

Program Co-Leader, Chemical Biology & Molecular Medicine



Jhanelle Gray, MD

- 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

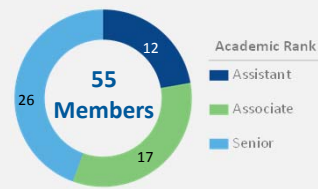
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External Advisory Council Report 2018

- **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



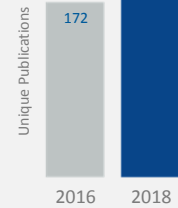
Peer Review Funded PIs

26
Clinical Trial PIs

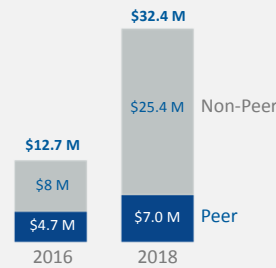
23
Collaborative Scientists

4

Publications



Grants (Annual Direct Costs)



Current

R01/Equivalent Projects
23 (14 PIs)

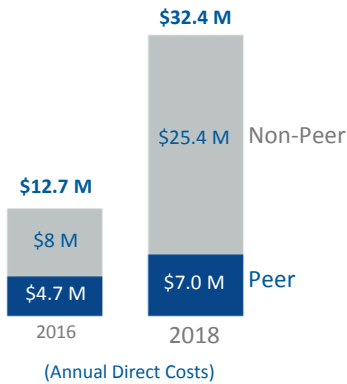
Annual Direct Costs
\$6.4M

2016 – Application | 2018 – Calendar Year

CBMM Program Grants

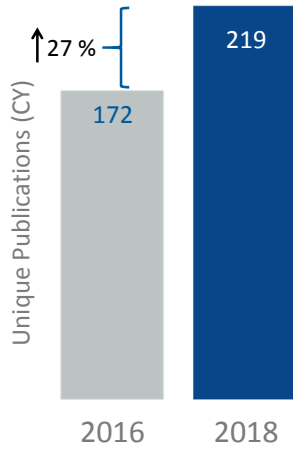
FY 2018:
Fold increase since 2016

| 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 |
|-------------------------|---|--------------------------------|
| <i>Lancet Onco/Haem</i> | 3 | Smalley, List, Komrokji |
| <i>Nat Commun</i> | 1 | Sebti |
| <i>JCO</i> | 2 | Strosberg, Lancet |
| <i>CCR</i> | 4 | Gray, Smalley, Padron, Fleming |
| <i>Leukemia</i> | 2 | List, Padron |
| <i>Blood</i> | 2 | Lancet, Tao |

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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

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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)



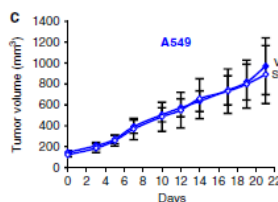
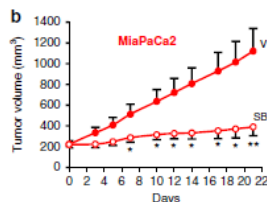
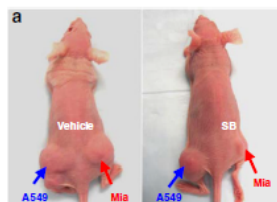
ARTICLE

DOI: 10.1038/s41467-018-07644-6

OPEN

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

Aslamuzzaman Kazi¹, Shengyan Xiang¹, Hua Yang¹, Daniel Delitto², José Trevino², Rays H.Y. Jiang³, Muhammad Ayaz¹, Harshani R. Lawrence¹, Perry Kennedy¹ & Said M. Sebti^{1,4}

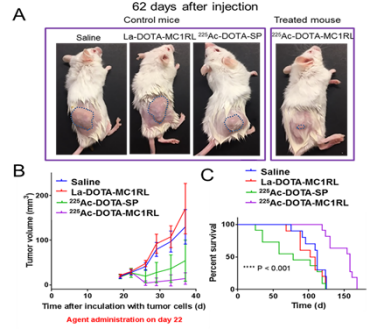
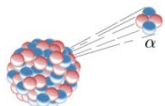


Said Sebti PhD

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**
 - ²²⁵Ac-DOTA-MC1RL development and preclinical testing
- 2018-9**
 - ²²⁵Ac-DOTA-MC1RL drug licensed
 - Morse, DL et al. *J Nucl Med*

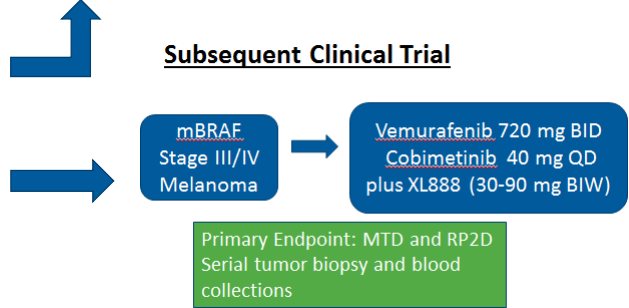
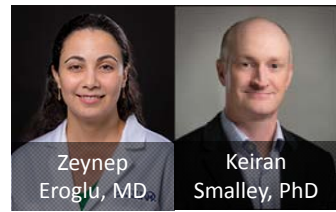


- Melanoma Research Alliance Grant
- First-in-human trial is in development
- Led by Dr Khushalani MCC- PI

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%) |



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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 <i>TP53m</i> 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)

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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.