
2. Enhance **quality of life** of patients & family
3. ~~Enhance **quality of cancer care**~~
4. Address cancer **health disparities**

Pending Aims

1. Develop & promote **prevention and early detection** of cancer
2. Enhance **quality of life** of patients & family
3. Advance cancer **health equity**

Thematic Area: Enhancing quality of cancer care (CCDR)

Health Outcomes & Behavior

Membership

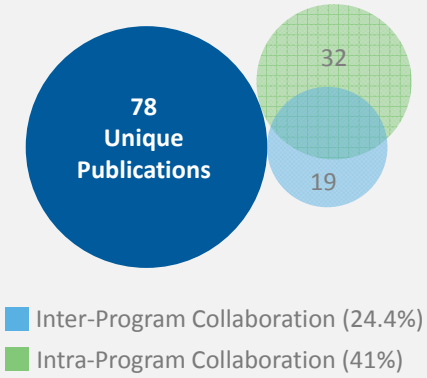
Academic Rank
- Assistant
- Associate
- Senior

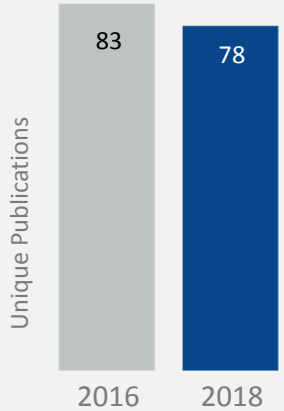
+ 5 USF-based

Peer Reviewed Funded PIs

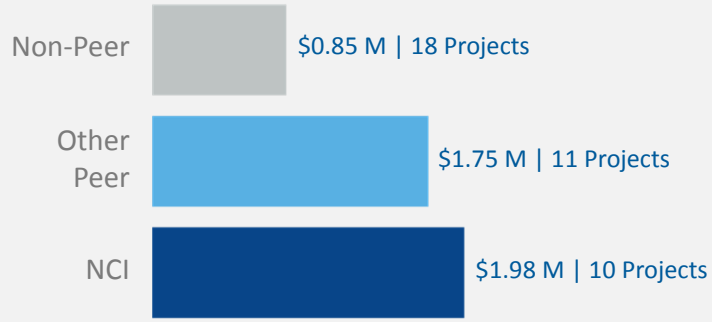
9

Publications

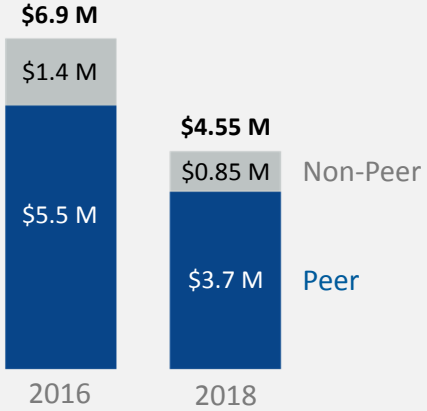




Grants (Annual Direct Costs)



Excludes 3 R25s, 1 K01, & 1 CCSG Supplement



Current

R01/Equivalent Projects

11 (7 PIs)

Annual Direct Costs

$3.1M

2016 – Application | 2018 – Calendar Year

Advice from 2018 EAC

Advice	Action
Consider dropping Aim 3	Dropped Aim 3
Build depth in other aims	Growing the HOB Program • Hired Dr. Christy (Aims 1, 3) • Hiring QOL/PRO (Aim 2) • Expecting 3-4 additional lines before CCSG

Look for ways to build CCD research
• Hires that “bleed” into CCD
• Encourage current faculty to move into CCD
	Fostering CCD research
	• Internal funding
	• Bringing in clinical scientists
	  • Protected research time
	  • Mentoring plan
	• External searches

Similar advice emerged from Program Retreat

Changes in Membership

New Faculty Member

- **Shannon Christy, PhD**
  - Assistant Member
  - Research:
    - Prevention & early detection (Aim 1)
    - Health Disparities (Aim 3)
    - Multi-level interventions
  - Previous R25 fellow

Upcoming Departures

- **Teresita Munoz-Antonia, PhD**
  - Health Disparities
- **David Drobes, PhD**
  - Tobacco Research
- **David Evans, PhD**
  - Tobacco Research

Recruitment - 4 Open Positions

- **Program Co-Leader (Aim 2-3)**
- **QOL/PRO (Aim 2)**
- **2 Open Area/Open Rank**
  (for Drobes/Evans)
  - Preference: Tobacco or CCDR

R01-Equivalent Grant Update – Last Year

	Type	PI(s)	Title	End Date
1	NCI R01	Brandon/Simmons	Expanding the reach of a validated smoking-cessation intervention: A Spanish-language RCT	7/21
2	FL JEK	Drobes	Facilitating smoking cessation with reduced nicotine cigarettes	2/21
3	FL B-C	Gwede	Community CARES: A Multilevel Intervention to Increase Colorectal Cancer Screening Adherence…	2/22
4	NCI P20	Meade/Cress	Southeast Partnership for Improving Research & Training in Cancer Health Disparities	8/21
5	NCI R01	8th Percentile		
6	NCI R01	8th Percentile		

R01-Equivalent Grant Update – Current

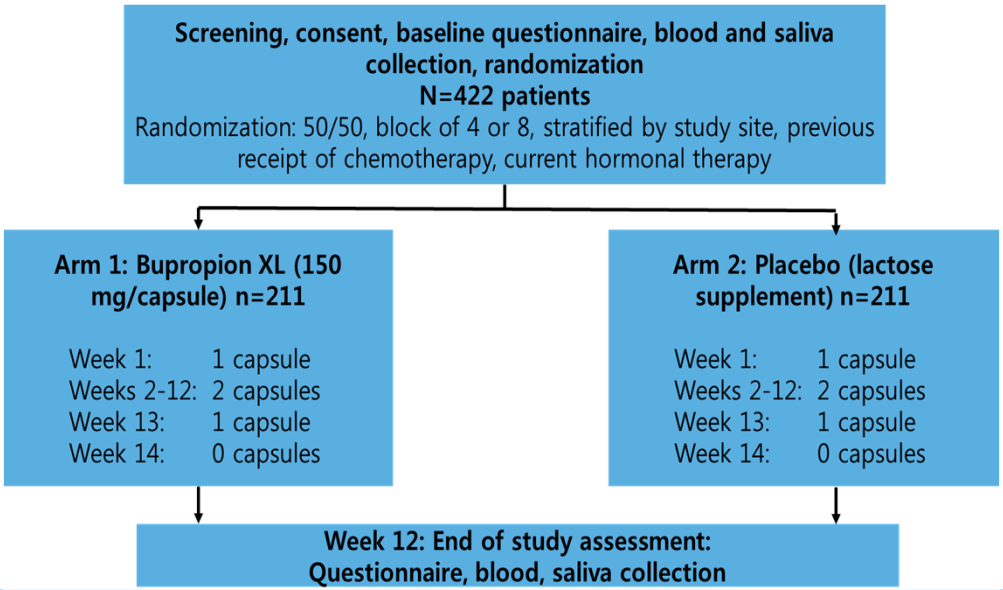
	Type	PI(s)	Title	End Date
1	NCI R01	Brandon/Simmons	Expanding the reach of a validated smoking-cessation intervention: A Spanish-language RCT	7/21
2	FL JEK	Drobes	Facilitating smoking cessation with reduced nicotine cigarettes	2/21
3	FL B-C	Gwede	Community CARES: A Multilevel Intervention to Increase Colorectal Cancer Screening Adherence…	2/22
4	NCI P20	Meade/Cress	Southeast Partnership for Improving Research & Training in Cancer Health Disparities	8/21
5	NCI R01	Jim	Improving Prediction of Chemotherapy-Induced Nausea: Integrating Genes, Behavior, and the Microbiome	5/23
6	NCI R01	Jim	Randomized Placebo Controlled Trial of Bupropion for Cancer Related Fatigue	5/23
7	NCCIH R34	Vinci	Development of a Mindfulness-Based Treatment for the Reduction of Alcohol Use and Smoking Cessation	6/21
8	NIDA R34	Impact Score: 21		3/22

R01 CA214647: Randomized Placebo-Controlled Trial of Bupropion for Cancer-Related Fatigue

URCC
NCORP Research Base

Co-Investigators:

- Hyo Sook Han, MD (CBMM)
- Howard McLeod, PharmD (CE)



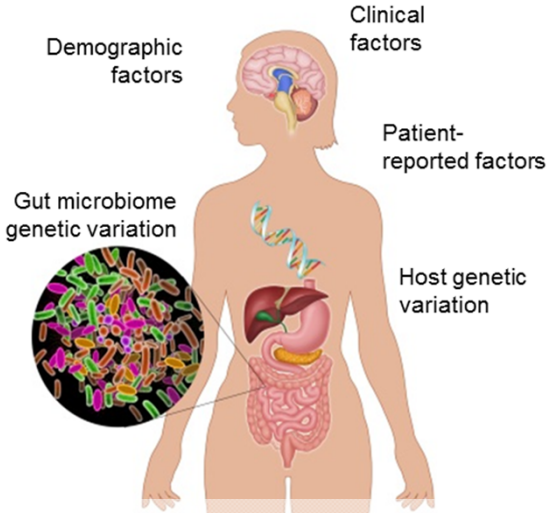
Study Aims:

1. To determine the efficacy of bupropion on fatigue (primary outcome), QOL, depression (secondary outcomes) in fatigued breast cancer survivors
2. To evaluate the tolerability of bupropion
3. To explore the effects of bupropion on inflammation and cortisol
4. To explore associations of CYP2B6*6 genotype with bupropion metabolism & fatigue

R01 CA219389: Improving Prediction of Chemotherapy-Induced Nausea & Vomiting (CINV): Integrating Genes, Behavior, & the Microbiome

Co-Investigators:

- Martine Extermann, MD (HOB)
- Richard Kim, MD (CBE)
- Youngchul Kim, PhD (CBMM)
- Howard McLeod, PharmD (CE)



Proposed Metagenomic Model of CINV

Study Aims:

1. To conduct the first GWAS of CINV
2. To use pathway analysis to identify new mechanisms (place genes in their functional context)
3. To develop & validate new risk prediction models based on genetic, clinical, & patient-reported risk factors
4. To explore composition and gene expression of gut microbiome as risk factors for CINV

Representative Publications

PAPER

WILEY

Associations between the smoking-relatedness of a cancer type, cessation attitudes and beliefs, and future abstinence among recent quitters

Úrsula Martínez[1] | Thomas H. Brandon[1,2,3] | Steven K. Sutton[2,3,4] | Vani N. Simmons[1,2,3]

Original Article

Psycho-Oncology
Journal of the Psychological, Social and Behavioral Dimensions of Cancer

Sleep Disturbance in Men Receiving Androgen Deprivation Therapy for Prostate Cancer: The Role of Hot Flashes and Nocturia

Brian D. Gonzalez, PhD[1]; Brent J. Small, PhD[2]; Mallory G. Cases, MPH, CPH[1]; Noelle L. Williams, MD[3]; Mayer N. Fishman, MD, PhD[4]; Paul B. Jacobsen, PhD[1]; and Heather S.L. Jim, PhD[1]

Cancer
American Cancer Society

Comparison of Health Communication Channels for Reaching Hispanics About Biobanking: a Pilot Trial

Jessica McIntyre[1] · Julio Jiménez[2,3] · Yonaira M. Rivera[1] · Steven K. Sutton[4,5] · Gloria Asencio[3] · Eida M. Castro-Figueroa[2,3] · Clement K. Gwede[1,5] · Thomas H. Brandon[1,5] · Susan T. Vadaparampil[1,5] · Vani N. Simmons[1,5] · Johanna Corchado[3] · Laura Moreno[1] · Kristen J. Wells[6,7] · Gwendolyn P. Quinn[1,4]

JOURNAL OF CANCER EDUCATION
An Interdisciplinary Journal that Aims to Reduce the Burden of Cancer in the World Through Effective Education
Springer

Question

How best to present two changes in our next CCSG?

- Converting Aim 3 into Thematic Area
- Removing USF-based members