SUMMARY STATEMENT

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(Privileged Communication)

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Principal Investigator

SELLERS, THOMAS A

Applicant Organization: H. LEE MOFFITT CANCER CTR & RES INST

Review Group: **NCI-A**
Subcommittee A - Cancer Centers

Meeting Date: **08/11/2016**
Council: **OCT 2016**
Requested Start: **02/01/2017**

RFA/PA: **PAR13-386**
PCC: **2IMD**

Project Title: **Moffitt Cancer Center Support Grant**

SRG Action: **Impact Score:25**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **1A-Both Children and Adults, scientifically acceptable**
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
19	1,918,736	3,231,968
20	1,976,571	3,329,387
21	2,036,966	3,431,117
22	2,095,413	3,529,567
23	2,161,670	3,641,172
TOTAL	10,189,356	17,163,211

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

RESUME AND SUMMARY OF DISCUSSION: In this competitive renewal application from the Moffitt Cancer Center, a free-standing Comprehensive Cancer Center, the overall mission is to reduce the burden of cancer through interdisciplinary translational cancer research leading to improved prevention strategies and therapeutic approaches. Support is requested for five programs, thirteen shared resources, Senior Leadership, Planning and Evaluation, Developmental Funds, Administration, Clinical Protocol and Data Management, Data and Safety Monitoring, and Protocol Review and Monitoring System.

The Moffitt Cancer Center continues to make strong progress in basic, translational, clinical, and population-based cancer research, and demonstrates exemplary service to the catchment area of the state of Florida. Dr. Thomas Sellers became Center Director in 2012. He has demonstrated strong leadership and has guided the Moffitt Cancer Center through major initiatives including development and implementation of a new strategic plan, reorganization of the research programs, and recruitment of talented new program leaders and senior leaders. There have been major research achievements in the research programs. Transdisciplinary collaborations among members are robust with several high impact publications. However, there is some unevenness among the research programs.

The newly organized Cancer Biology & Evolution (CBE) Program, rated as Excellent to Outstanding, is based on the novel idea of combining evolutionary conserved biology to the pathways dysregulated in cell growth and tumorigenesis. This program is led by outstanding investigators and shows great potential. There are effective transdisciplinary intra- and inter-programmatic collaborations that have led to several publications in high profile journals and the award of two multi-project grants. However, the program is still at nascent stage and its full clinical impact is yet to be demonstrated. The Chemical Biology & Molecular Medicine (CBMM) Program, rated as Excellent to Very Good, aims to integrate chemical biology and system biology techniques, ultimately leading to new therapeutic approaches for cancer patients. Seminal contributions to identifying novel therapeutic strategies were reported in the previous funding period. However, plans to translate these discoveries have not yet come to fruition. The Cancer Epidemiology (CE) Program, rated as Exceptional, has made significant scientific accomplishments in the past five years, as evidenced, for example, by major discoveries in ovarian cancer epidemiology and biology, and FDA approval of Gardasil in men. Dr. Kanetsky, who replaced the former Program Leader in 2013, has brought a coherent focused approach to the goals of the program and is superbly qualified to bring the program forward into new levels of success. The overall scientific quality of the program is exceptional and the cancer focus in the peer-reviewed research base is very strong. There has also been a clear emphasis on addressing cancer-related health problems in the catchment area. The Health Outcomes & Behavior Program (HOB), rated as Outstanding, is to be commended for the breadth, depth and scientific quality of its research and for the increased publication rate with strong intra- and inter-programmatic collaborations. However, of concern is the reduction in NCI funding and the decrease in accrual to external peer-reviewed clinical trials. The Immunology Program (IMM), rated as Excellent, continues to make seminal contributions to the development of novel immunotherapeutic approaches, especially in melanoma and lung cancer, with successful translation of these discoveries to the clinic. This program leverages the solid interdisciplinary Immune and Cellular Therapy clinical service, the Immunotherapy Working Group, and a GMP-compliant Cellular Therapy Core. Although funding levels are strong with several training awards and multiple industry-sponsored trials, there has been a decline in the levels of NCI funding in comparison to the previous funding period.

The five programs are supported by thirteen shared resources. The Cell Therapies, Collaborative Data Services, Flow Cytometry, Molecular Genomics, Survey Methods, and Tissue Cores are rated Exceptional, the Small Animal Imaging Lab Core is rated Exceptional to Outstanding, while the Analytic Microscopy, Biostatistics, Cancer Informatics, Chemical Biology, Image Response Assessment Team and Proteomics Cores are rated Outstanding. The value of these shared resources is readily apparent. The leaders and staff are highly qualified, and the facilities are exemplary. All the shared resources are cost effective and provide high quality services to the five programs.

Clinical Protocol and Data Management (CPDM), rated Outstanding, is highly effective in centrally managing and reporting cancer clinical trials. Quality control, investigator training and efforts to include underrepresented groups in clinical trials are well established. However, there is a decrease in external peer-reviewed clinical trials. The Data and Safety Monitoring is rated as acceptable. The Inclusion of Women, Minorities and Children in Clinical Research are each approved. The Protocol Review and Monitoring System (PRMS) is also approved, although a minority of the Site Visit Committee voted for conditional approval. Consideration should be given to including greater number of experienced clinical investigators as well as basic science scientists, radiologists and pathologists to provide basic and translational research expertise in the Scientific Review Committees. An additional concern relates to the potential overcommitment of Dr. Sullivan and Dr. Lush, who play important oversight functions in both CPDM and PRMS.

The organization and administration components are very strong. Senior Leadership, rated Outstanding, includes a group of highly qualified leaders. Planning and Evaluation, rated Exceptional, has supported effective strategic planning and program reorganization. Developmental Funds, rated Exceptional, had a significant impact on the support of pilot projects and development of shared resources, including the strong and widely used Collaborative Data Services shared resource. Administration, rated Exceptional, shows clear evidence of significant contributions toward the effectiveness of the Moffitt Cancer Center.

The Essential Characteristics are met and rated as follows: Physical Space is rated Exceptional; Organizational Capabilities is rated Outstanding; Transdisciplinary Collaboration and Coordination is rated Outstanding; Cancer Focus is rated Exceptional; Institutional Commitment is rated Exceptional, and the Center Director is rated Outstanding to Exceptional.

Overall, the Moffitt Cancer Center remains on a very positive trajectory to produce high impact cancer research and effectively serve its catchment area. The strong leadership of Dr. Sellers and his team, combined with robust institutional support, are major strengths. While there is some unevenness among the research programs, the Moffitt Cancer Center is clearly poised to make significant advances in cancer research and care over the next several years. This application is of high impact due to the strong depth and breadth of science across basic, clinical, and population-based cancer research and support for the requested five years is appropriate.

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OVERALL DESCRIPTION (provided by applicant): The H. Lee Moffitt Cancer Center & Research Institute (MCC) continues its ambitious trajectory of innovative cancer research and translation to benefit the gulf coast region of Florida and beyond. As a free-standing 501(c)3 not-for-profit institution with the sole purpose “to contribute to the prevention and cure of cancer,” all research funding ($71.8M), publications (2,430), and clinical research (>1,600 interventional accruals/ year) are cancer focused. Research and clinical space has expanded dramatically since the last renewal to more than 2 million square feet, and patient clinical volume places MCC among the largest Centers in the United States. MCC has benefitted from recent, ongoing annual state legislature funding of approximately $25 million, in addition to more than $39 million of annual institutional research support. The 142 MCC members span the basic, clinical, and population sciences. They are organized into five highly collaborative, multidisciplinary programs with exceptional levels of intra- (35%) and inter-programmatic (18%) publications. Under the leadership of Dr. Thomas Sellers, the third MCC Director, a Research Strategic Plan (RSP) was developed and implemented for “Moffitt 3.0.” Four of six Associate Center Directors are new; and new leaders have been appointed in every program, with bold goals and specific aims. Two of the 13 shared resources have been significantly restructured (Chemical Biology, Molecular Genomics), and one new resource created (Collaborative Data Services) to better meet the changing needs of MCC scientists. Implementation of the strategic plan has been bolstered by substantial institutional investment, especially in basic science, immunotherapy, and clinical research infrastructure, including the recruitment of 45 new faculty members, of whom 32 are CCSG members. MCC is a leader in immunotherapy, and more than 40% of overall clinical trial accrual is to investigator-initiated studies. MCC population scientists initiated significant new efforts in cancer prevention and outcomes that include vaccines, tobacco cessation, and health disparities. This is particularly true in the unique cancer problems in the catchment area – notably lung cancer, melanoma, and HPV-prevention. MCC’s Total Cancer Care protocol, the ground-breaking research strategy to realize the promise of personalized medicine, has continued to thrive, resulting in dramatic utilization of the Tissue Core and the formation of the Oncology Research Information Exchange Network (ORIEN) that now includes eleven cancer centers across the nation, with several more poised to join the consortium this year. MCC requests funding for: five scientific programs, 13 shared resources, two clinical research components, planning and evaluation, administration, leadership, four staff investigators, and developmental funds. CCSG funds are leveraged more than 10-fold with institutional resources to maximize impact on cancer prevention, treatment, and cure in the catchment area, the state of Florida and beyond.

PROJECT NARRATIVE: The H. Lee Moffitt Cancer Center & Research Institute (MCC) is a free-standing 501(c)3 not-for-profit institution with the sole purpose “to contribute to the prevention and cure of cancer.” By fostering transdisciplinary research, MCC translates unique capabilities in basic, clinical, and population science, as well as training and education, to benefit the patients, caregivers, and professionals through the catchment area, the state of Florida, and beyond. As a founding member of the Oncology Research Information Exchange Network (ORIEN), MCC is also extending the benefits of precision medicine through national collaboration.

CRITIQUE:

OVERALL CRITIQUE: The H. Lee Moffitt Cancer Center and Research Institute (MCC) is a free-standing 501(c)3 not-for-profit institution that was established by the Florida legislature in 1981. MCC received NCI designation in 1997 and comprehensive status in 2000. This competing renewal application for a Cancer Center Support Grant (CCSG) requests five years of support for 5 research programs, 13 shared resources as well as senior leadership, research Program Leaders, planning and evaluation, administration, developmental funds, four staff investigators, clinical trials office, protocol review and monitoring system, and protocol-specific research. Dr. Thomas Sellers, appointed in July 2012, is the Center Director. Overall, Dr. Sellers led a strategic planning initiative and has orchestrated several changes in the Cancer Center since the last competitive renewal. The senior leadership was reorganized. Changes include the promotion of Dr. Paul Jacobsen, former Program Leader for Health

Outcomes & Behavior, to Associate Center Director (ACD) of Population Science; the recruitment of Dr. John Cleveland as ACD of Basic Science; appointment of Dr. Julie Djeu, former Program Leader of the Immunology Program, to the newly created position of the ACD of Education & Training, and the recruitment of Mr. Brian Springer to hold the position of ACD of Research Administration. Drs. James Mulé and Dan Sullivan were retained as ACD of Translational Science and Clinical Science, respectively. The new senior leadership team is comprised of well qualified leaders that have the potential to excel.

In addition, programs were reorganized and program leadership was modified. Program structure now includes 5 programs consisting of Cancer Biology & Evolution (CBE), Chemical Biology & Molecular Medicine (CBMM), Cancer Epidemiology (CE), Health Outcomes & Behavior (HOB), and the Immunology Program (IMM). Dr. Sellers appointed six new Program Leaders, four of whom were internal promotions: Dr. Claudio Anasetti (Immunology), Dr. Thomas Brandon (Health Outcomes & Behavior), Dr. Robert Gatenby (Cancer Biology & Evolution), and Dr. Kenneth Wright (Immunology, interim). Two Program Leaders were recruited externally: Dr. Peter Kanetsky (Cancer Epidemiology) and Dr. John Cleveland (Cancer Biology & Evolution, interim). Two newly recruited Program Leaders, who will join MCC in the next few months, were identified at the site visit, Dr. Elsa Flores, Cancer Biology & Evolution Program and Dr. Jose Conejo-Garcia, Immunology Program. Both recruits appear to be outstanding scientists. While the leaders are strong, oversight of the scientific programs was uneven and not equal to the collective strength of the leadership team.

The MCC has 142 members. There are no non-aligned members. Peer reviewed funding for the MCC is approximately $28.8 million (direct costs). NCI funding is approximately $19.0 million (direct costs). During the last funding period, the MCC recruited 45 new faculty, of which 32 are CCSG members. Reflecting positively on the emphasis to enhance collaborative research is an overall collaborative publication record of 39%. There are 11 multi-project grants and a number of multi-PI grants. Additionally, investments in Cancer Center space, including clinical and research facilities, were apparent. A major strength of the MCC continues to be the overall quality of basic and clinical research.

Cancer Biology & Evolution (CBE) currently is co-led by Drs. Robert Gatenby and John Cleveland (interim) and is rated Excellent to Outstanding merit. The program has 24 members, who are highly collaborative with 22% intra-programmatic and 33% inter-programmatic publications. The program was reorganized to investigate and define the dynamics that govern the biology and therapeutic responses of cancer and to deliver new agents and develop strategies to prevent and treat refractory or relapsed malignancies. The program has approximately $6.0 million (direct) in peer reviewed funding with approximately $4.5 million from the NCI. The program has a strong publication record with 436 publications, many of which are in high impact journals. The publications reflect a strong science base for the program. An additional strength is the presence of two multi-project grants (U54 and U01). Weaknesses include insufficient evidence that the approaches will lead to new scientific knowledge and discoveries and the lack of clinical validation of the observations.

Chemical Biology & Molecular Medicine (CBMM), led by Drs. Eric Haura and Said Sebti, is rated Excellent to Very Good merit. CBMM is a realignment of the former Experimental Therapeutics (ET) Program that was renamed after incorporating some faculty from the former Molecular Oncology & Drug Discovery Program. The CBMM program has 46 members, of which 24 are predominately laboratory-based and 22 with expertise in clinical trials. Peer reviewed funding totals approximately $6.8 million with a solid cancer focus of approximately $5.8 million from the NCI. Program members produced a total of 1001 publications, of which 35% were intra-programmatic and 35% were inter-programmatic. While a less than optimal number of articles with CBMM members as first or senior author appeared in high impact journals, there are examples provided within each theme that meet the stated goals of the program. Strengths of the program include high quality of basic, translational and clinical research, a solid funding base and a large clinical trials portfolio with strong investigator-initiated trials. Weaknesses include diffuse nature of the themes/aims, limited evidence of high impact

publications, declining accrual to externally peer-reviewed and institutional studies, and limited evidence of success in developing new therapeutic approaches.

Cancer Epidemiology (CE) is led by Dr. Peter Kanetsky and was rated Exceptional merit. The program has 24 members. The reorganized program has high quality research and scientifically strong membership and an important vision for genetic and molecular epidemiology. The program has approximately $5.0 million in total peer reviewed funding with approximately $3.4 million in cancer focused funding. Publications showed strong scientific achievement with 713 publications listed for the program with many in high profile journals. Intra- and inter-programmatic publications were solid at 27% and 24%, respectively. The program has a T32 for postdoctoral training. The CE Program clearly demonstrates the value it brings to MCC, is very supportive of integrative team science and adds value to MCC by supporting integrative intra- and inter-programmatic research while addressing cancers relevant to the catchment area.

Health Outcomes & Behavior (HOB) is led by Dr. Thomas Brandon and is rated Outstanding merit. The program has 27 members. Peer reviewed funding for HOB is approximately $7.9 million (total) with approximately $3.3 million from the NCI. Overall, member publications are strong with members publishing 592 articles of which 39% were intra-programmatic and 24% were inter-programmatic publications. The program clearly impacts the catchment area with substantial NCI funded research focused on disparities and relevant to the catchment area. Strengths include cancer focus, the presence of a U54, and the presence of high quality science. There is concern about the decrease in NCI funding. Additional weaknesses include decrease in accrual to external peer reviewed trials and limited description of future priorities and vision.

Immunology (IMM) is co-led by Drs. Claudio Anasetti and Kenneth Wright (interim) and is rated Excellent merit. The program has 26 members with approximately $4.9 million in total peer reviewed funding, approximately $1.9 million of which is from the NCI. The program published 598 peer reviewed articles with 31% intra-programmatic and 39% inter-programmatic publications listed. There is a solid mix of basic and clinical investigators who have a strong cancer focus and impactful clinical studies. Strengths include a T32 training grant, the presence of a Skin SPORE, although only one project is in the program, and solid impact of developmental funds. At the time of the site visit, NCI R01 funding is less than optimal. In addition, there are missed opportunities to collaborate with other programs.

Thirteen shared resources were proposed by the Center for CCSG support. The shared resources are uniformly strong and widely used by the MCC membership. The shared resources of the Center are rated as follows: Analytical Microscopy, Outstanding, Biostatistics, Outstanding; Cancer Informatics, Outstanding; Cell Therapies, Exceptional; Chemical Biology, Outstanding; Collaborative Data Services, Exceptional; Flow Cytometry, Exceptional; Image Response Assessment Team, Outstanding; Molecular Genomics, Exceptional; Proteomics, Outstanding; Small Animal Imaging Lab, Exceptional to Outstanding; Survey Methods, Exceptional; and Tissue Core, Exceptional.

The Clinical Protocol and Data Management was rated Outstanding merit. Data and Safety Monitoring per NIH Policy is acceptable. Protocol Review and Monitoring System is approved, although a minority of the Site Visit Committee voted for conditional approval. Concerns include small number of experienced senior clinical investigators, absence of a basic scientist, diagnostic radiologist and pathologist on the SRC standing committee and the presence of only a 4 member quorum requirement. The components, Inclusion of Women in Clinical Research, Inclusion of Minorities in Clinical Research, and Inclusion of Children in Clinical Research, are approved.

A well-qualified but newly reorganized Senior Leadership team was rated Outstanding merit. Overall, Senior Leadership is comprised of a highly productive and committed senior core of leaders who are well qualified to lead the Center. Senior Leadership effectively promotes cancer focused research

reflecting the catchment area and training initiatives. However, the unevenness of program quality generates concern that they have coalesced into a team that sets the vision and leads the MCC.

Planning and Evaluation was rated Exceptional merit. The leadership structure, Internal and External Advisory Boards, along with various meetings and retreats among programs, provide needed support for planning and evaluation in the reorganized MCC. Planning and Evaluation process for the Moffitt Cancer Center is well organized and provides strong internal mechanisms to support the Cancer Center in making substantive contributions across the spectrum of cancer research, prevention and treatment.

Developmental Funds was rated exceptional merit. Developmental Funds used during the previous funding period had a substantial impact on the support of pilot projects, the development of shared resources and impact of staff investigators was positive.

Administration was rated exceptional merit. The Administrative Core is led by newly recruited Mr. Brian Springer. The administrative infrastructure appears to adequately support the mission of the Cancer Center through the provision of essential services, management expertise, and program support for the Center's research. During the last funding period, the Administrative Core focused on streamlining and improving support functions, which appeared to be successful.

The Essential Characteristics of the Cancer Center are fulfilled and are rated as follows: Physical Space is rated Exceptional merit. The facilities have been upgraded and expanded during the previous funding period. These facilities provide state-of-the-art facilities for MCC activities and adequate space is available for future growth. Dr. Sellers indicated at the site visit that a new building will be constructed in the new future to house additional faculty. Funds for the building are in place.

Organizational Capabilities is rated Outstanding merit given the effective structure and process that has allowed the Center to make significant progress in reorganizing programmatic structure and the Center leadership. Dr. Sellers, as MCC Director, occupies leadership positions within the Institute that enhance the activities of the Center. Membership criteria are well-described and training appears to be adequate.

Transdisciplinary Coordination and Collaboration was rated Outstanding. There is a solid level of transdisciplinary and translational collaborations among members and there are a multitude of mechanisms that the Center has implemented to promote these interactions. The MCC supports an overall collaborative publication rate of 39%. The infrastructure is in place to move discoveries toward application, including working groups, shared resources and clinical trials proficiency.

Cancer Focus is rated Exceptional merit. There is strong focus on cancer research as defined by the objectives of the research programs, the collaborations between laboratory investigators, and many of the grants and contracts awarded. There is substantial breadth, depth, and significance of the cancer-related research within the individual research programs, publications, and peer-reviewed research support.

Institutional Commitment is rated Exceptional merit. Total MMC research funding and support is approximately $144 million, which includes institutional operation support of approximately $31 and state funding at approximately $36 million. There is a team science policy in place at the MCC. Overall, the institution is highly supportive of the Cancer Center.

Center Director is rated Outstanding to Exceptional. Dr. Sellers is highly qualified and has authority over all resources at the Center. His position in the Center, while meeting CCSG guidelines, has been diminished by the reorganization at the H. Lee Moffitt Research Institute through the separation of CEO

position from the Cancer Center director position. In addition, the discussions at the site visit generated concerns that Dr. Sellers exercises adequate leadership over the clinical components of the Center.

Criterion Scores: Significance 2, 3, 3; Investigator(s) 1, 2, 2; Innovation 2, 3, 3; Approach 3, 3, 3; and Environment 1, 2, 2.

Overall Impact: In summary, the MCC continues to make significant contributions to the cancer research effort with strong innovative scientific productivity. The Center is collaborative and has a strong cancer focus. The senior leadership team is comprised of well qualified leaders that have the potential to excel. Dr. Sellers has orchestrated several changes in the Cancer Center since the last competitive renewal. The leadership and program reorganization produced uneven program quality. The shared resources are uniformly strong and widely used by the MCC membership. The institution provides state-of-the-art facilities for MCC activities and adequate space is available for future growth. The MCC has strong institutional support, which will serve the Center well as its leaders work to improve the programs and elevate the Center to the next level. The overall impact of the application is high due to the strong depth and breadth of science across basic, clinical, and population-based cancer research and support for 5 years is appropriate.

COMPREHENSIVENESS

The Moffitt Cancer Center carefully balances laboratory, clinical, and community based research. MCC programs and discoveries harbor a strong cancer focus, and have been impactful. Some concerns do exist in that few programs outside Cancer Epidemiology and Health Outcomes & Behavior clearly articulated research that addresses the specific needs of the catchment area. The ability to translate findings into the clinic is exemplified in that >40% of clinical trial accrual is to investigator-initiated clinical trials. Community based research and outreach is strong, and significant efforts for prevention, detection, and control are ongoing. The specialized needs of the catchment area have been generally identified and are addressed in MCC's research programs. Furthermore, Moffitt's "Total Cancer Care" protocol, first developed toward the goal of implementing personalized/precision medicine in South Florida, has been expanded and adopted by 10 other Cancer Centers via the ORIEN network. Training mechanisms were well articulated and integrated into programs. Overall, the depth and breadth of research at Moffitt Cancer Center and demonstrated impact on the catchment area meets the criteria for comprehensive status.

Assessment: Approval

IRG NOTE: In response to the Site Visit Report, written comments were received from the principal investigator in a letter dated June 6, 2016. The comments and the Site Visit Report were carefully considered by the members of NCI IRG, Subcommittee A, during the discussion, final assessment, and scoring of the application. Corrections and changes have been made, where appropriate.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): **ACCEPTABLE** (Also, see the heading, Data and Safety Monitoring)

DATA AND SAFETY MONITORING PLAN: **ACCEPTABLE**

INCLUSION OF WOMEN PLAN (Resume): **ACCEPTABLE** (Also, see the heading, Inclusion of Women in Clinical Research.)

INCLUSION OF MINORITIES PLAN (Resume): **ACCEPTABLE** (Also, see the heading, Inclusion of Minorities in Clinical Research.)

INCLUSION OF CHILDREN PLAN (Resume): **ACCEPTABLE** (Also, see the heading, Inclusion of Children in Clinical Research.)

VERTEBRATE ANIMAL (Resume): **ACCEPTABLE**

BIOHAZARDS: **ACCEPTABLE**

ADDITIONAL REVIEW CONSIDERATIONS:

RESOURCES SHARING PLANS:

Data Sharing Plan: ACCEPTABLE. The application does address the NIH Policy on Data Sharing.

Sharing of Model Organisms for Biomedical Research: ACCEPTABLE. The application does address the NIH Policy on Sharing of Model Organisms for Biomedical Research.

Genome-Wide Association Studies (GWAS): ACCEPTABLE. The application does address the NIH Policy on Genome-Wide Association Studies.

RESEARCH PROGRAMS

Program 1: Cancer Biology & Evolution

DESCRIPTION (provided by applicant): Cancer Biology & Evolution (CBE) is a first-in-kind CCSG Program that emerged from systematic in-house collaborations of mathematicians, evolutionary biologists, and basic and clinical cancer researchers. Although these research teams investigate cancer via traditional means, they include mathematicians and theorists who integrate multi-scalar data through quantitative models founded on evolutionary first principles. Specifically, the CBE integrates the genocentric focus of conventional cancer research into broader Darwinian dynamics where: (i) evolution selects for cellular adaptive phenotypes that emerge in complex ways from both mutations and changes in the expression of normal genes; and (ii) the fitness of each cancer cell is dependent on environmental context and will vary with temporal and spatial changes in the tumor milieu. Mathematicians play critical roles in the CBE Program by deconvoluting the nonlinear dynamics that are manifest in complex open systems such as cancer and by developing and applying mathematical models and computer simulations. The unique scientific “ecosystem” of the CBE has driven the formation of innovative multidisciplinary teams that are investigating virtually every aspect of cancer biology and therapy through a quantitative evolutionary lens. The overall goals of CBE are to investigate and define the complex dynamics that govern the biology and therapeutic responses of cancer, and to deliver new agents and strategies to prevent and treat refractory or relapsed malignancies. Specifically, CBE Members: (i) generate and apply sophisticated experimental models and methods to define and quantify spatial and temporal dynamics of molecular, cellular, and tissue properties during cancer development, progression, metastasis, and treatment (Aim 1); (ii) develop and test theoretical models, which are based on evolution by natural selection and are parameterized by experimental data, to define cancer dynamics and inform new strategies for control and treatment (Aim 2); and (iii) design new studies and clinical trials that test model predictions, to deliver effective, adaptive therapies into the clinic, and to refine the understanding of cancer biology and therapy (Aim 3). CBE teams have implemented these goals through: (i) combining *in vivo* and *in silico* models to

understand, prevent and treat metastasis; (ii) targeting never genes, i.e., genes where mutations are never or rarely observed, to produce a durable treatment response; (iii) exploiting tumor dynamics to "steer" cancers toward a less invasive evolutionary trajectory; (iv) modeling tumor evolutionary strategies that result in therapy resistance; and (v) mathematical models that have been translated into adaptive, personalized clinical trials. The CBE Program has 24 members from nine different academic departments. During the past funding cycle, CBE Members have published 399 cancer-related articles, with 22% representing intra-programmatic publications and 32% being inter-programmatic publications. Total annual grant funding for the CBE Program is robust and is currently at $9.1 million; $8.2 million is peer-reviewed, including $6.3 million from NCI.

CRITIQUE: Cancer Biology & Evolution (CBE) is a revised version of the former Molecular Oncology Program & Drug Discovery Program. The CBE's tenet is that cancers are complex, multi-scale, open dynamic systems that can be modeled based on evolutionary principles using mathematical models and computer simulations. The CBE adopted the principles of evolution as a central driver that governs cancer biology and the response to therapy. The CBE is composed of 8 mathematicians, physicists, evolutionists, or computer science members and 16 basic and clinical research members. The goals of the CBE are to 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. In Aim 1, experimental models are applied to define and quantify spatial and temporal dynamics of molecular, cellular, and tissue properties during cancer development, progression, metastasis and treatment. In Aim 2, theoretical models based on evolution by natural selection and parameterized by experimental data are developed to define cancer dynamics to develop new strategies for control and treatment. Aim 3 involves new studies and clinical trials that test model predictions to deliver effective, adaptive therapies into the clinic and to refine the understanding of cancer biology and therapy to develop computational models to predict response and evolution of resistance. The program lists $9.8 million in total funded grants ($4.5 million from NCI), 436 cancer-related publications, 22% intra-programmatic and 33% inter-programmatic publications. The program members are active users of the shared resources.

Strengths of the CBE include innovative, cutting-edge and novel approaches to cancer using the principles of evolution and computational tools; successful multi- and transdisciplinary collaboration between experimentalists and computationalists evidenced by NCI U54 and U01 grants; and translation of mathematical modeling to preclinical animal models (e.g., bone metastatic prostate cancer) and clinical trials (e.g., adaptive therapy concept applied to abiraterone therapy in metastatic castration resistant prostate cancer). Despite these strengths, there is insufficient evidence that these approaches will lead to new scientific knowledge and discoveries. The program is considered still at nascent stage with its full clinical impact yet to be demonstrated.

Plans moving forward are to include new multidisciplinary research teams to study evolutionary principles of tumor-immune cell interactions, metabolic evolutionary dynamics, mathematically-informed adaptive radiotherapy in head and neck cancer, and modeling and optimizing delivery of hypoxia-activated pro-drugs in the clinic. The MCC supported the recruitment of seven new members of the program, and the plan is to recruit five new faculty in the next five years.

Some endpoints remain unmet, however, in terms of funding, publications, collaborative publications, and new areas of research it appears to be doing extremely well. The program makes timely use of cores, there are monthly program meetings, and CBE members also participate in at least one of the four Centers of Excellence at MCC. In addition, there are both intra- and inter-MCC program collaborations between differing laboratories, several of which have led to high profile publications in the very best cancer related journals. Finally, the idea of combining evolutionary conserved biology to the pathways dysregulated in growth and carcinogenesis is novel and will likely result in important discoveries in cancer prevention and tumorigenesis.

Regarding future goals and proposed aims, the focus on new evolutionary conserved biology pathways would appear to be a major strength of the CBE Program. In addition, using clinical samples and tumor data is also a major strength and adds both a translation focus as well as the potential for future development of bench to bedside research. This has already been shown by the outline of two clinical trials that have already been opened by this program.

Program Leader(s): Robert A. Gatenby, MD, Co-Leader, is a world leader in cancer evolution and mathematical oncology, and is the Chair of the Department of Radiology and a Senior Member of the Department of Integrated Mathematical Oncology (IMO). He is the PI of U54 grant on the role of evolution and the microenvironment in cancer biology and therapy. John L. Cleveland, PhD, Interim Co-Leader, is an expert in cancer genetics and is Associate Center Director of Basic Sciences at MCC. Dr. Cleveland is a dedicated mentor and has instituted a hyper-mentoring program at MCC that insures career advancement of junior members. Their expertise and roles are complementary, and together they form strong leadership of the program. A new Co-Leader of the CBE Program, Dr. Elsa Flores, was introduced at the site visit. While her scientific accomplishments are impressive, her leadership of this program is yet to be demonstrated.

Assessment: Excellent to Outstanding merit.

Budget: The budget is recommended as requested.

Program 2: Chemical Biology & Molecular Medicine

DESCRIPTION (provided by applicant): The overall goal of the Moffitt Cancer Center (MCC) Chemical Biology and Molecular Medicine (CBMM) Program is to integrate chemical biology and systems biology technologies to develop new therapeutic approaches for the treatment of cancer. The CBMM Program evolved through a strategic merging of the prior Experimental Therapeutics (ET) Program and the drug discovery activities of the Molecular Oncology and Drug Discovery (MODD) Program. This addressed an overlap noted at the prior review and the change was endorsed by MCC's EAC and the NCI. The realignment allows for focused activity in specific areas of excellence within CBMM and better aligns members with focused aims. Along with research in chemistry and drug discovery and clinical trials, the CBMM now includes members interrogating signaling pathways that regulate cell proliferation and survival to identify new targets for cancer therapeutics. Inclusion of basic scientists, chemists, and clinical researchers creates unique opportunities to rapidly translate novel strategies into the clinic, while conversely also increasing the flow of observations from the clinic back to the laboratory for mechanistic testing. To better capture cancer signaling events and opportunities for drug discovery, a major area of growth within CBMM has been target discovery using system-level unbiased mass spectrometry-based proteomics. This strategy has successfully defined mechanisms of acquired resistance in refractory cancers as well as new therapeutic strategies for treating patients. Further, drug discovery science has evolved to enable design of not only single but also dual-targeting small molecule therapeutics using novel chemical probes, solving drug-target structures with x-ray crystallography and structure-based drug design. Tumor profiling technologies, including genomics, proteomics, and imaging, are being fully used for targeted agent clinical trials, defining small molecule mechanisms of action, refining prognostic and predictive markers, and studying the process of drug resistance. As a consequence of these changes, CBMM membership has been consolidated from 57 (30 Scientific, 27 Clinical Trialists) to 43 members (21 Scientific, 22 Clinical Trialists) including 10 new basic science and 15 clinical investigators. CBMM has been successful in obtaining $17.9M in total annual funding, including $10.8M in industry-supported clinical trials, $6.0M in NCI funding, and $0.9M in other peer-reviewed funding. During the current funding period, members published 915 articles, with 318 (35%) of these publications representing intra-programmatic collaborations, 320 (35%) inter-programmatic, and 334 (37%) representing inter-institutional publications with other NCI-designated Cancer Centers. The Program accrued 3,995 patients to interventional clinical trials, including 3,897 to treatment intervention trials.

CRITIQUE: The Chemical Biology and Molecular Medicine (CBMM) Program is a realignment of the former Experimental Therapeutics (ET) Program that was renamed after incorporating some faculty from the former Molecular Oncology & Drug Discovery Program. Rationale for this new alignment includes response to the previous critique, which noted overlap between the two programs, and the merger was approved by the EAB and NCI. The focus of the program is to integrate chemical biology and systems biology technologies, toward the goal of developing new therapeutic approaches for cancer treatment.

Proposed aims of the program are to: 1) identify, validate, and characterize therapeutic targets in refractory and metastatic cancers; 2) design small molecule probes to modulate oncogenic targets and pathways; 3) develop and implement mechanism based therapeutic trials.

As described, success in this program would be defined by rapid translation of novel strategies into the clinic coupled with identification of clinical observations that should be prioritized for mechanistic analysis in the laboratory. While there is some evidence that rapid translation can occur with this programmatic structure, breadth and depth in investigator-initiated trials emerging from CBMM discoveries is limited. In the last funding cycle, enrollment to externally peer reviewed studies has declined from a peak of 186 in FY 2011 to 97 in FY 2015, and institutional trials from a peak of 280 in FY 2011 to 187 in FY 2015.

The CBMM Program currently consists of 46 members, of which 24 are predominately laboratory-based and 22 with expertise in clinical trials. There are 10 new basic science and 15 new clinical investigators now included in CBMM. Membership is well balanced amongst senior and junior faculty members, and membership is reviewed quarterly for cancer focus. Mentoring programs are also in place for clinical members, but appears less robust for basic science members.

Multiple program activities were described, including monthly program meetings, Phase 1 meetings and retreats, a Systems Medicine Working Group, a Lung Cancer Center of Excellence, a Drug Discovery Research Project Team, and a Multiple Myeloma Working Group. Less clear is how these venues and/or working groups are utilized to achieve the self-described "post-genomic" goals of the program for discovering mechanisms of drug resistance through systems biology and translating these to the clinic. For example, it is unclear how or if the laboratory-based members of the program are connected to the Phase 1 meetings, and what mechanisms are utilized to connect the themes and foster successful collaborations between the basic and clinical scientists in this diverse program.

Funding levels in the CBMM are moderately strong given the size of the program. At present, the program garners $21.3 million in annual total funding, of which ~$6.8M is total peer-reviewed funding. $12.2 million are derived from industry supported clinical trials, $5.8 million from NCI funding and $0.9 million from other peer-reviewed funding. These metrics are consistent with the robust cancer focus of the program. Eighteen out of 24 scientific members hold peer-reviewed funding, and there are no peer-reviewed training grants. Further, careful review of program funding shows that the CBMM Program cites 2 U01 grants. Of some concern is that for a program of this size, there are few other team-based science grants, such as P01s, SPOREs, and other center-type grants.

Scientific output from the CBMM Program has been exceptional with regard to metrics. In the current funding cycle, CBMM members published a total of 1001 articles, of which 35% were intra-programmatic, 35% were inter-programmatic, and 36% were derived from inter-institutional publications with other NCI designated Cancer Centers. While a less than optimal number of articles with CBMM members as first or senior author appeared in high impact journals, there are examples provided within each theme that meet the stated goals of the program. For example, major discoveries were generated with regard to: understanding mechanisms of adaptive BRAF inhibitor resistance (Paraiso et al., *Cancer Discovery*), mutations governing adaptive responses to dasatinib (Bai et al., *Canc Res*), preclinical

assays to predict chemosensitivity in multiple myeloma (Khin et al., *Canc Res*), clinical assessment of pacritinib in patients with myelofibrosis (Komrokji et al., *Blood*), development of novel Ack1 inhibitors (Lawrence et al., *J Med Chem*), etc. In parallel to these achievements, a number of clinical trials were developed for hematologic malignancies, melanoma, lung, and GI cancers.

Value added by MCC to the CBMM Program was well described, and includes recruitment of productive faculty (including 13 new faculty between 2011-15), access to shared resources (especially the Proteomics Core, which is essential for success of the CBMM Program), and to developmental funds. In the last funding cycle, pilot funds were given for recruitment and to initiate new research initiatives for CBMM members. Less clear is what percent of CBMM investigators awarded pilot funding successfully converted these funds into national grants or major discoveries.

While impactful discoveries were reported during the last funding period, stated ambition to promote the transition of discoveries by CBMM members into novel therapeutics is on an upward trajectory. Evidence of bench to bedside translational was somewhat limited, and accrual to interventional trials associated with CBMM has decreased in the last funding cycle (from a peak of 876 accruals in 2011 to 787 in 2015). As noted above, further concerning is that accrual to institutionally sponsored and externally peer-reviewed trials has markedly decreased.

In summary, strengths include the solid scientific discoveries, translational research, and to some degree, development of novel clinical interventions. Concerns revolve around the diffuse nature of the themes/aims, limited evidence of high impact publications, and only limited evidence of success in stated goals for developing new therapeutic approaches. As this program is also expected to serve as the key translational outlet for the Center, it was considered that that there were opportunities missed for converting discoveries from other programs into new clinical studies.

Program Leader(s): The CBMM Program is co-led by accomplished investigators with complementary expertise. Dr. Haura is a physician scientist that has been a Program Leader for six years, and brings expertise in thoracic oncology. He also serves as Director of the Lung Cancer Center of Excellence, and has an admirable track record of peer-reviewed funding and publication of high-impact studies. The second Program Co-Leader, Dr. Sebti, has been a Program Leader at the Cancer Center for 15 years, and has significant expertise in understanding mechanisms of drug activity and resistance. He brings additional strength in translation, and is associated with over 100 patents and discovery of 10 now licensed technologies. Plans for working together toward the goals of the program were well articulated. Less clear in this joint governance structure, is what the distinct roles are of the individual Co-Leaders.

Assessment: Excellent to Very Good merit.

Budget: The budget is recommended as requested.

Program 3: Cancer Epidemiology

DESCRIPTION (provided by applicant): The goal of the Moffitt Cancer Center (MCC) Cancer Epidemiology (CE) Program is to contribute to a reduction in the cancer burden through research to identify risk factors across the cancer continuum comprising etiology, progression, and outcome, and the translation of that knowledge into successful prevention and early detection interventions. Rapid increases in information enabled by advances in technology have provided the opportunity to clarify underlying causes of cancer pathogenesis. The complexity of the collection of diseases known as cancer requires a robust approach and consideration for a broad array of biomarkers. The identification of markers that alter susceptibility to cancer allows for the development and testing of clinical cancer prevention strategies. To achieve its goal, the CE Program is organized into three specific aims focused on 1) identification and testing of acquired biomarkers of cancer risk and outcome, 2) examination of inherited susceptibility markers and associations with cancer risk and outcome, and 3) discovery and

testing of promising approaches for the prevention and early detection of cancer. CE members investigate how biomarkers, some of which are modifiable, impact disease onset, progression, and outcome and whether these biomarkers can be brought forward into the clinical and public health realms for translational impact. Work is conducted in close collaboration with colleagues in the Health Outcomes and Behavior (HOB) Program, who seek to better understand behaviors that affect mutable biomarkers and modify those behaviors to decrease cancer risk and promote early detection. Thus, the specific aims of CE are highly complementary to those of HOB, and there is considerable synergy between members of both programs.

The program comprises 24 members from six academic departments. Peer-reviewed funding is $6.7M in annual total costs, and the portion of this funding derived from NCI is $5.8M, representing 86% of the program's peer-reviewed funding. Program members have published 635 cancer-relevant scholarly articles including 58 in high impact journals (impact factor >10). In total, 174 (27%) of all publications represent intra-programmatic collaborations, 147 (23%) represent inter-programmatic collaborations, and 292 (46%) reflect inter-institutional collaborations with other NCI-designated Cancer Centers. Indeed, CE members currently have 37 inter-institutional collaborative awards. Scientific investigations led by program members have helped advance knowledge of risk factors, including methylation markers, human papilloma and other viruses, microRNA signatures, and genetic polymorphisms, for numerous cancers that are the major contributors to mortality and morbidity in the MCC catchment area, and for other cancers. CE Program members also are active in translating their work through developing better vaccines, botanical chemopreventive agents, and automated digital imaging to impact clinical and public health practice.

CRITIQUE: This is the third cycle for the Cancer Epidemiology (CE) Program, which was rated Exceptional on its prior review. At that review, there was $9 million in funding, of which 90% was from NCI. There was extensive research focused on biomarkers as well as on HPV and its relationship to a variety of cancers. The leader of the program, Dr. Giuliano, was a nationally renowned leader in HPV epidemiology, who had played a major role in the establishment of HPV vaccination as a standard of care in the United States and globally, and this work was reflected in the content of the program's science. Dr. Giuliano has given up leadership of the program and there has been a decline in funding for the program. Nonetheless, the leadership of the Center has made a remarkable effort to sustain the remarkable success of the prior 5 years. Their investment and commitment is apparent and laudable. They have brought in a new talented and energetic leader to lead the program forward into new areas and to new levels of success.

The choice of Dr. Kanetsky was an inspired one and it seems clear from the recruitments to date, the new (or at least re-emphasized) commitment to genetic and molecular epidemiology, and the success of these endeavors, that he has brought a coherent focused approach to the goals of the program. In return, the program is and seems likely to remain, a national leader in genetic markers for cancer and the identification of new markers. Dr. Kanetsky is a MPI on a SPORE Developmental Research Project to investigate metabolomics of melanoma. He also directs the T32 post-doctoral training program in molecular epidemiology of cancer and is instrumental in the training and mentoring of the next generation of epidemiologists. Dr. Kanetsky is President-elect of the American Society of Preventive Oncology.

This multidisciplinary program aims to contribute to a reduction in the cancer burden through better knowledge of the influences of disease across the cancer continuum. The CE Program is organized to address three aims: (1) identify and test whether acquired biomarkers can predict cancer risk and outcome; (2) examine the association of inherited susceptibility markers; and (3) discover and test the efficacy of promising approaches for prevention and early detection of cancer.

The CE Program at MCC comprises 24 members from six academic departments. Peer-reviewed funding is $5 M in annual total costs, with $4.3M from the NCI. In the current award period, CE

members have published 713 cancer-relevant scholarly articles, of which 27%, 24%, and 48% represent intra-programmatic, inter-programmatic, and inter-institutional collaborations, respectively. The overall scientific quality of this program is exceptional, and the cancer focus in the peer-reviewed research base is very strong. Collaborations across all levels are very impressive. There has been a clear emphasis on addressing cancer-related health problems in the catchment area. CE members have used 11 of the 13 shared resources/core facilities at the MCC and received 15 Program Developmental/Pilot Project Awards, reflecting value added by the Center.

Significant accomplishments are highlighted by studies leading to FDA approval of Gardasil in men for two indications and major discoveries in ovarian cancer epidemiology and biology, and important collaborative work to reliably measure breast density. Scientific accomplishments have been many during the past 5 years. The focus on Aim 1, identification of acquired biomarkers in cancer risk and outcomes, has been carried out through studies of cervical cancer, the effects of endogenous retinoic acid, the natural history of HPV infections among males, HPV infection and the risk of non-melanoma skin cancer, lifestyle influences on breast cancer incidence, and epigenetic biomarkers of cancer risk (focused on prostate cancer, lung and pancreatic cancers as well as cervical and anal cancers). The first aim is further supported by high-impact studies in HPV and infrastructure of the HIM study for inter-programmatic work with the Health Outcomes & Behavior Program members, as well as R01 grant funding in breast cancer and epigenetic biomarkers at risk.

There have been numerous significant scientific accomplishments since the last funding cycle. There have been studies that have focused on identifying and testing whether acquired biomarkers can predict cancer risk and outcome including: Natural History of Genital HPV Infection in Men Differs from that in women; Oral HPV Infection in Men; Viral Etiology of Non-Melanoma Skin Cancers, as three examples. Dr. Chen and collaborators have conducted novel research on inherited genetics of brain tumor development and survival. Drs. Kanetsky and Elder continue to focus on discovery of novel melanoma susceptibility loci. Dr. Sellers' work on ovarian cancer genetic susceptibility has also had tremendous success to date.

The CE Program clearly demonstrates the value it brings to MCC. The CE Program is very supportive of integrative team science and adds value to MCC by supporting integrative intra- and inter-programmatic research while addressing cancers relevant to the catchment area. Furthermore, CE Program members have ongoing research efforts addressing important questions relating to health disparities.

The CE program is following their strategic plans and have clear 'Future Plans' that include the recruitment of new faculty members, expanded data exchange through the Oncology Research Information Exchange Network (ORIEN), improving clinical translation in pharmacogenomics and personalized medicine, better disease prediction, prognosis and outcomes using radiomics and the reaching of a broader range of underserved and/or minority patients as MCC's focus on health disparities is expanded.

Program Leader(s): Dr. Peter Kanetsky is Chair of the Department of Cancer Epidemiology and Genetics as well as a Professor in the Department of Oncological Sciences at the University of South Florida School of Medicine. He was recruited from the University of Pennsylvania in 2013 to replace Dr. Giuliano. He received a PhD in Epidemiology from Columbia University and did a postdoc at University of Pennsylvania under Dr. Tim Rebbeck, where he subsequently remained on the faculty and as a member of the Abramson Cancer Center. He is very well known for his work in the genetics of testicular cancer and melanoma. He has been the driving force in the large number of recent recruitments and is clearly an energetic potent force to be reckoned with.

Assessment: Exceptional merit.

Budget: The budget is recommended as requested.

Program 4: Health Outcomes & Behavior

DESCRIPTION (provided by applicant): The overall goal of the Moffitt Cancer Center (MCC) Health Outcomes and Behavior (HOB) Program is to contribute to the prevention, detection, and control of cancer through the study of health-related behaviors, health care practices, and health-related quality of life. Work toward this goal involves research across the disease spectrum – from prevention and detection through to survivorship or advanced disease. To accomplish its goal, the Program's Specific Aims are: (1) Understand the determinants of behaviors that can lead to prevention and early detection of cancer and develop effective methods of promoting those behaviors; (2) Understand and improve the quality of life of patients and family members throughout the disease course; (3) Contribute to the evidence base, and synthesis of evidence, regarding delivery of cancer care and clinical outcomes; and (4) Understand and intervene upon the social, cultural, and behavioral determinants of cancer-related health disparities.

The program comprises 27 members [20 MCC faculty; seven University of South Florida (USF) faculty] from 12 different academic departments (six MCC and six USF). During the reporting period, 547 cancer-related articles have been published, with 218 (40%) representing intra-programmatic collaborations and 135 (25%) representing inter-programmatic collaborations. Inter-institutional collaborations with other NCI-designated Cancer Centers represent 164 (30%) of the publications. Total grant funding for the program currently is $9.1 million in annual total costs, of which $7.5 million is peer-reviewed, including $3.0 million from NCI.

Program members conduct hypothesis-driven observational and intervention research on the major cancers affecting the catchment area—lung, prostate, breast, colorectal, cervical—with respect to prevention, screening, quality of life, cancer care delivery, and outcomes. Additionally, toward the goal of reducing cancer-related health disparities, program members conduct community-based participatory research in concert with organizations embedded in the catchment area. In collaboration with colleagues from other programs and institutions, translational research by HOB members is driving public health policy and clinical practice.

CRITIQUE: The overall goal of the MCC Health Outcomes & Behavior (HOB) Program is to contribute to the prevention, detection, and control of cancer through the study of health-related behaviors, health care practices, and health-related quality of life. The HOB Program's four aims are: (1) Health Behaviors and Interventions; (2) Quality of Life; (3) Delivery of Cancer Care and Clinical Outcomes; and (4) Health Disparities.

The program consists of 27 members (29 in 2011 review) from 12 academic departments. While grant funding remains strong, the amount overall and NCI specific funding has decreased since the last review. Fourteen members of the total 17 MCC scientific members (82%) are currently funded. There is a U54 Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE) grant, Moffitt Cancer Center-Ponce School of Medicine Partnership, co-led by Drs. Munoz-Antonia and Dan Sullivan (CBMM), with investigators from all five MCC programs.

Collaborative publications are strong and there is an increase in the number of overall publications. During the reporting period, 592 cancer-related articles were published, with 39% intra-programmatic and 24% inter-programmatic collaborations. Inter-institutional collaborations with other NCI-designated Cancer Centers represent 32% of the publications. This compares with 357 peer-reviewed publications over the 2010 reporting period, with 38.4% intra-programmatic and 14.8% inter-programmatic collaborations.

The Health Outcomes & Behavior Program is notable for the breadth, depth and scientific quality of its research. Transdisciplinary and translational research among its members and with other program members is illustrated by the multiple number of projects involving several members within the program and those on other projects also involve members from the other four programs.

The program's first goal focuses on health behaviors and intervention. Research includes strategies to prevent tobacco use, smoking cessation, and investigation of different forms of smoking. Notable research includes a R01 awarded to Dr. Simon (R01 CA154596) testing intervention strategies and a R01 awarded to Dr. Brandon (R01 DA037961) investigating dual use. Program members participate in a 12-site project funded by NIDA and the FDA (U54 DA031659) to test the effects of low-nicotine cigarettes. Another area of research strength includes studies on decision making for colorectal and prostate cancer. Drs. Quinn, Vadaparampil, Roetzheim, Meade, and David Shibata conducted focus groups with patients in federally qualified health centers to investigate patients' perceptions about colorectal cancer screening and preferences for education (U54 CA153509). There is also on-going research to maximize HPV screening led by Dr. Vadaparampil.

The program's second goal focuses on improving quality of life of patients and family members. Dr. Jim and her colleagues are funded (R01 CA164109) to collect objective sleep and physical activity data via actigraphy and circulating markers of inflammation in women with gynecologic cancer during and after chemotherapy. Drs. Jim, Jacobsen, and Small have also been addressing cognitive impairment associated with chemotherapy ("chemo brain") and published in *JCO* a meta-analysis examining cognition in breast cancer patients treated with chemotherapy. Dr. Craig (R01 CA160104) conducted national online surveys of people with and without cancer regarding their preferences between pairs of health outcomes. Dr. Lengacher, with Dr. Jim (R01 CA199160), is conducting a second clinical trial to investigate symptom clusters with a focus on assessment of cognitive functioning. This study will also examine the effects of the intervention on healthcare utilization and costs, with the goal of advancing the intervention toward eventual implementation.

The third goal focuses on outcome and delivery of health services. Dr. Extermann recently received NCI funding (R01 CA168677) to compare treatments for older patients with acute myeloid leukemia. Dr. Jacobsen and his collaborators (Drs. Meade, Quinn, Jhanelle Gray (CBMM), Rachid Baz (CBMM), Gregory Springett (CBMM) and Dan Sullivan (CBMM)), conducted a multi-investigator study that showed that cancer patients randomized to receive an intervention that specifically addressed misperceptions and concerns about clinical trials showed more positive attitudes toward trials and a greater willingness to participate than patients who received standard educational information about clinical trials.

The fourth goal seeks to understand and address social, cultural and behavioral determinants of cancer-related disparities. This was a new area of focus in the last funding period and has considerably gained in strength and funding. MCC, in collaboration with 20 local community-based organizations, formed the Tampa Bay Community Cancer Network (TBCCN) in 2005. TBCCN is currently funded by an NCI Community Networks Program (CNP) grant (U54 CA153159) to Drs. Meade and Gwede as MPIs, with several HOB members (Drs. Jacobsen, Susan McMillan, Roetzheim, Vadaparampil, Quinn, Simmons, and Sutton) as co-investigators. This funding provides support for an infrastructure for community organizations and pilot grants targeting issues in health disparities and builds off a previously awarded P20 grant. Community based with underserved populations is also being conducted by the outreach team (Drs. Brandon, Gwede, Quinn, Simmons, and Vadaparampil) of the MCC-Ponce Partnership, funded by the Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE) program in 2012 (U54 CA163068). Drs. Munoz-Antonia and Dan Sullivan (CBMM) are the MCC-based Multi-PIs. Research funded by the U56 that preceded the present grant included studies of culturally-appropriate communication with Hispanic patients and families, assessing community needs, and the creation and feasibility testing of Spanish language tobacco interventions. These earlier studies led to an ongoing pilot RCT in the current U54 testing different culturally-tailored communication

modalities for educating Spanish-speaking individuals about the importance of biobanking and a new R01-equivalent grant from the Florida Biomedical Research Program (5JK03; PI: Dr. Simmons) for a RCT to test the efficacy of a Spanish-language smoking cessation intervention. A related NCI grant (R01 CA199143; MPI: Drs. Brandon and Simmons) is pending.

The clinical trial accrual for the program is strong. Of concern is the substantial drop in externally peer-reviewed trials (2,370 to 484) and low number of individuals accrued to Cooperative trials (2 each in FY 2014 and FY 2015).

The program impacts the catchment area with NCI funded research focused on disparities and research that impacts individuals living in the catchment area.

Program Leader(s): The Program Leader, Dr. Brandon was promoted to HOB Program Leader in January 2012 when the previous Program leader, Paul Jacobsen, PhD, was promoted to Associate Center Director of Population Science. Dr. Brandon has been at MCC since 1997, when he established the working group in tobacco research. Dr. Brandon has been continuously funded since 1991 and was PI on three R01-funded projects during the last funding period. Dr. Brandon currently has one R01. Dr. Brandon serves as Associate Director on the training program in Behavioral Oncology Education and Career Development, funded by the R25T grant to Dr. Jacobsen (R25 CA090314) that provides an infrastructure and plan for mentoring postdoctoral fellows. Dr. Brandon represents the program in MCC governance committees, including the Scientific Leadership Committee (SLC), Core Leadership Committee (CLC), Membership Committee, and Population Science Executive Committee. He is qualified for his leadership position.

Assessment: Outstanding merit.

Budget: The budget is recommended as requested.

Program 5: Immunology

DESCRIPTION (provided by applicant): The overall goal of the Moffitt Cancer Center (MCC) Immunology (IMM) Program is to define the mechanisms by which tumors evade rejection by the immune system and to develop strategies to thwart them. Fundamental discoveries by IMM members have led to novel immunotherapy trials that directly benefit cancer patients. Key to the Program's success is the close integration of IMM clinical, translational, and basic scientists that facilitates rapid progression of novel immunotherapies from the bench to bedside. The goals of Specific Aim 1 are to advance and translate T-cell therapies for solid tumors and hematologic malignancies, by bringing laboratory and pre-clinical studies of the IMM Program to the patient bedside in the form of novel investigator-initiated clinical trials. Specific areas of focus include: (1) adoptive T-cell immunotherapy using *ex vivo* expanded tumor-infiltrating lymphocytes and genetically modified immune effector cells; (2) mechanistic strategies to improve adoptive cell therapy; (3) restoration of tumor-specific responses by immune checkpoint inhibitors, histone deacetylase inhibitors (HDACi), and vaccination; and (4) defining gene expression signatures of immune responders. MCC infrastructure that supports IMM members includes: (i) the Immunotherapy Working Group that conceives interventional trials; (ii) a Good Manufacturing Practice-compliant Cellular Therapy Core Facility; and (iii) the interdisciplinary Immune and Cellular Therapy clinical service to deliver therapy to patients. The goals of Specific Aim 2 are to define molecular and cellular mechanisms that can exploit innate and adaptive immunity against cancer. Here, IMM members seek to discover and develop molecular approaches to harness the immune system. Collaborative studies include those assessing T-cell recruitment and suppression, natural killer cell control, myeloid-derived suppressor cell expansion, and selective HDACi immune modulation. These initiatives have generated several innovative approaches that control these processes, including therapeutic translation into clinical trials. The goals of Specific Aim 3 are to prevent graft-versus-host disease (GVHD) while maintaining the potency of graft-versus-leukemia and

other blood cancers following hematopoietic cell transplantation (HCT). The IMM Program has made significant impact in this arena, including the discovery that Th17 cells have a central role in the severity of GVHD and in the response to therapy. The approaches to prevent GVHD and maintain anti-tumor response include: (1) adoptive transfer of donor Tregs specific against host minor-histocompatibility antigens; (2) targeting the common IL-12/IL-23 p40 receptor chain; (3) targeting JAK2 or STAT3; and (4) defining gene expression signatures associated with operational tolerance following allogeneic HCT. The Program is composed of 25 members from 10 different academic departments. During the reporting period, 534 cancer-related articles were published, with 167 (31%) intra-programmatic and 207 (39%) inter-programmatic. Grant funding for the Program is $18.8 million, of which $7.0 million is peer-reviewed, including 43% from NCI.

CRITIQUE: The Immunology (IMM) Program is composed of 25 members (10 Senior Members, 5 Associate Members, 9 Assistant Members and 1 Instructor). Thirteen are new faculty who have been recruited since the last renewal. Eight of the new members have obtained external funding. The Program Co-Leaders mentor the junior members in grant writing and manuscript review. There is a T32 Training Grant in Immunology. There is $3.29 million (direct costs) in peer reviewed projects, and $9.48 million in non-peer reviewed projects, for a total of $12.77 million. NCI peer reviewed funding equals $1.14 million. The program is also the home for a P50 on skin cancer (Vernon Sondak, PI). The program was productive with 598 cancer-related papers, with many in high impact journals, with 31% intra- and 39% inter-programmatic publications. This number is significantly lower than the level of NCI awards in the previous funding year (4.8 million). This decrease in funding is likely related to the departure of a senior investigator, Dr. Jeffrey Weber, and the addition of several junior faculty members to the program.

The overall goal of the IMM is to define the mechanisms by which tumors evade rejection by the immune system and to develop strategies to thwart them. There are three specific aims. The goals of Specific Aim 1 are to advance and translate T-cell therapies for hematologic malignancies and solid tumors. Impressive advances have been made using *ex vivo* expanded tumor-infiltrating lymphocytes and genetically modified immune effector cells, and the use of immune checkpoint inhibitors alone or in combination with histone deacetylase inhibitors, and vaccines. In addition, progress has been made in defining gene expression partners of patient immune responders.

The goals of Specific Aim 2 are to define molecular and cellular approaches to harness innate and adaptive immunity against cancer. Fundamental discoveries identifying regulation of important immune cell subtypes in Aim 2 are well integrated with immunotherapy in the clinic by the inclusion of TIL based therapies, cell-based vaccines, checkpoint inhibitors and advancing the use of BMT for the treatment of blood based malignancies.

In regard to Specific Aim 3, the goals are to prevent graft-versus-host disease (GVHD) following hematopoietic cell transplantation. One notable discovery has been that Th17 cells have a central role in the severity of GVHD and in the response to standard GVHD therapy. Current efforts are being made to prevent GVHD by transfer of donor Tregs specific to host minor-histocompatibility antigens, by targeting the IL-12 / IL-23 p40 receptor chain, targeting JAK2 or STAT3.

The members had several notable successes during the last funding period. Drs. Scott Antonia and Jeffrey Weber led the development of anti-PD1 and anti-CTLA-4 immunomodulatory therapies for lung and melanoma cancers. Dr. Weber also demonstrated that BRAF inhibitor resistance can be delayed by using dabrafenib and trametinib. Drs. Djeu and Wei collaborated with members of other MCC programs to identify a novel miRNA (miR183) immune escape mechanism by suppressing a key signal adaptor protein in NK cells. The implication is that targeting this mechanism could restore NK function and improve outcomes in patients newly diagnosed with lung cancer. Dr. Anasetti discovered that while there was no clear difference in survival, relapse, non-relapse mortality, or acute GVHD in patients receiving bone marrow or peripheral stem cell transplants, that the use of peripheral stem cells is

associated with a higher risk of GVHD. Finally, Dr. Sondak has collaborated with members of other programs to demonstrate that HDAC inhibitors enhance tumor immunogenicity and T-cell infiltration to augment the effectiveness of CTLA-4 and PD-1 blockade. These studies have led to a phase 1 trial combining ipilimumab with a pan HDAC inhibitor to treat un-resectable melanoma patients as part of the skin cancer P50 led by Dr. Sondak.

The program is a leader in state-of-the-art immunotherapy trials and MCC is one of only 5 Centers approved for the production of TILs. The program interacts closely with the CTC shared resource, which has undergone a 4-fold expansion since the last renewal. This has resulted in 27 investigator initiated interventional trials with a total accrual of 658 patients. Plans for the upcoming funding period include several investigator initiated TCR/CAR-T interventional trials for both hematological and solid tissue malignancies. These will be paired with a clinical service (immune and cellular therapy) to manage toxicities associated with CAR-T therapies.

There has been outstanding support from the MCC in regard to the formation of the Immunotherapy Working Group that develops clinical intervention trials, a GMP-compliant Cellular Therapy Core Faculty, and the interdisciplinary Immune and Cellar Therapy clinical service to treat patients. There are a variety of meetings and seminars that support the goals and activities of the Program, which include the IMM Program and Research-in-Progress meetings, Immunology Journal Club, Grand Rounds and Working Groups.

The main cited value of the Immunology Program to the MCC is the facilitation of collaborative team science across programs and the Immune and Cellular Therapy clinical service, which facilitates the development of novel immunotherapies. In terms of overall scientific quality, members of the program have consistently published high impact articles with a strong focus on translational science and clinical outcomes using immunotherapeutic agents. Core usage by program members is strong and several collaborative activities including meetings, seminars, and working groups add considerable value to the Center. In addition, the breadth of immunotherapy trials that this program supports brings great value to MCC. Funding levels are very good with several new training awards, and multiple industry-sponsored trials. At the time of the site visit, NCI R01 funding is less than optimal although the program has successfully competed for a P50 Melanoma SPORE. Scientific and scholarly productivity during the last funding cycle has been strong, although the loss of Dr. Weber, a world leading trialist in immune therapy, has had a negative impact on the program. Faculty recruitment has been brisk and the developmental funds have been used to support strong pilot grants for the new junior members. Many of these new junior members have successfully competed for new training grants, and it will be very important for the future of the program for them to continue developing vigorous independently funded research programs.

Program Leader(s): Claudio Anasetti, MD, is a Co-Leader and is Chair of the Department of Blood and Bone Marrow Transplantation. He is also Medical Director of the Cell Therapies Core. Kenneth Wright, PhD, has served as interim Co-Leader of the IMM Program and Chair of the Department of Immunology since December 2013. His research relates to new therapeutic approaches with natural killer cells against lymphoma. A new Co-Leader, Dr. Jose Conejo-Garcia, was introduced at the site visit. He has a very strong research history although it is too early to gauge his leadership skills in this new position.

Assessment: Excellent merit.

Budget: The budget is recommended as requested.

SHARED RESOURCES

Analytic Microscopy Core

DESCRIPTION (provided by applicant): The Analytic Microscopy Core (AMC) Facility was established in 1999 to provide MCC members with access to equipment and technical expertise that are needed to perform high-level microscopy experiments. These services allow members to visualize and quantify complex cellular and sub-cellular processes in multiple dimensions. The specific aims of the AMC are to provide: 1) assistance with study design for use of microscopy, 2) access to advanced microscopy systems and image analysis platforms, and 3) training on use of AMC's microscopy systems and image analysis technologies. State-of-the-art microscopy equipment located in the AMC includes confocal, wide-field fluorescence, multiphoton, stereo, live cell, intravital, whole slide scanning, and laser capture microdissection (LCM) microscopy systems. The AMC's image analysis capabilities include image quantification, automated segmentation, co-localization, 3D rendering, motion tracking, and deconvolution. The AMC is staffed by four full-time specialists who are skilled in both microscopy and cancer-related research fields, and it is led by Marilyn Bui, MD, PhD, (Scientific Director), who is an American Board of Pathology-certified pathologist with extensive experience in cancer research and digital pathology. The AMC staff work closely with members to design, image, and analyze experiments, allowing members to obtain high-quality and reproducible data. Further, the AMC collaborates with other Shared Resource Facilities at MCC to manage complex projects and to ensure proper handoffs of materials and data. Given the costs of modern microscopy systems and the logistics involved with outsourcing microscopy experiments, the services provided by the AMC are an essential resource for MCC members. Over the past five years, the AMC has experienced a 50% increase in usage, supporting 154 publications. During the most recent fiscal year, the AMC supported 58 members, and 83% of total usage was for peer-review-funded members. Since the last review, the AMC has added several new microscopy systems, including wide-field fluorescence, confocal, multiphoton, LCM, and three live cell imaging platforms. These new technologies have sustained high levels of usage at the AMC and have provided members with the most advanced microscopy platforms and services. Moving forward, the AMC will continue to evaluate and provide state-of-the-art equipment and services to meet the future microscopy needs of MCC members.

CRITIQUE: The Analytic Microscopy Core (AMC) was established in 1999 and provides MCC members access to state-of-the-art microscopy facilities and image analysis platforms. Equipment includes confocal, wide-field fluorescence, multi-photon, stereo microscopy, live cell microscopy, intra-vital microscopy, whole slide scanning and laser capture micro dissection capabilities. Post microscopy analyses and three dimensional rendering and time-lapse capabilities are also included as part of the services provided. Several new microscopy systems have been added since the last review, which helps to maintain high levels of usage. Plans are in place to upgrade and expand capabilities (e.g., super resolution microscopy).

The AMC is led by Marilyn Bui, MD, PhD, a pathologist with extensive experience in cancer research and digital pathology, and staffed by four full-time specialists. In the past year AMC supported 58 MCC members, 83% of total usage was for peer-review funded members.

In response to the previous review, the AMC has increased the percent effort of the scientific director and clarified the relationship with information technology. AMC has multi-core collaborations. The communication and workflow seem to work well and are managed by the Core Leadership Committee. Customer satisfaction surveys seem to be a great way to get formal feedback from users. However, the last survey was in 2014. Increased frequency of feedback may help to quell problems sooner. The AMC has supported 102 members from all 5 programs and contributed to 154 publications. The development of an intravital and multiphoton service enables internal performance of this service to the benefit of MCC members.

The scientific director and core facility manager meet monthly. This frequency seems a bit low, especially given the overall role and increased percentage effort from the scientific director.

In summary, the AMC is a well-run resource serving a critical need for numerous MCC investigators. The progress appears excellent with an increase in usage and number of publications.

The Director, Dr. Bui, and full time staff members are all exceptionally well qualified. Though each staff member brings his or her own specialty, they are cross-trained on all equipment.

Assessment: Outstanding merit.

Budget: Currently 10% of the AMC budget is from CCSG. The proposed level of funding from CCSG is 16% or $58,213 up from $37,416. The budget is recommended as requested.

Biostatistics Core

DESCRIPTION (provided by applicant): The overall goal of the Biostatistics Core (BC) is to provide statistical design and analysis expertise supporting the research efforts of Moffitt Cancer Center (MCC) members. Service begins with analytical design and determination of sample size (e.g., grant and clinical trial submissions), leading to project conduct, monitoring of accumulating research data on active projects, and manuscript development. The BC provides key quantitative analytical results, including tables, figures, and scientific conclusions. Faculty biostatisticians provide education and training in biostatistics, participate actively in the Scientific Review Committees (SRC) and Protocol Review & Monitoring Committee (PRMC), and serve as reviewers for internal grant applications.

The BC's Specific Aims are to: 1) Support members by providing high-quality biostatistical design and analysis services; 2) Educate and train investigators on biostatistical resources and tools; and 3) Develop and implement methods for state-of-the-art statistical analyses. The BC also supports the conduct of research through involvement on various oversight committees (e.g., SRC and PRMC).

The BC includes nine faculty, seven staff biostatisticians, a Core Facility Manager and a Project Manager. Faculty biostatisticians dedicate 50% to 60% of their effort to the BC and are supported by grant funding, revenue from clinical trials, and institutional support. Staff biostatisticians and the Core Facility Manager are dedicated to the BC and are supported by chargebacks, revenue from clinical trials, and institutional support. BC faculty and staff are involved at all stages of scientific research, from study design to publication of research findings. Most BC efforts involve BC faculty-staff teams. During the past funding cycle, the BC played significant roles in both the Lung and Skin SPORE grants. In addition, BC biostatisticians are part of every investigator-initiated therapeutic clinical trial conducted at MCC.

Over the past five years, the BC has supported over 500 clinical trials, research efforts across all five research programs, and research projects that have received SRC approval. In the most recent fiscal year, the BC supported 78 members, with 75% of usage for peer-reviewed-funded members. There are two BC faculty members on each of four SRCs and the PRMC.

CRITIQUE: The Biostatistics Core (BC) was established in 1998 and provides state-of-the-art collaborative support in the design and statistical analysis of research projects. The BC consists of nine faculty, seven staff biostatisticians, a core facility manager, who are supported by numerous grants and contracts (faculty) as well as charge-back (staff). BC faculty and staff play a critical role in investigator-initiated therapeutic clinical trials, and BC faculty serve as active members of the Scientific Review Committees (SRCs) and Protocol Review & Monitoring Committee (PRMS). Specific aims are to: 1) support members by providing high-quality biostatistics design and analysis services, 2) educate and

train members on biostatistics methods and resources, and 3) develop and implement additional statistical methods as needed for state-of-the-art statistical analyses.

The resource was rated as Outstanding at the 2011 CCSG site visit. The reviewers recommended development and implementation of novel clinical trial designs, coordination with the Cancer Informatics Core, clarity on roles and responsibilities for omics data analysis between BC and other computational or informatics resources, and collaboration with mathematical oncology investigators. The BC proactively responded to these recommendations by recruiting a Bayesian adaptive design expert, increasing capacity for next generation sequencing analyses and psycho-social analyses, participating in a multi-core process, and developing statistical collaboration with mathematical oncology researchers.

During the FY 2015, the BC was utilized by 78 members (75% peer-review funded members). The BC contributed to over 200 publications and 500 clinical research studies during the last five years and played a significant role in preparation of the Lung and Skin SPORE grant applications. Important synergy between the BC and the Cancer Informatics Core (CIC) has been achieved through the combined Department of Biostatistics and Bioinformatics. There is a clear description of how new requests for services are initiated (Biostatistics Assistance Form) and a robust tracking system in place (Laboratory Information Management System) to track usage and trends in utilization to accurately track future utilization.

Strengths of this resource include a strong leadership by Dr. Michael Schell, who has been the BC Director since 2005, a team of highly qualified, competent biostatisticians collectively representing a diverse range of statistical expertise, combined with a high usage and scientific impact. Computing resources and academic environment are outstanding.

Only very minor weaknesses are noted for clinical trial designs and methodology development in Aim 3. A review of selected protocols reveals that many of the trial designs is fairly standard and not utilizing or incorporating novel trial designs. In addition, one of the aims of the resource is to develop and implement novel methodologies, and the quantity, quality and scientific impact of this aim are not well documented.

In summary, strengths of the BC include the strong leadership, a team of highly competent and qualified faculty and staff, high utilization and scientific impact. However, the BC is encouraged to invest in novel clinical trial designs, strengthen activities supporting Aim 3, a multi-core project management process, and engage in data science initiatives and reproducible research practice.

Assessment: Outstanding merit.

Budget: The requested CCSG amount of $196,629 represents 11% of the total operating budget with 57% projected to come from chargebacks and 32% from other institutional funds. The budget is recommended as requested.

Cancer Informatics

DESCRIPTION (provided by applicant): Analyzing, managing, and interpreting data accumulated in the age of accessible genomics involves tremendous challenges. A shared resource consisting of informatics and computational scientists, a group of specially trained professionals who understand both biomedical and computer science methodologies, fills the collaboration gap between members, IT professionals, and computational scientists. The overall goal of the Cancer Informatics Core (CIC) is to facilitate the biomedical and translational research of Moffitt Cancer Center (MCC) members through implementation and development of methods and tools to record, integrate, manage, analyze, visualize,

and share biomedical, behavioral, and clinical data. To accomplish its goal, the CIC's Specific Aims are to:

1) Support members' 'omics projects with bioinformatics project design, analysis, biological interpretation, and visualizations: The CIC provides bioinformatics and big data analysis and collaborates closely with the Biostatistics Core (BC) to provide seamless analytical services for member projects involving expression profiling, next-generation sequencing, and proteomics. Services include QC, normalization, batch correction, phenotypic analysis, and biological pathway enrichment.
2) Support members' data management and reporting needs with study-specific informatics tools: Complex, study-specific data are collected for member biomedical research studies, including large multiproject studies such as SPOREs.
3) Provide educational opportunities to train members and staff on the use of bioinformatics resources and tools: Public resources are available for members and staff to extract biomedical data and knowledge, leveraging work of the entire scientific community. The CIC provides training for members for awareness of and access to these resources directly.

The CIC includes three faculty members, a core facility manager, five staff scientists, and three software developers. CIC bioinformatics faculty devote 50-70% effort to MCC collaborative research activities, supported by CCSG, other grant, and institutional funding. Staff scientists and software developers are dedicated 100% to the CIC, supported by CCSG funding, chargebacks, and institutional support. CIC faculty and staff members are involved in all stages of scientific research, from supporting experimental design (with the Biostatistics Core) to publication of research findings. The CIC has provided significant impact in member research studies through bioinformatics analysis in genomics, proteomics, and expression profiling resulting in high-impact publications in journals such as *Nature Genetics* and *Cancer Research*. Over the past five years, the CIC has supported scientific projects of members of all programs, resulting in 62 publications. In the most recent fiscal year, the CIC supported 35 members, with 84% of usage by peer-review-funded members.

CRITIQUE: The Cancer Informatics Core (CIC) was established in 2006 to provide expert informatics, bioinformatics and computational support to MCC members. The overall goal of the CIC is to facilitate the biomedical and translational research through implementation and development of methods and tools to record, integrate, manage, analyze, visualize, and share biomedical, behavioral, and clinical data. Specific aims are to provide: 1) support for omics projects, 2) support for data management and reporting needs, and 3) education and training in the use of bioinformatics resources. The CIC consists of three faculty members, a core facility manager, five staff scientists and three software developers. In FY 2015, the CIC was utilized by 35 members from all five research programs (85% peer-reviewed funded). The CIC faculty and staff contributed to 62 publications for the last five years.

The CIC was rated Outstanding at the last CCSG review. The reviewers commended development of the data warehouse infrastructure for the Total Cancer Care Initiative, while expressed concerns for bioinformatics support for omics data generated by next generation sequencing and other high throughput technologies. The data warehouse and the Total Cancer Care Initiative's informatics support has moved to a new shared resource "Collaborative Data Services Core" (CDSC), while CIC has focused on bioinformatics and computational support for high-dimensional data. The CIC appropriately responded to the previous critiques by expanding bioinformatics support capability for next-generation sequencing data (RNASeq and DNASeq), including hiring new faculty and staff, developing data analysis pipelines, and establishing a coordination process, which delineates roles and responsibilities between data generation cores, CIC, Biostatistics, and CDSC. The process is assisted by a dedicated project manager (Ms. Melissa Avedon) and in-house project management software to insure proper handoff of the project from one core to another, communication among the investigator and cores, and project tracking. Education and training activities on the use of public data resources, such as TCGA, cBioPortal and UCSC Genome Browser, are highly commendable, as these resources are increasingly utilized to generate preliminary or exploratory data as well as external confirmation data. The

computational resources are impressive including 32-core IBM 3950 server, 24-core Dell PowerEdge R900 server, Dell PowerEdge R610 server, and 832-core 3.8TB RAM Linux cluster with access to >400 TB high capacity network storage.

The recruitment of Dr. Jae K. Lee as Chair of an integrated academic Department of Biostatistics & Bioinformatics is additional strength as the recruitment and subsequent reorganization of the department resulted in enhanced interactions and collaborations between BC and CIC. As some aspects of the role of the CIC and BC overlap or at least are heavily dependent on each other, it is a clear strength that the academic environment facilitates collaboration between the two groups. The CIC is well integrated into the overall CCSG Program having supported members of all programs with evidence of scientific impact demonstrated by some 62 publications in the past 5 years. Under the new leadership, the core's services have expanded to include non-genomics high dimensional data, such as data from mobile technology capabilities and molecular visualization tools.

Only very minor concerns are noted with respect to CIC's moderate usage relative to high utilization of molecular genomics core and MCC's emphasis on personalized medicine, as well as a lack of description on reproducible research practice. The core is encouraged to take a more proactive and leading role in implementing and disseminating reproducible research practices in the MCC computational community; continue to expand expertise and capacity in high-dimensional, non-genomics data, such as imaging data and multiplex immunological data; increase its usage; and track and monitor educational and training outcomes. It is also important to identify any barriers in accessing core services directly or via data generation cores or CDSC. A multi-core project coordinator will be clearly helpful in this regard.

Steven Eschrich, PhD, serves as the Scientific Director. Dr. Eschrich is an Associate Member in MCC's Department of Biostatistics & Bioinformatics. He received his PhD in Computer Science & Engineering from the University of South Florida in 2003. He has extensive experience in molecular analysis in translational cancer research including microarrays and proteomics. He is highly qualified to lead this shared resource. Dr. Eschrich is assisted by two other faculty (Teer and Berglund) and five staff scientists and 3 software developers, who are all highly trained and capable to serving this resource.

In summary, strengths of the CIC include the strong leadership, a team of highly competent and qualified scientific staff, robust usage, multi-core coordination efforts, and outstanding scientific contributions. The CIC is encouraged to strengthen its usage, expand educational activities and poise itself for challenges of big data, management and integration of heterogeneous data sources.

Assessment: Outstanding merit.

Budget: The requested CCSG amount of $111,486 represents 7% of the total operating budget. The resource is supported by 45% chargebacks and 48% by institutional funding. The budget is recommended as requested.

Cell Therapies Core

DESCRIPTION (provided by applicant): The overall goal of the Cell Therapies Core (CTC) is to provide service to members to facilitate translation of promising therapies for patients with cancer. The CTC manufactures cellular products in support of novel, investigator-initiated clinical studies, while maintaining compliance with standards set by the U.S. Food and Drug Administration (FDA) and other accrediting bodies. To accomplish this goal, the CTC's Specific Aims are to:
1) Develop new technologies for translation of cellular therapies
2) Provide regulatory assistance in support of cellular therapies
3) Educate and train scientists and clinicians committed to careers in cellular therapies
4) Produce the highest quality cellular products for immunotherapy clinical trials

The CTC works with members through all stages of a clinical trial, including collaboration during pre-clinical planning. The CTC technical director, manager, and quality staff assist with preparation of protocols, funding/grant applications, INDs, and other regulatory submissions. Once the cellular therapy agent under study is administered to the patient, the CTC analytic laboratory may continue to assist in post-treatment immune monitoring or, when desired by investigators, may directly conduct the immune monitoring studies. The CTC has four key areas of activity:

1. New product development, wherein new cell therapy products undergo pre-clinical scale-up, testing, and validation
2. Cell collection and cryostorage to obtain mononuclear cells, lymphocytes, and antigen presenting cells for production of cell therapy products and immune monitoring studies
3. Cell therapy product manufacturing, including dendritic and tumor cell-based gene-modified and un-modified vaccines and purification and/or expansion of T lymphocytes (T regulatory cells, tumor infiltrating lymphocytes, tumor antigen-associated T cells, chimeric antigen receptor T cells)
4. An analytic laboratory that performs the dual functions of product quality testing and post-treatment immune monitoring

During the project period, the CTC supported 19 cancer center investigators involved in 27 projects and 39 publications. In FY2015, the CTC supported 15 projects, of which 87% represented member projects and 55% of total usage supported peer-review-funded members.

CRITIQUE: The mission of the Cell Therapies Core (CTC) is to produce high quality cellular products for use in immunotherapy trials while keeping within the scope of applicable regulatory standards. The CTC provides service to members of the MCC who are leading translational projects focused on developing new therapies for cancer patients. The services offered include scale up of cell therapy concepts from basic laboratory to clinical trials, assistance in preparing IND to be approved by the FDA, the production of clinical grade cell therapy products to support clinical trials, and the monitoring of immunologic function of patients on clinical trials. MCC is one of only 5 institutions nationally approved for producing clinical grade tumor infiltrating lymphocytes for therapeutic applications. Immune monitoring of patients includes the measurement of plasma cytokine levels, ELISPOT and cell based analysis for various IFNγ and other relevant cytokines, characterization of immune cell subsets by flow cytometry, and preparation of blood lymphocytes for cryostorage. Staff members and fellows are also trained for assay standardizations.

The FDA accredited and CLIA certified CTC has a very high value for the continuing emphasis in MCC on translational immune based therapies for tumors. The CTC appears to have met the goal of providing assistance through all stages of clinical trial development. During the last funding cycle, 27 projects were supported from 19 MCC investigators, and 39 publications resulted from these studies. During the last year, the CTC supported a total of 15 projects for 8 members, of which 87% were MCC member projects. The vast majority of these investigators are understandably from the Immunology Program. These projects are a mix of clinical trials and feasibility studies for the design of clinical trials. The facility is heavily subsidized by MCC, which is stated to contribute 50% of the operating budget in the upcoming year. An additional 42% is captured by chargebacks and the request is for an additional 8% CCSG support. Usage by member peer reviewed (55%) and member non-peer-reviewed (18%) support totals 73%. Numerous clinical trials are listed, which cover protocols involved in virally transduced dendritic cells for improved antigen presentation, combination therapies utilizing adoptive cell transfer of TILs with immune modulating antibodies, adoptive cell transfer plus BRAFi for patients with metastatic melanoma, and the validation of survivin as a new clinical target in multiple myeloma.

The CTC was rated Excellent to Outstanding during the last review, with the reviewers questioning the availability of immune monitoring assays to support outcome analysis of patients on clinical trials. These assays are now performed in either the investigator's research laboratory or the CTC. There is an institute-wide immune monitoring technical working group consisting of stakeholders that oversee

immune monitoring assays in patients. The several goals of this group include coordinating immune monitoring for clinical trials of new cancer immunotherapies, developing, validating and optimizing new immune therapy technologies, standardizing current immune based assays for patients receiving novel immunotherapies, and promoting the development of new biomarkers. The CTC has undergone significant improvements since the last review. From 2011 to 2013, these include the buildout of a new 10,000 sq. ft. space, which includes new laboratories, clean rooms and cell storage facilities, the development of the immune monitoring technical working group, and the recruitment of several individuals with expertise in quality assurance, IT, and product development. These improvements were in direct response to the previous critique.

The CTC continues to be led by James Mulé, PhD, who has substantial expertise with cellular therapies; effort requested is 5% for Dr. Mulé. Support for the core manager, Dr. Linda Kelley, is also requested (5%). The core is heavily staffed with individuals who manage the core (10%), monitor quality assurance (10%), oversee cell production under IND (10%), and oversee development and validation of immune monitoring assays (10%).

Assessment: Exceptional merit.

Budget: The budget is recommended as requested.

Chemical Biology Core

DESCRIPTION (provided by applicant): The Chemical Biology Core (CBC) offers Moffitt Cancer Center (MCC) members access to state-of-the-art technology, instruments, expertise and infrastructure necessary for studying proteins involved in tumorigenesis. The CBC also provides synthetic and medicinal chemistry services for synthesizing chemical probes and to develop lead candidates into compounds that are suitable for pre-clinical cancer efficacy and safety studies. The specific aims of the CBC are to: 1) assist in study design, implementation of synthesis of chemical probes, X-ray crystallography, and protein production via consultation and collaborations; 2) provide members with resources to study the structure of proteins involved in tumorigenesis; and 3) provide access and training on state-of-the-art instrumentation to members.

The CBC is composed of two highly specialized sections, Chemistry and Protein Crystallography, which provide services in Synthetic/Medicinal Chemistry, Protein Crystallography, and Biochemistry. The CBC employs five experienced full-time staff, who provide expertise in chemistry, drug discovery and development, protein production, crystallography and biochemistry, and cancer biology. Chemistry services offered by the CBC include: 1) synthesis of focused libraries for hit-to-lead-optimization of new anti-cancer compounds; 2) synthesis of complex small molecules as chemical probes; 3) medicinal chemistry and scale-up synthesis, to provide pre-clinical compounds for potency, selectivity, efficacy and safety studies; 4) analytical chemistry services, to determine physicochemical properties of potent compounds; 5) and synthesis of tagged chemical probes for affinity-based chemical proteomics studies. The CBC also provides support for cloning, expression, large-scale purification of target proteins, X-ray crystallography, high-resolution structure determination, structure-guided synthesis, protein-protein and protein-ligand/drug interactions, and structure of protein-inhibitor complexes. Facilitating this work, the CBC provides members access to high-end instrumentation and associated training. Over the past five years, chemistry, protein production, and crystallography services have supported the projects of 49 members, including services critical for 14 new research grant awards to members. The CBC contributed to 52 publications via synthesis of compounds, protein production, and high-end instrumentation, and core staff were co-authors on the publications of 24 members. During the most recent fiscal year, the CBC provided service for 23 members in four research programs: CBMM (12 members), CBE (6), IMM (3), and CE (2). Regarding use of the CBC, 81% was by peer-review-funded members. The CBC also provided preliminary data, technical sections, and consultation for 21 research

proposals during the most recent year. The CBC is supported by institutional and CCSG funds and will continue to provide outstanding chemical biology and state-of-the-art technologies to MCC members.

CRITIQUE: The Chemical Biology Core (CBC) was established in 2004 and has evolved to perform a series of services involved in drug discovery and development activities at MCC. CBC personnel assist in study design, synthesis of chemical probes and structural analyses, including protein production. CBC personnel also provide access to and training on state-of-the-art instrumentation. At the time of the previous CCSG review, the CBC was rated highly (Excellent to Outstanding). Two main concerns were raised, and they included: (1) only modest member usage outside of one research program, and (2) need for enhanced coordination, organization, and prioritization of core services. In response to this review, as well as in response to a rigorous internal review undertaken by the MCC, the CBC has been re-organized to provide more focused expertise, services, and education. The MCC has made significant investments in cutting-edge equipment to enhance CBC scientific capabilities. The CBC has now outsourced high-throughput screening (HTS) services so as to focus its efforts on chemical synthesis, medicinal chemistry, protein production, biophysical characterization of purified proteins, and X-ray crystallography services. CBC supported 52 publications and submission of 21 grant applications in 2015 as well as funding of two new grants (R01/VA).

The technologies available are state-of-the-art and match the level of expertise in the personnel and the approaches used in projects. The services span the entire range of chemical synthesis, biophysical analysis, protein and X-ray crystallography. There is an emphasis in core technologies that align with the overall types of protein targets under investigation; disease relevant protein-protein interactions. There is a very high capacity represented in the overall staffing and scope of infrastructure with major growth in the total operating budget.

The CBC appears to have met the needs of the MCC members. Over the past 5 years, the CBC provided service to ~40 MCC members, which represents a significant increase in MCC member use since the previous CCSG review. Questions related to broad usage, capacity, quality control, prioritization of projects/targets and state-of-the-art of the machinery were addressed at the site visit. New plans to expand and monitor research were also addressed at the site visit.

With respect to operational expenses, it is clear that a substantial and noteworthy investment in this shared resource has been made by MCC since the last review of the CCSG. The Center has provided critical funds to support faculty and staff as well as to support non-recurring expenses for instrumentation and space. A chargeback system is well conceived and has potential for recovering additional operational expenses.

Since the previous CCSG review, Dr. Harshani Lawrence was appointed Scientific Director and Core Facility Manager. She has significant experience in synthetic and medicinal chemistry and in the design of biologically active molecules for drug discovery/development and chemical biology research. Dr. Ernst Schonbrunn remains as the scientific Co-Director with expertise in protein crystallography. These two leaders have complementary skill sets and research expertise, and they play a critical role in maintaining the high quality of this core. The CBC is supported by several key personnel, and they include Yunting Luo (research specialist assigned to the Chemistry Section, 0.6 calendar months), Dr. Mohammad Ayaz (research specialist assigned to the Chemistry Section, 0.6 calendar months), and Dr. Kathy Yang (research specialist assigned to the Protein and X-ray Crystallography Section, 0.6 calendar months). Dr. Andreas Becker is a Senior Staff Scientist who is assigned full-time to the Protein and X-ray Crystallography Section but for whom no support for CCSG funding is requested.

Assessment: Outstanding merit.

Budget: For the next funding period, the total operating budget is proposed at $681,656, with 75% of this amount being supported by MCC, 16% coming from service/chargebacks, and only 9% coming from CCSG support. The budget is recommended as requested.

Collaborative Data Services Core

DESCRIPTION (provided by applicant): An important cancer research challenge is accessing substantial quantities of patient data collected while providing clinical care. At the last CCSG review, the reviewers encouraged the Moffitt Cancer Center (MCC) to develop a service facilitating member access to the data customarily collected on all cancer patients that is needed to conduct high-impact transdisciplinary research. As a result, in 2013, the MCC developed a core expressly designed to facilitate access to patient data, leveraging the MCC enterprise-wide Health Research Informatics (HRI) data warehouse with discretely captured patient-level data (e.g., patient questionnaires, cancer registry, electronic health records, billing, and the Tissue Core biospecimen archive) on over 475,000 MCC patients. This MCC initiative developed the Collaborative Data Services Core (CDSC), now a fully-functioning core. The CDSC is a unique shared resource that facilitates MCC member use of patient-reported clinical, tumor, and biospecimen data in support of innovative research across all research programs. The CDSC supports members with three primary services: consultation, data provisioning, and study-specific medical record abstraction. The specific aims that drive the CDSC are to:

1) Promote and facilitate cutting-edge translational research by providing members access to high-quality discrete patient-level data linked within MCC's enterprise-wide data warehouse and cost-efficient collection of clinical data from patient medical records;
2) Assist investigators at the early stages of developing research projects with consultations on study data access and project feasibility through provisioning of aggregate count data from the MCC HRI data warehouse;
3) Promote data access and data provisioning by providing individual or small group training, workshops, and data concierge training.

The CDSC is led by Scientific Director Erin Siegel, PhD, MPH, who has extensive experience conducting epidemiological studies utilizing the HRI resource. The CDSC is also supported by a Facility Director, a Core Manager, and six staff members. In fiscal year 2015, the CDSC fulfilled service requests for 79 members across all five CCSG programs, which represents 72% of the total usage; 47% of usage was in support of peer-review funded members. During the five-year project period, the CDSC has contributed to at least 102 peer-reviewed publications and 31 peer-reviewed funded grants. The CDSC provides unique data provisioning and manual data abstraction services integrated in a typical project workflow in collaboration with several shared resources, including the Tissue Core, Biostatistics Core, and Cancer Informatics Core; it provides members access to enterprise-wide patient data to conduct cutting-edge, high-impact translational and personalized medicine research.

CRITIQUE: The Collaborative Data Services Core (CDSC) was created in response to the prior review, in which MCC was encouraged to develop a service to facilitate member access to data customarily collected on all cancer patients. This core is designed to facilitate access to patient level data including patient questionnaires, cancer registry, electronic health records, billing, and the Tissue Core biospecimen archive of > 475,000 MCC patients, including close to 100,000 participating in the Total Cancer Care protocol. The aims are to: 1) promote and facilitate cutting-edge translational research; 2) assist investigators at the early stages of developing research projects; and 3) promote data access and data provisioning.

In FY 2015, the CDSC fulfilled service requests for 79 members across all 5 CCSG programs, representing 72% of total usage. The CDSC has provided services leading to at least 15 peer-reviewed grants, and has contributed to 31 peer-reviewed funded grants and 102 peer-reviewed publications.

The CDSC represents a monumental effort to capitalize on data available through the cancer registry, electronic medical records, and the Tissue Core to propel cancer research forward. This core, established in response to the prior review, received a substantial institutional commitment, and is complementary to the Total Cancer Care protocol.

The quality of services is very high and services provided are cost-effective. The core is highly accessible. Requests are prioritized for members with peer-reviewed grants, then members with non-peer-reviewed grants, then non-members.

The core has responded to member requests in establishing an abstracting system to curate information regarding disease recurrence and response to treatment.

As a leader in patient data collection and utilization for research, it would be ideal if MCC could consider new ways to input data at the point of care that could then be surveyed for research. No weaknesses were identified.

The CDSC Scientific Director, Erin Siegel, PhD, MPH, has extensive experience conducting epidemiological studies utilizing the HRI resource. He is highly qualified. The staff is also highly qualified and their time allotment is appropriate for the volume of service.

In summary, the CDSC represents a new generation of cores focused on providing data in a HIPAA compliant fashion for medical research. MCC has established this core in a short period of time, with considerable institutional commitment, and demonstrable benefit to members in terms of grants generated.

Assessment: Exceptional merit.

Budget: The budget is recommended as requested.

Flow Cytometry Core

DESCRIPTION (provided by applicant): The Flow Cytometry Core Facility (FCC) of the Moffitt Cancer Center (MCC) provides centralized and cutting-edge flow cytometry services for MCC members for their cancer-related research. Flow cytometry is an indispensable analytical tool for cell biology, immunology, and translational research efforts at MCC. The goals of the FCC are to support members with highly skilled staff and advanced flow cytometry technologies, which provide: 1a) Accurate measurements and analyses of multiple parameters at the single-cell level; 1b) The ability to rapidly purify target populations, to assess specific cellular functions, and to molecularly characterize purified cell populations; 2) Assistance in experimental design, data analysis and interpretation, as well as with the preparation of grants and manuscripts; and 3) Delivery of training and education in flow cytometry technologies and methodologies.

The Scientific Director of the FCC is Julie Djeu, PhD. The FCC is staffed with highly trained instrument specialists who have more than 40 years in combined experience in research-based flow cytometry. The facility is equipped with seven benchtop analyzers, two cell sorters, a multiplex bead array analyzer, and an automated bead sorter. The FCC has added new instrumentation and upgraded systems to expand its services to members and to provide access to modern flow cytometry technologies. The FCC employs the use of a Laboratory Information Management System (LIMS) to consolidate usage tracking, scheduling, and billing functions. The LIMS also provides a secure repository for project and data management, which is accessible by members and their laboratory staff. The FCC has contributed to 171 peer-reviewed publications during this review period compared with 112 the previous review period. In the most recent fiscal year, the FCC provided service for 53 members, with 89% of total usage for peer-review-funded members.

CRITIQUE: The Flow Cytometry Core (FCC) provides services to a large number of investigators and adds value to the overall research missions. Established in 1990, the facility is well-equipped and was consistently rated highly in prior reviews, with only a few minor concerns noted in the previous review. The facility provides service to all of the programs at MCC, with the heaviest users being members of IMM, CBE and CBMM. More than 50 members have been supported by the facility and this support has led to 171 peer-reviewed publications, an increase of 52%. The vast majority of the users are MCC members, 89% of which have peer-reviewed support. The resource provides a data directory for individual user secured storage directories. Usage is monitored by a laboratory information management system administered by the staff. The FCC has clearly described interactions with other shared resources.

Importantly, the FCC is accessible to all members at all hours, with on-site technical assistance during normal working hours. The rate structure and chargebacks are reasonable and provide an exceptional value to members. Fee-based training is provided to encourage independent use of the flow cytometry analyzers. Since the last site visit, much of the equipment has been upgraded and/or replaced in order to maintain state-of-the-art. Importantly, FCC is involved in new protocol development, supporting foundational/basic science and clinical flow cytometry needs. During the last funding period, new equipment was added, including the purchase of an ImageStream Mark II, which has both sorting and imaging capabilities, and of an iQUE screener plus, which permits sampling of very small volumes from 96 or 384 well plates. Overall, the FCC is providing a valuable service that enhances the transdisciplinary science of the MCC. The FCC also participates in the Southeast Shared Cytometry Interest Group, which includes other regional NCI-designated Cancer Centers. The purpose is to share findings and advances in cytometry based research.

One minor concern from the last review was that usage of the core relative to capacity was unclear. Chargebacks during the previous funding cycle constituted 89% of the operating cost. Future plans include the purchase in 2016 of a Fluidigm CyTOF Helios mass cytometer, which will be used to significantly increase capacity for performing high dimensional multiparametric analysis for biomarkers discovery, signal pathway analysis, and identification of cell subsets to address tumor heterogeneity.

The facility is directed by Julie Djeu, PhD, (5% effort requested), who has 40 years of experience in tumor immunology. She has directed the facility since its inception in 1997. Jodi Kroeger (20% effort requested) is the core facility manager responsible for daily oversight and management of the facility. Effort (5%) for Mr. John Robinson is also requested. Mr. Robinson assists Ms. Kroeger in the daily operations of the core. An experienced and capable oversight committee meets regularly and provides input, which is acted upon by MCC and FCC leadership.

Assessment: Exceptional merit.

Budget: The budget is recommended as requested.

Image Response Assessment Team

DESCRIPTION (provided by applicant): Radiology began as a discipline that specialized in the visualization of anatomy. In the context of cancer, modern technologies and innovations transformed imaging into a non-invasive tool that not only assesses solid tumor size and shape but also interrogates the spatial heterogeneity within tumors on the basis of their radiologic appearance, metabolism, and physiology. The overall goal of the Image Response Assessment Team (IRAT) Shared Resource is to enhance the scientific quality of clinical studies, by offering a single point of entry for Moffitt Cancer Center (MCC) members to access traditional and advanced quantitative image analysis services. To this end, efforts are organized around three Specific Aims, which are to: 1) maintain and improve the high reliability and fast turnaround times for RECIST (Response Evaluation Criteria in Solid Tumors)

and other standard tumor assessment metrics; 2) improve therapeutic trials at MCC by translating research advances in radiomics and multi-parameter MRI (mpMRI) analyses into turnkey imaging biomarker services; and 3) provide members with access to non-traditional imaging endpoints for therapeutic trials. IRAT consists of five full-time staff and provides quantitative image-based tumor metrics to support investigator-initiated, cooperative group, and industry-sponsored clinical trials at MCC, and is part of the national consortium of Cancer Center IRATs. IRAT has essential roles in the MCC mission “to contribute to the prevention and cure of cancer,” by providing the support and services necessary to integrate both traditional and innovative imaging endpoints into clinical trials and by providing quality assurance and control throughout the process to yield scientifically valid results. With rapid advances in treatment paradigms such as immunotherapies, IRAT provides improved imaging endpoints to meet the needs of these cutting-edge studies of MCC members. IRAT has witnessed sustained increases in the volume of quantitative image response assessment services provided. A total of 298 new trials requiring imaging response assessment were activated in FY11-15, rising from 39 in FY11 to 65 in FY15. Developing an infrastructure for IRAT has permitted the pursuit of other funded trial opportunities that use advanced and/or investigational imaging techniques, analyses, and novel biomarkers. For example, IRAT is supporting multiple grant applications and funded projects by members investigating radiomic and mpMRI imaging biomarkers in retrospective and prospective clinical and pre-clinical studies. During the past project period, IRAT served 34 members from 4 MCC Programs. Overall usage by members was 94%, with 63% of total usage supporting members with peer-reviewed funding. IRAT-supported studies resulted in a total of 62 peer-reviewed scientific publications during this period.

CRITIQUE: The Image Response Assessment Team (IRAT) shared resource provides quantitative image-based tumor metrics for the support of MCC investigator-initiated clinical trials as well as for cooperative group and industry based trials. This shared resource has provided support of trials that increased from 39 in FY 2011 to 65 in FY 2015, and has been used to advance investigational imaging techniques, analyses, and novel biomarkers. During the past project period this core provided support for 34 members from four of the MCC programs, with 63% of total usage supporting members with peer reviewed funding. In addition, IRAT-supported studies resulted in a total of 62 peer-reviewed scientific publications during this period.

Overall, this core is making very strong progress. It appears to have increased in overall size, number of investigators using the core, as well as the quality of the highlighted projects. The publications from the use of the core have been published in strong journals that are appropriate for the clinical based work that has been accomplished. It also appears that the core is continuing to drive imaging as part of the current and future direction of the clinical mission of the Cancer Center. The examples of the published data are outstanding and represent very strong examples of translational research. It also appears that the highlighted work is coming from multiple areas of the Cancer Center as well as from four of the five CCSG programs that clearly shows the interdisciplinary strength of this core.

New therapeutic trials are operationally reviewed by IRAT for imaging requirements. Investigator-initiated trials (IITs) and trials with advanced imaging endpoints are assigned an appropriate lead radiologist co-investigator from the Diagnostic, Interventional, or Nuclear Medicine Division. The lead radiologist and IRAT coordinator meet with the study investigator to discuss the protocol, review the source documentation requirements, and establish the workflow. Custom Tumor Measurement Worksheets (TMW) are then created and distributed to study coordinators by IRAT. To maintain the integrity of data flow, once the study is opened, IRAT tracks the workflow by study and by patient.

Radiomic and mpMRI imaging biomarkers are being developed by members under the Quantitative Imaging Network (QIN) funded by the NCI (U01 CA143062). To increase access to these advanced imaging biomarkers beyond the original QIN-funded studies, IRAT now offers these capabilities on a chargeback basis. IRAT has developed a workflow whereby radiologist-identified lesions are semi-automatically segmented and rendered in 3D, followed by calculation of a large number of pre-defined

radiomic and/or mpMRI features for each lesion, and then by generation of features reported from computed tomography (CT), positron emission tomography (PET)-CT, or mpMRI images. The data in the report can then be used to build quantitative predictive models for patient clinical outcomes.

IRAT offers Imaging Manual preparation, scanner validation methodology, and phantom manufacturing as required, for testing non-traditional imaging biomarkers of drug distribution, drug activity, target distribution, and/or tumor response, in clinical studies. IRAT offers custom software tools for quantitative analysis of CT, PET/PET-CT, and MRI (e.g., iron oxide nanoparticle enhanced, diffusion-weighted, dynamic contrast enhanced) images, in compliance with the FDA “Guidance on Computerized Systems Used in Clinical Trials.” Here, the primary focus of IRAT is to support and enhance American College of Radiology Imaging Network (ACRIN) and cooperative group trials. The core also established a collaborative agreement with Imaging Endpoints, LLC, to provide centralized quantitative image analysis services that support multisite pharma sponsored trials. Here IRAT’s goal is to leverage this relationship to increase opportunities at MCC for investigator-initiated clinical studies with non-standard or advanced imaging endpoints.

There were a few minor concerns from the last site visit including the absence of a radiation oncologist on the IRAT committee as well as work to assess radiotherapy response. In this regard, Jacob Scott, MD, PhD, was added to the committee. However, he is a Clinical Instructor in the Department of Radiation Oncology and was only added in the summer of 2015. In addition, the IRAT program does not appear to have made much progress in incorporating either Radiation Oncology or Radiation Oncology Departmental clinical trials into the program. Since most of the patients are newly diagnosed, this seems like a lost opportunity to monitor patient responses during therapy.

Dr. Raghunand was recruited to MCC in 2014 to be the new Director of Radiology Research and is an Associate Member in the Cancer Imaging & Metabolism Department and a member of the CBMM Program. He is also involved in the Clinical Research Action Committee, which monitors MCC’s clinical research activities. Dr. Raghunand has 41 peer-reviewed manuscripts in the validation of contrast agents and imaging methods and has been co-investigator on 11 investigator-initiated and pharma-sponsored clinical trials. He has served on a P50 *In vivo* Cellular and Molecular Imaging Center, SPORE, K-awards, R15 grant proposals, and NIH study sections. Dr. Outwater was recruited in November 2009 and is a Senior Member of the Department of Diagnostic Imaging & Interventional Radiology. He has over 100 manuscripts on imaging research and diagnostic imaging with his primary interest in gynecological and abdominal MRI. Overall, the leadership of this shared resource is outstanding with two very well established and experienced leaders with expertise in imaging as well as excellent publication records. In addition, the support staff is very knowledgeable.

In summary, the IRAT shared resource was well reviewed in the last site visit and it has clearly met the goals set forth five years ago and seems well placed to make additional advancements in the next five-year CCSG cycle.

Assessment: Outstanding merit.

Budget: The budget is recommended as requested.

Molecular Genomics Core

DESCRIPTION (provided by applicant): The overall goal of the Molecular Genomics Core (MGC) is to facilitate research at the Moffitt Cancer Center (MCC) by providing high-quality genomics services that are state-of-the-art, timely, and competitively priced. The MGC has three specific aims centered on education, consultations, and services. MGC’s sustainability model is based on promoting education in technological aspects of genomics, which builds interest in their use to answer specific scientific questions. The MGC then offers members free consultations to refine experimental design and to

support grant applications. These components lead to funded grant applications further driving demand. The MGC has three aims, to provide: 1) specific experimental design consultations to members; 2) high-quality molecular genomics services to members; and 3) high-quality genomics education to members.

The MGC comprises six full-time staff and provides the following services: whole exome and targeted DNA sequencing, mRNA and small RNA-Seq, ChIP-Seq, quantitative PCR, Sanger sequencing, cell line authentication, NanoString nCounter analysis, and microarray services including expression, single nucleotide polymorphisms (SNPs), copy number variants (CNV), and methylation arrays using a variety of platforms.

The MGC has a major impact on the MCC by developing and providing cutting-edge services to members with a focus on facilitating precision medicine to benefit patients. The MGC works closely with the TC and the CIC to provide seamless integration of sample acquisition, data generation, and analysis. The impact of the MGC is exemplified by the number of MGC-supported top-tier publications that include clinical and molecular data, such as Dr. Koomen's novel approach of massively parallel sequencing of the immunoglobulin variable regions in multiple myeloma patients (Remily-Wood, 2014) and Dr. Eric Padron's characterization of a chronic myelomonocytic leukemia cohort at the molecular level (Padron, 2014).

In response to the prior review, the MGC underwent a significant realignment of its aims to improve services for members and to incorporate new technologies such as targeted and exome sequencing, RNA- and ChIP-Seq, NanoString and cell line authentication. As a result, MGC revenues increased by 293% over the past funding cycle, and the MGC is heavily used by members from all five programs. During the most recent fiscal year, the MGC served 64 MCC members, with 88% of total utilization by peer-review-funded members.

CRITIQUE: The Molecular Genomics Core (MGC) is a critically important resource for MCC. There were multiple concerns with MGC at the last review cycle, which weighed heavily on the assessment of the core. There were concerns that the facility was underutilized and that it did not provide a sufficient expertise in technologies, such as Next Gen sequencing. There were additional concerns that the leadership of the core did not appreciate the need for complex bioinformatics analysis that is necessary to interpret these data in a meaningful way. Furthermore, the core did not have the capability of targeted hybrid capture, whole genome sequencing and RNASeq. Finally, concerns were raised that the CCSG request for support far exceeded what could be justified, considering the challenges that were identified.

MCC leadership has moved aggressively to respond to these concerns. Dr. Alvaro Monteiro was appointed as the new Core Director. He is a member of the Cancer Epidemiology Research Program and a senior member of the Cancer Epidemiology Department. He has extensive experience in the handling of complex data bases, large scale sequencing, and bioinformatics analysis and he is funded by several U-series awards from NCI.

As a result of the changes instituted, this resource now provides extensive expertise and technologies that facilitate a wide variety of genomic analyses. Capabilities include Massively parallel sequencing, Exome and Targeted DNA Sequencing, RNASeq, TCR (T-cell receptor) v-Beta Sequencing, ChIP-Seq, Mitochondrial DNA Sequencing, NanoString Analysis, Microarray Analysis, Cell Line authentication, Sanger sequencing and q-RT-PCR. The core provides staff training for cutting-edge approaches to genome science and the staff attendance to technology conference is sponsored by the core. There is also a journal club in which staff members participate to keep up with emerging technologies, single cell analysis, etc. There is a clear description of how this core integrates both vertically (with other shared resources) and horizontally (with other regional core facilities). As an example, genomic analysis of tissues involves timely extraction of tissues from the Tissue Core, processing in MGC, and handing off

data to the Cancer Informatics Core for analysis. Requests that are beyond the capabilities of the core are handled by guiding members to outside service centers and the core assists with negotiating agreements, tracking and shipping samples. Expert consultation in study design is provided free of charge, and there are efforts to provide up to date genomics educational opportunities to members.

The scientific highlights of work supported by the core is impressive and examples are cited from all five programs. These studies include developing targeted RNASeq to determine the type, isoform, sequence and gene expression levels in multiple myeloma patients, leading to the development of a quantitative proteomics assay that will be used for patient monitoring. Additional studies include identifying clinical relevant markers of EMT in early stage non-small cell lung cancer. These studies involved developing gene expression signatures from the Moffitt Total Cancer Care microarray data, and the core has then worked to replicate these signatures using custom Nanostring nCounter code sets. Importantly these studies have been done on both FFPE and frozen tissues for both retrospective and prospective studies. Studies have been completed, leading to the identification of key circulating miRNAs to stratify patients with intraductal papillary mucinous neoplasms who are at risk for developing pancreatic ductal carcinoma. Genomic analyses are also being used to predict transplant recipients who are at risk for developing GVHD. All of the studies listed in the application are supported by NCI or ACS peer-reviewed funding and they have all been published. Collectively, the core has supported over 90 peer-reviewed publications during the last funding period.

There is a well described management structure for the core. This is a rapidly moving technology and financially it makes sense for the core to outsource certain projects, which can be done more economically or efficiently elsewhere, and personnel work with members to make this determination. This can allow for the core staff to focus on developing/adapting more cutting-edge technological services. The core is tightly integrated with the Cancer Informatics Core, and the two shared resources work together on projects to optimize experimental design, discuss budgets and timelines. Data processing is handled by the Cancer Informatics Core via a shared network storage system and members are integrated into the communications. The core is indispensable to MCC and it is used by members of all five programs, the vast majority of usage is by members with peer reviewed funding. The core is largely supported by chargebacks (89%) and the request for CCSG support is 4% of the operating budget. As a result of the changes to the core, its revenues have substantially increased by 293% over the last funding period. Clear future plans for the upcoming funding period are discussed and include developing capabilities for single cell analysis, genome editing services, and improving the technology to measure circulating cell free DNA.

Assessment: Exceptional merit.

Budget: CCSG budget support is requested for the director (5%), a core facilities manager (20%) and 4 additional staff with varied responsibilities important for the successful operations of the core (at 10% for each individual). The budget is recommended as requested.

Proteomics Core

DESCRIPTION (provided by applicant): The Proteomics Core (PC) provides state-of-the-art protein chemistry services for Moffitt Cancer Center (MCC) members and cutting-edge analytical techniques to qualitatively and quantitatively assess protein expression, interactions, activity, mutations and post-translational modifications (PTMs). The core was established in 2003 and was scored “Outstanding” in the 2011 review. Experiments can be conducted with cell line and animal models as well as with patient specimens, including diverse tissue types and biofluids. The scope of these studies ranges from detailed molecular characterization of a single protein to proteome-wide profiling. The overall aims of the Proteomics Core are to: 1) consult and collaborate with members in the design and execution of proteomics experiments; 2) provide instrumentation and highly trained staff to support members; and 3) train members and their staff. The PC is comprised of four full-time staff and provides liquid

chromatography-tandem mass spectrometry (LC-MS/MS) peptide sequencing for discovery proteomics, and liquid chromatography-multiple reaction monitoring mass spectrometry (LC-MRM) for targeted quantification. Studies performed in the PC include those that examine protein-protein interactions (using immunoprecipitation or tandem affinity purification), drug targets (chemical proteomics), signaling (phosphoproteomics), proteome-wide acetylation or ubiquitination, sequential enrichment of PTMs, and the effects of different perturbations on selected proteins or the proteome (e.g., drug treatment, siRNA knockdown, CRISPR knockout). Further, the PC provides sample multiplexing using metabolic labeling (SILAC) or chemical labeling (iTRAQ/TMT) techniques for comparative proteomics. Finally, the PC uses an integrated pipeline of discovery proteomics to explore cancer biology and target quantification for highly precise biomarker measurements that can be translated from model systems into patient specimens. PC interactions with the Molecular Genomics Core (MGC) are necessary for combined proteogenomic analysis; and with the University of Florida South East Center for Integrated Metabolomics, to support proteometabolomics. Downstream interactions with the Biostatistics Core (BC) and the Cancer Informatics Core (CIC) contribute to understanding and evaluating the results of complex proteomics experiments. During the project period, the PC supported users across four and contributed to 47 publications, an increase from 15 publications in the 2006-2010 funding period. In the most recent fiscal year, the PC supported 26 members, with 90% of total usage by peer-review-funded members. Using financial support provided by the CCSG and Institutional funds, the PC continues to provide state-of-the-art equipment, technologies, and services to meet the current and future needs of MCC members.

CRITIQUE: The Proteomics Core (PC) has the mission of providing state-of-the-art technologies to quantify tumor associated changes in protein expression, identification of proteins complexes, and post-translational modifications of proteins. The technologies utilized by this core are rapidly evolving and the core is critically important for defining the complete “omics” landscape of tumors. The mission of the core is encompassed by three specific aims, which include providing expertise to members in the design and use of proteomic approaches, providing proteomic services to members, and training and educating MCC members in proteomics. Proteomic services include molecular characterization of proteins and protein complexes, proteome wide analysis of expression, activity and post-translational modifications and targeted quantification in cancer biology, therapeutic response and biomarker development. Major services include sample preparations of proteins and peptides, and Mass Spectrometry analysis for protein identification, including MALDI-MS, LC-MALDI, LC-MA/MS, PTM analysis and quantification and LC-MRM for targeted peptide detection. Proteome wide services using SILAC or iTRAQ/TMT approaches are also provided. The core provides peptide synthesis, which includes synthesis of affinity purification baits, peptide based therapeutics or antigens for antibody development. Finally, the core collaborates with the South East Center for Integrative Metabolomics (SECIM) at the University of Florida for discovery metabolomics services. The core currently has 6 mass spectrometers, 3 of which are new since the last review, for discovery and targeted proteomics and 12-channel peptide synthesizers.

The activities of the proteomics core are integrated with multiple cores to facilitate informatics analysis of complex data, proteomic analysis of tissue samples and integrating information with molecular genomics, flow cytometry and metabolomics. The core provides centralized access to equipment that would not otherwise be available to members with cancer related projects. The core has supported 47 publications in the last 5 years, which is an impressive 300% increase since the last review cycle. The core is located in 2000 sq. ft. of space in the Moffitt Research Building. Site licensed software, including Proteome Discoverer, Sequest and Mascot databases search engines are available for members’ use. Additional software packages are being developed and made available to the MCC members. The core is managed by a Shared Resource Advisory Committee, which has contributed to focus and development of new core capabilities during the previous funding period. The core provides services for 4 of the 5 programs and 92% of operating costs are supported by the MCC and charge-backs for services. A clear plan for prioritizing member access is included.

During the last funding period, the core has provided key support for multiple projects, which focused on the molecular characterization of proteins and protein complexes, identification of cancer therapeutic targets using chemical proteomics and phosphoproteomics. Several studies in targeted quantification in cancer biology and biomarker development were also supported, including work correlating protein biomarkers in melanoma cell lines, mouse xenografts and clinical trials using frozen tissue specimens. This work was supported by a P50 SPORE in skin cancer.

There is an ambitious agenda described for future development in the next funding cycle. This includes further collaborating with UF-SECIM for developing activity based proteomics developing capabilities in metabolomics, lipidomics and proteometabolomics. Three funded projects are currently being supported. Additional plans are in place for instituting flow cytometry-mass spectrometry for immunoproteomics for characterizing critical immune cell surface ligand and receptor triggered signaling pathways. The development of CLIA approved biomarkers and imaging will be done in collaboration with the CLIA development laboratory. There are plans for developing the capability of sequential enrichment of post-translational modified/glycosylated proteins and collaborating with the Molecular Genomics Core to integrate genomics data with proteomics data - this will require extensive interactions with the Biostatistics Core and the Cancer Informatics Core.

While these are laudable goals, they are extremely ambitious in scope. At the site visit clarifications were requested on how these plans were developed. On the one hand a general mechanism was discussed, however in other cases (plans to develop lipidomics, metabolomics and proteometabolomics) it was less clear. There is also significant interaction with the Molecular Genomics Core so as to provide “proteogenomics” analyses, and interaction with the Biostatistics and Cancer Informatics Cores for the purposes of data analyses. Less clear is what mechanism is used by the Proteomics Core, the Molecular Genomics Core, and the Cancer Informatics Core.

The core is led by Dr. John Koomen, who is a member of the Chemical Biology and Molecular Medicine Program. He has been working on biological mass spectrometry for the last 19 years with an interest in the mechanisms of human disease. He is a tenured Associate Member of the Molecular Oncology Department and he is NCI funded. Staffing includes a core facility manager, two research specialists and a staff scientist who is being recruited to fill a recent vacancy. The core is managed centrally by the Department of Laboratory Research Operations.

Assessment: Outstanding merit.

Budget: Support is requested for the core director (5%), the core facility manager (20%), and three supporting staff each at 10%. The budget is recommended as requested.

Small Animal Imaging Lab Core

DESCRIPTION (provided by applicant): The goal of the Small Animal Imaging Lab (SAIL) Core Facility is to provide state-of-the art imaging resources to Moffitt Cancer Center (MCC) members for their basic and translational preclinical studies of rodent cancer models. The SAIL has expanded its services to offer a wide array of multimodality imaging, including MRI, hyperpolarized MRI, CT, PET, SPECT, beta particle, ultrasound, bioluminescence, and fluorescence imaging. These systems allow members to follow tumor development, progression, metastasis and the response to therapy in animal models using quantitative imaging. SAIL provides detection at high spatial resolution of a number of functional, metabolic and anatomical changes, including hypoxia, pH, temporal sensitivity to cellular density, blood flow, and glucose uptake and metabolism. These parameters can be quantified using SAIL’s expertise in image feature extraction and analysis to generate an integrated analysis of tumor biology *in situ*.

Animal tumor models are critical for understanding the biology of cancer and the complex responses of distinct tumor types to therapy. Imaging of these animal subjects is a core technology that can precisely

define cancer behaviors. Further, as most of these modalities provided by the SAIL are available in the clinic, results with animal tumor models can be readily translated into clinical trials and clinical practice. Multimodality imaging is the key focus of the facility as this provides a broad range of technologies that assist members with their basic and pre-clinical research programs. Over the next funding period, the Specific Aims of the SAIL Core are to:

Aim 1. Assist members in experimental design, interpretation of results, and manuscript and grant preparation.
Aim 2. Provide and expand *in vivo* and ex vivo imaging and analytical technologies for research involving small animal cancer models.
Aim 3. Provide training and educational opportunities regarding small animal imaging technologies and approaches for members.

During the previous award period, SAIL served members from three programs and contributed to 45 publications. In the most recent fiscal year, SAIL served 21 members, with 87% of total usage by peer-review-funded members. The SAIL uses a Laboratory Information Management System (LIMS) to consolidate usage tracking, scheduling, and billing functions. The LIMS also provides a secure repository for project and data management, which is accessible by members and their laboratory staff.

CRITIQUE: The goal of the Small Animal Imaging Lab (SAIL) core facility is to provide state-of-the-art imaging resources for MCC members for their basic and translational preclinical studies in rodent cancer models. Imaging resources include MRI, hyperpolarized MRI, CT, PET, SPECT, beta particle, ultrasound and biophotonic imaging. The goals of the SAIL are to assist with experimental design and results interpretation, to provide and expand imaging technologies for cancer models and provide training and educational opportunities for MCC members.

The importance of this resource is evidenced by its usage and in the past year 87% of the usage was from peer-reviewed members. The SAIL uses a laboratory information management system (LIMS) to consolidate usage, tracking, scheduling and billing. It also provides a secure repository for project and data management. Since the previous review, additional PhD investigators have been added as well as new equipment. SAIL offers a full spectrum of anatomic, functional and metabolic imaging.

Very good strategic alliances with other cores are in place with workflow integration provided through the LIMS. The umbrella IACUC protocol is a key strength and advantage to promote pilot studies. Having the imaging core within the animal vivarium is a key advantage. A commercial DNP system (hyperpolarized MRI) has been newly installed. This makes possible the imaging of metabolites in real time. A new Bruker 7T system has been purchased that includes state-of-the-art upgrades to further strengthen their equipment portfolio.

However, it is not entirely clear how image data analysis is handled. Reliance on collaboration rather than a “fee for service” model could be limiting if interest in or time for a collaborative relationship does not exist.

In summary, the MCC SAIL resource was established in 2009. It has already become an extensive and important resource for MCC that is accessible to the membership. The infrastructure, staff and services are very strong. Example experimental results nicely demonstrate the strength of the core as well as the significance of the science being undertaken. A minor weakness is that details regarding the service provided and actual prices charged are not adequately provided. For example, it is not clear how non-imaging scientists evaluate their data, or if they are trained or pay the SAIL staff for analysis services. This can be an important limitation for expanding and maintaining the user base and interest in using the imaging services.

Dr. Gillies is well known and highly respected in the area of cancer imaging. He brings a wealth of experience and success to this core. Dr. Gillies has gathered a high caliber staff with complementary experience and roles in support of animal handling and imaging.

Assessment: Exceptional to Outstanding merit.

Budget: While the CCSG currently provides funds for 11% of the SAIL budget, they are requesting a small increase for CCSG funds to cover 15% of the budget. This includes a small percentage of support for the PI and staff. The budget is recommended as requested.

Survey Methods Core

DESCRIPTION (provided by applicant): The goal of the Survey Methods Core (SMC) is to assist Moffitt Cancer Center (MCC) members with survey research design, implementation, and execution. The SMC aims to: 1) consult with potential users on selection and implementation of existing survey tools and/or design of new applications and approaches; 2) support members by providing high-quality survey-related services utilizing scannable and web-based applications; and 3) educate and train investigators and staff on qualitative research methods and resource tools.

The SMC consists of two full-time and one part-time bilingual (Spanish/English) staff members. The SMC assists with all phases of the survey process, including testing recall, comprehension, and alternative wording for survey instruments; assessing various interviewing techniques and respondent incentives; and comparing data collection modalities. The SMC provides expertise in the selection of published measures and tools and development of new, study-specific measures. In addition, it provides training and assistance in all aspects of cognitive interviewing, including focus groups, individual interviews, think-aloud sessions, and other methods used to study respondent and interviewer reactions to survey questions, response categories, and procedures. Training in data collection and analysis are offered twice a year to MCC as a whole and individually as needed to members and their staff on a project-specific basis. The SMC provides expertise in the production of survey forms and their electronic processing once completed by respondents, including data capture by conducting telephone interviews and using an SMC-designed web-based survey as the method of entry. Users receive verified raw data tables in a form suitable for statistical analysis, often conducted by the Biostatistics Core.

SMC services add value and affect cancer care delivery, quality of life, prevention, detection, and health disparities research through access to cognitive interviewing techniques to ensure that novel survey questions can be completed as intended. Utilization of participant self-reported information in a valid and reliable manner is improved through consultation and pre-testing. Efficiency in data collection is increased through the use of scannable forms and web-based surveys. This is particularly beneficial for large-scale studies or studies that administer surveys at multiple sites, to have the process streamlined and standardized for data collection. The SMC employs the use of a Laboratory Information Management System (LIMS) to consolidate usage tracking, scheduling, and billing functions. The LIMS also provides a secure repository for project and data management, which is accessible by members and their laboratory staff. During the prior award period, the SMC assisted 47 users from all five Programs and supported 65 peer-reviewed publications. In the last fiscal year, the SMC provided service for 19 members, with 86% of total usage by peer-review-funded members.

CRITIQUE: The Survey Methods Core (SMC) is a heavily used resource for MCC members that provides services aimed at the conduct of survey research. It provides consultation, survey forms and survey development, study design, sampling and data collection. Collected data forms can be transformed into a format that is easily transferred into data for analysis. In addition, SMC personnel can assist with the setup of focus groups and interviews.

This is a very heavily used shared resource for one of its type with 47 users and has been used across all 5 programs of the Cancer Center. For all of this, it has 1 leader at 10% of time and 30% in 2 other personnel, a truly cost-effective shared resource. Over 80% of its fees stem from non-CCSG paybacks. Nonetheless, it has contributed to 65 papers and multiple grants.

The Director, Dr. Quinn Gwendolyn, is a member of the HOB Program and an expert in the use of survey methods in cancer research, including focus group methodologies, qualitative research methods and mixed methods research. Her expertise in qualitative research is a strength. The SMC employs two full-time staff members and one half-time bilingual staff member. The qualifications of staff are outstanding, and the time commitment is appropriate.

Assessment: Exceptional merit

Budget: The budget is recommended as requested.

Tissue Core

DESCRIPTION (provided by applicant): The Tissue Core (TC) serves as the central biorepository for Moffitt Cancer Center (MCC). Opened in 1992, the overall goal of the TC is to collect, process, store, and release high-quality, well-annotated biospecimens in support of basic, population, clinical, and translational research. TC biobanking activities at MCC have three foremost specific aims:

1. Serve as a centralized MCC biobanking resource for the collection, processing, and storage of human biospecimens in support of member science;
2. Implement biorepository best practices and quality metrics that ensure members' access to high quality biospecimens;
3. Develop and promote policies, guidelines, and procedures that facilitate members' efficient access to human biospecimens in a regulatory-compliant manner.

The TC is housed in a 2,800 square foot facility and staffed by 20 highly trained Biorepository Specialists, Staff Scientists, a Research Pathologist, and a Manager that collectively support investigator-driven studies and the general banking operations. TC services are housed within three distinct sections: Intake & Acquisition, Sample Processing Lab, and Research Histology Services. Collectively, the three sections provided support for 206 protocols during fiscal year 2015 (FY15). The TC provides a wide variety of services such as collection of fresh frozen tissue, general histology, immunohistochemistry, nucleic acid extraction, construction of tissue microarrays (TMA), and release of archived biospecimens. Moreover, in support of investigator-driven studies, the TC incorporates specific needs and applications into project-specific SOPs, which often include contributing to the study design and collection strategies to optimize biospecimen handling. Overall, the TC offers 81 distinct biobanking and biospecimen-related services that meet or exceed NCI best practice recommendations and College of American Pathologists (CAP) Biorepository Accreditation standards to ensure high-quality biospecimen collection and processing validated through standardization, documentation, and emphasis on quality management. In addition to contributing to 173 publications during the past five years, the TC's high-quality biobanking infrastructure was instrumental in MCC's successful Lung SPORE, Skin SPORE, BMaP-3, TCGA, and CPTAC submissions. During the prior period, the TC provided significant support to members, demonstrated by a yearly average of nearly 73,000 service units, with FY15 representing a record year of usage with 85,708 service units. In FY15, TC services were utilized by 86 members distributed across all five CCSG programs, with 78% of total usage by peer-review-funded members.

CRITIQUE: The Tissue Core (TC) is the central biorepository for MCC, supporting investigator-initiated studies as well as general tissue banking operations. The three specific aims are to: 1) serve as a centralized biobanking resource; 2) implement biorepository best practices and quality metrics; and 3) develop and promote policies, guidelines, and procedures that facilitate access to biospecimens in a

regulatory-compliant manner. The major services are: 1) tissue intake & acquisition; 2) tissue sample processing (including nucleic acid extraction); and 3) research histology services (including IHC and tissue microarray construction). The TC is housed in a 2,800 square foot facility and staffed by 20 individuals, including biorepository specialists, staff scientists, one research pathologist, and one manger. The TC provided an average of 73,000 service units per year. TC services were utilized by 86 members across all 5 research program areas, with 78% of total usage by peer-review-funded members.

This core supports the Total Cancer Care protocol, which provides members access to solid tumor tissue, matched biospecimens (blood, normal tissue), and associated clinical data. This is an ambitious endeavor, requiring extensive infrastructure. An absolute strength of the TC is its ability to coordinate tissue sample collection, processing, and retrieval using rigorous standards. The TC is to be lauded for attaining College of American Pathologists Biorepository Accreditation.

The TC has been productive in terms of service units, support of team science grants, and associated publications. Their services are accessible, of high quality, and provided in a cost-efficient manner to members.

In summary, the TC serves as the foundation for MCC initiatives such as the Total Cancer Care protocol, and plays a vital role in team science awards. The status of the TC is elevated by its development of SOPs that result in reliable cost-effective service.

The key personnel are experienced, and the Scientific Director (Anthony Magliocco, MD) is a leader in his field.

Assessment: Exceptional merit.

Budget: The budget is recommended as requested.

CLINICAL PROTOCOL & DATA MANAGEMENT (CPDM)/CLINICAL TRIALS OFFICE & DATA AND SAFETY MONITORING

Clinical Protocol and Data Management

DESCRIPTION (provided by applicant): Clinical Protocol & Data Management (CPDM) functions at Moffitt Cancer Center (MCC) include 1) trial design, development, and conduct; 2) oversight of safety and compliance; 3) ensuring data quality and education of personnel; and 4) appropriate accrual of women and minorities. A collaborative team of approximately 190 CPDM professionals provides centralized management and support of all types of clinical trials, including investigator-initiated (IITs), industry or other sponsor-initiated, Experimental Therapeutics Clinical Trials Network (ET-CTN), and National Clinical Trials Network (NCTN). CPDM support for members includes: protocol development; budget development and contracting; regulatory and IND/IDE management; protocol activation; patient enrollment; coordination of study-related patient care; research drug administration and care services; correlative science (pharmacokinetics/pharmacodynamics) sample coordination; data collection and reporting; monitoring of IIT studies and data and safety monitoring through the Protocol Monitoring Committee (PMC) and Data Safety & Monitoring (DSM) Committee; audit preparation and coordination; minority outreach and navigation for accrual to clinical trials; clinical trials management system (CTMS, OnCore) administration and reporting; staff workload management; and staff education and training.

During the review period (FY2011-2015), the CPDM team successfully accrued and coordinated a combined total of 11,851 patients to clinical interventional trials (therapeutic, prevention, and supportive care), including accrual at affiliate sites.

CPDM provides centralized safety and compliance oversight to members through timely monitoring of investigator-initiated interventional trials, coordination of the PMC, and corporate compliance audits of MCC clinical research trials, policies, and processes. Results of monitoring and audits are utilized by the PMC for comprehensive review.

MCC has developed and maintains proactive efforts to provide programs and services to women, minorities, and other underserved populations through culturally and linguistically relevant care, education, and internal and community outreach. Faculty members conduct research on minority health disparities, informing these programs and services. In addition, the ACD for Clinical Science and the VP of Diversity and Community Relations co-lead a multi-disciplinary Minority Clinical Research Committee to address issues related to minority accrual at MCC. CPDM resources are closely integrated in these efforts.

CRITIQUE: Clinical Protocol & Data Management (CPDM) provides: 1) assistance and oversight of trial design, development, and conduct; 2) oversight of safety and compliance; 3) ensures data quality and education of personnel; and 4) appropriate accrual of women and minorities.

In the prior review the resource was rated as Outstanding. The primary concern was that the prioritization of resource allocation should be better defined. In response, MCC created a CPDM Resource Float Pool and developed a protocol acuity/workload tool to facilitate CTO resource allocation to the various disease-based programs. The “Pool” covers staff vacancies to reduce gaps in staff coverage and keep studies on track.

The CPDM team includes 190 CPDM professionals that provide centralized management and support of clinical trials. Clinical trials include investigator-initiated trials (IITs), industry-sponsored trials, Experimental Therapeutics Clinical Trials Network (ET-CTN), and National Clinical Trials Network (NCTN). The CPDM provides support for the MCC members and trials. There is a wide range of services that includes protocol development, contracting/budget development, IND/IDE management, protocol activation, patient enrollment, coordination of study-related patient care, research drug administration and care services, correlative science (pharmacokinetics/ pharmacodynamics) sample coordination, and data collection and reporting.

The CPDM team also provides data and safety monitoring through the Protocol Monitoring Committee (PMC) and Data Safety & Monitoring (DSM) Committee and audit preparation and coordination. It facilitates minority outreach and navigation for accrual to clinical trials. It also provides clinical trials management system (CTMS, OnCore) administration and reporting, staff workload management, and staff education and training.

During the review period (FY 2011-2015), the CPDM team successfully accrued and coordinated a combined total of 11,851 patients to clinical interventional trials (therapeutic, prevention, and supportive care), including accrual at affiliate sites.

MCC has developed and maintains proactive efforts to provide programs and services to women, minorities, and other underserved populations through culturally and linguistically relevant care, education, and internal and community outreach. Faculty members conduct research on minority health disparities, informing these programs and services. In addition, the ACD for Clinical Science and the VP of Diversity and Community Relations co-lead a multi-disciplinary Minority Clinical Research Committee to address issues related to minority accrual at MCC. CPDM resources are closely integrated in these efforts.

CPDM provides effective management and reporting on Cancer Center clinical trials. It effectively oversees safety and compliance oversight and provides timely monitoring of investigator-initiated interventional trials.

The average timeline for SRC submission to IRB approval for IIT interventional studies improved from 193 days in FY 2011 to 85 days in FY 2015.

The CPDM provides effective qualify control. It is effective in providing compliance audits of MCC clinical research trials, reviewing and monitoring policies, and processes. Results of monitoring and audits are utilized by the PMC for comprehensive review. The CPDM provides staff education and training.

The resource supports over 11,851 subjects accrued to clinical trials. Trials range from low to high complexity. Accrual is reasonable based on the number/type of clinical trials supported. Importantly the core also facilitates minority outreach and navigation for accrual to clinical trials.

In summary, this is an effective well-run CPDM that supports a large number of clinical trials. There is timely review of clinical trials and the average timeline for SRC submission to IRB approval for IIT interventional studies improved from 193 days in FY 2011 to 85 days in FY 2015. The CPDM is strong in its training initiatives and efforts to include underrepresented groups in clinical trials. However, there is a reduction in the total accrual of patients on to interventional clinical trials over the past 5 years and drop in external peer-reviewed clinical trials.

Personnel: The Interim CPDM Medical Director for CRS is Dr. Dan Sullivan. He is also an important member of the MCC Senior Leadership, where he serves as Associate Director of Clinical Science. He is an exceptionally well-qualified and experienced clinical investigator and certainly has the credentials to serve in this capacity. However, he also oversees the entire PRMS, and so it would appear that he is overcommitted in terms of his responsibilities. Thus, concerns exist as to whether Dr. Sullivan can effectively oversee CPDM and PRMS, which represent large and significant clinical research oversight functions. The overcommitment and multiple roles of Dr. Sullivan had been raised at the time of the previous CCSG review; this issue was not entirely resolved through the written document or at the site visit. Moving forward, the MCC Director and Senior Leadership must have Dr. Sullivan immediately focus his time on only one of these roles. Dr. Richard Lush is the Director of the CPDM Protocol Review and Regulatory Affairs. He has the appropriate research background for this position. However, as with Dr. Sullivan, Dr. Lush also plays an important role in the oversight of PRMS. It would seem more appropriate for Dr. Lush to focus on only one of these clinical research functions CPDM or PRMS, but not both. A CPDM Medical Director position has been developed and is under active recruitment. This future recruitment will reduce Dr. Sullivan's overall commitments, while providing appropriate separation between CPDM and PRMS.

Assessment: Outstanding merit.

Budget: The budget is recommended as requested.

Data and Safety Monitoring

CRITIQUE: The MCC Data and Safety Monitoring Plan first received NCI approval in 2002, and it has been continuously updated to ensure the coordinated oversight of clinical research being conducted at MCC. The most recent MCC DSMP was approved by the NCI on May 2, 2016 and was available for review at the site visit.

The Associate Director of Clinical Science, Dr. Dan Sullivan, has overall responsibility for data and safety monitoring at MCC, and the Protocol and Monitoring Committee (PMC) is the MCC's review and oversight committee for these efforts. The PMC is chaired by Dr. Mayer Fishman and the other members of the PMC include Vice-chair Dr. Richard Kim and clinical investigators representing the various oncology disciplines, as well as a clinical pharmacist and a biostatistician. There is no senior-

level, seasoned clinical investigator on the PMC who would have the appropriate level of clinical research expertise with respect to data and safety monitoring, and the MCC Director and Senior Leadership should consider placing such a senior clinical investigator on this important oversight committee.

The PMC has a separate and distinct function from the PRMS, SRC, and IRB, and its main goals are to: (1) assess safety by reviewing serious adverse event reports (SAEs) and deviation reports from investigator-initiated clinical studies and to monitor their timely and appropriate reporting to the respective oversight agencies (IRB, FDA, or NCI), (2) review audits of investigator-initiated clinical trials, (3) review interim data and safety reports from investigator-initiated studies, and (4) review the interim and final reports from the external Data Safety and Monitoring Board. The PMC has the authority to approve, recommend changes to the protocol, suspend, or close a study based on the SAEs and deviation reports that are reviewed monthly.

Since the previous CCSG review, two significant changes have been made to the monitoring and oversight function of clinical research within the MCC. The first was an expansion of the monitoring activities and the hiring of a dedicated manager to oversee this important function. MCC has significantly increased the number of internal monitors from 2 to 5 (4 licensed staff members and 1 BS-trained staff member). This monitoring group reviews all investigator-initiated clinical studies to ensure that the appropriate monitoring plan language is included in each protocol, to ensure that the protocol requirements are clearly written and no inconsistencies are present within the protocol document, to ensure that patient eligibility is documented within the medical record, and to monitor on-going interventional studies as required in the DSMP. In addition to this expansion of the internal monitoring staff, MCC has made the important investment to hire staff focused on quality assurance (2 FTE's) and training and education (3 FTE's).

No metrics were included in the application as to the number of audits reviewed, SAEs and deviations reports reviewed by the MCC DSMC in 2015 nor were any metrics given as to corrective actions or recommendations for trial suspension and/or termination. At the site visit, a summary of activity of the DSMC was provided. In FY 2015, a total of 69 investigator-initiated studies were open, and there was a review of 438 SAEs, 413 deviations, and 39 audits. Of the 39 audits, 31 were found to be acceptable and another 8 were deemed to be acceptable with corrective action.

Assessment: Acceptable.

Budget: Support is requested for the CRC Chair (1.8 calendar months) and for the CRC coordinator (3.96 calendar months). The budget is recommended as requested.

Inclusion of Women in Clinical Research: The catchment area comprises 47% women. The data provided indicate that the number of females enrolled onto interventional trials is 52.9% and 44% on treatment trials. The Center has adequate representation of women. Furthermore, plans were presented to increase accrual by opening breast cancer trials.

Assessment: Approval.

Inclusion of Minorities in Clinical Research: The MCC is committed to inclusion of all patients and has developed and maintained many proactive efforts to provide programs and services to minorities and other underserved populations. A Minority Clinical Research Committee was organized in 2010 and meets every other month. It is currently comprised of four working groups: Education and Navigation, Clinical Research, External Collaborations and Catchment Area Research.

The MCC is to be commended for the efforts to improve the inclusion of minorities in research. Since the last submission of the CCSG, the accrual of African American patients to intervention trials, for

example, has increased to 8.0% in FY 2015 (compared to 3.6% in FY 2009). The MCC has developed a robust set of activities aimed at increasing participation including study subject navigators, community outreach, establishment of satellite sites, and targeted physician recruitment. Additionally, plans for future activities are impressive and include mandatory diversity training, further outreach by partnering with area hospitals, and assistance in transportation.

Accrual to studies and treatment numbers appear to be appropriate for the MCC patient population and there is continuing effort to match the catchment area cancer population. One area of minor weakness is the lack of specificity regarding how problems with accrual identified in the middle of enrollment are handled. This question was posed during the site visit but specific practical steps were not shared.

Assessment: Approval.

Inclusion of Children in Clinical Research: In general, treatment of childhood cancer is not done at Moffitt. They have a clinical affiliation with a nearby pediatric specialty hospital, All Children's Hospital in St. Petersburg, where they refer children for treatment and perform collaborative projects. An example of a collaborative project is funding a vaccine trial in pediatric patients that are post-BMT in neuroblastoma.

Assessment: Approval.

PROTOCOL REVIEW AND MONITORING SYSTEM

DESCRIPTION (provided by applicant): The MCC Protocol Review & Monitoring System (PRMS) provides internal oversight of the scientific aspects of all clinical trials. This includes full authority for opening, closing, and determining appropriate prioritization of all studies. To conduct PRMS processes, MCC utilizes four Scientific Review Committees (SRCs) supported by staff coordinators. The PRMS has processed more than 500 protocols for initial review over the past three years. The average time from submission to full board review is approximately 20 days. Committee coordinators review the materials submitted for completeness and work with the study team to acquire any additional information needed for the scientific review process. Upon review of the complete information package (protocol, investigational brochure, and surveys), the coordinator evaluates the protocol to determine if it qualifies for expedited review or requires a full SRC board review. If the coordinator believes the study qualifies for expedited review (e.g., NCI, NCTN, or ETCTN), the coordinator routes the study for confirmation and approval. If the study requires a full board review, the coordinator will schedule the study on the next available open agenda. The four SRCs have meetings scheduled throughout the month to ensure a timely review. The PRMS also reviews all amendments to studies. Amendments that change study objectives, outcome measures or the study population, and other major changes are sent to full SRC board for review. The PRMS processed over 500 amendments to studies in FY15 with 100 requiring a full SRC board review. The PRMS is also responsible for monitoring the scientific progress of all MCC studies. Studies are monitored at each six-month anniversary of their activation date. Those studies that significantly fall below their anticipated accrual rate are flagged for discussion at the full SRC board. At that time, the board reviews the progress of the study and also the explanation and corrective action plan from the PI to determine if the study is likely to meet its accrual goal. If the SRC determines the study will not meet the accrual goal or is no longer scientifically important, then the study is closed by the SRC.

The specific aims of the PRMS are as follows:
- Aim 1: Establish and maintain a review committee of sufficient size and breadth of expertise to conduct a critical and fair scientific review of cancer-related research protocols involving human subjects
- Aim 2: Conduct a thorough scientific review of all cancer-related clinical protocols conducted at the MCC based on specific, pre-determined review criteria

- Aim 3: Prioritize all MCC clinical trials
- Aim 4: Monitor scientific progress for ongoing clinical trials

CRITIQUE: The MCC has established and implemented the Protocol Review and Monitoring System (PRMS), which provides oversight of the scientific quality of all cancer-related clinical trials. The goals of the PRMS are accomplished by the four Scientific Review Committees (SRC), and the MCC PRMS has the full authority for determining the appropriate prioritization, opening, and closure of all clinical studies being conducted at MCC. At the time of the previous CCSG review in 2011, the PRMS was approved as it had all of the appropriate policies, procedures, and staff in place. However, the site visit team recommended that continued focus was required in 3 main areas: (1) increased rigor in monitoring and closing poorly accruing trials, (2) establishing clear metrics for time to protocol activation and review to ensure compliance with the new OEWG guidelines, and (3) overcommitment of Dr. Dan Sullivan, who was overseeing both the Clinical Research Services and the PRMS.

The SRC provides a comprehensive review of the protocol with detailed criteria for approval and disapproval. In the application, it is stated that the review process begins with the appropriate disease groups and that each trial must be approved and prioritized by the appropriate working group prior to submission to the SRC. There are well-defined criteria for prioritization of clinical trials within the MCC. The highest level of priority is for external peer-reviewed institutional studies, followed by non peer-reviewed institutional investigator-initiated studies, followed by NCTN cooperative group studies, with industry-sponsored studies having the lowest priority. In 2015, a new protocol feasibility process was implemented within the Phase 1 working group to provide a detailed assessment by the disease team's initial study review. This process is now being expanded to include all of the disease teams within MCC during the next funding period.

Each SRC consists of a Chair, Vice-chair, and up to 11 to 13 other voting members with expertise in disciplines including medical oncology, surgical oncology, radiation oncology, hematology, pharmacy, and biostatistics. The membership of the committee is diverse, and appears to have appropriate representation from the various oncology disciplines. Members of the Clinical 1 and 2 SRCs represent medical oncology, surgical oncology, radiation oncology, pharmacy, biostatistics, while the members of the Tissue & Data SRC represent medical oncology, epidemiology, biology, biorepository and biostatistics. Members of the Behavioral SRC represent behavioral science, psychology, and biostatistics. Importantly, each committee includes two biostatisticians to ensure that at least one is present at the discussion in case of a conflict of interest. In further review of the clinical research committee rosters, an additional concern relates to the relatively small number of senior, seasoned clinical investigators. In addition, the 2 SRCs that review clinical research protocols do not include a basic scientist, diagnostic radiologist, and pathologist on the standing committee, which raises concerns that these two committees do not have sufficient breadth of scientific expertise. At the very least, these individuals should be available to review clinical trials on an *ad hoc* process, and Dr. Sullivan confirmed at the site visit that investigators with expertise that is not represented on the committees are asked to review specific protocols on an *ad hoc* basis. Ideally, however, these individuals should be permanent members of the 2 clinical research SRCs, especially given the focus on investigator-initiated clinical studies with translational correlative science. As stated in the application, a quorum consists of 4 voting members and one statistician with approval by a majority vote. A serious concern with such a small number of members required to be at each meeting is whether this would allow for an appropriate level of in-depth discussion of the clinical protocols. It would seem that at least 50% of each SRC committee should be present for these meetings.

In calendar year 2015, the SRC reviewed 331 new studies. The distribution of these protocols was as follows: 21 Cooperative Group, 29 External Peer-Reviewed, 97 Industry, and 184 Institutional. An additional 132 clinical trials underwent expedited review. Of the 199 clinical trials undergoing full scientific review, 181 were approved without revisions, 108 were approved with minor revisions, and 36 were tabled for significant alterations.

Several important issues were identified in review of the clinical binders that were provided with this application. Overall, the binders that were provided for review by the CCSG site visit team were not well organized, and greater attention to detail should be taken to organize them in such a way so as to facilitate review. None of the binders included a disease-specific form to identify the priority level of the proposed protocol within the given disease team nor was their sign-off from the disease team leader. The binders were also not complete. For example, in protocol MCC17651, only one review was included and no statistical review for this study was included in the documents. The other studies that were reviewed were external NCI peer-reviewed studies. Even with these studies, their relative prioritization needs to be reviewed and discussed within the specific disease team as well as with the SRC to ensure that there are sufficient patient resources as well as financial resources to support the proposed study and that the protocol fits with the overall priorities of the Cancer Center. The MCC should also consider assigning priority scores by the individual reviewers as well as by the SRC committee as a whole, which would be helpful in terms of study prioritization.

On page 1663 in the application, metrics relating to study activation are provided. This timeline represents the average time from SRC submission of a clinical protocol to IRB approval. There has been significant improvement in this study activation timeline for therapeutic investigator-initiated clinical trials (166 to 104 days) and interventional investigator-initiated clinical trials (194 to 85 days), respectively, and CPDM and MCC are to be credited for this dramatic improvement. However, the one timeline metric that was not included in this table relates to the time it takes from IRB approval to the actual opening of the study for patient accrual, which in some centers can still take an additional 2-3 months. At the site visit, Dr. Sullivan clarified that it normally took an additional few weeks to open up the studies for patient enrollment once IRB approval was obtained.

The SRC has the authority to close protocols due to inadequate progress. All clinical trials are reviewed at 6-month intervals from their date of activation for scientific progress by the SRC. The specific accrual criteria that would require full SRC review of scientific progress is outlined in Table 4 on page 1668 of the application. A total of 70 studies were reviewed by the SRC in FY 2015. However, review of overall patient enrollment at the Center shows that there are a number of active protocols with very low or no accrual.

The final concern relates to the potential overcommitment of both Drs. Sullivan and Lush in the PRMS and the CPDM. In Dr. Sullivan's role as Associate Director of Clinical Science at the Center, it is entirely appropriate for these two important clinical research elements to report to him, and at the site visit, he stated that he is serving as Interim Medical Director of CPDM until an individual is recruited in to that position and that he does not sit on any of the PRMS SRC committees and his role in PRMS was mainly to appoint the respective committee Chairs, Vice-chairs, and members.

Overall, the Protocol Review and Monitoring System appears to have the appropriate policies, procedures, and staff. There are several issues, however, relating to the true effectiveness of the PRMS, which will need to maintain rigorous standards in prioritizing, monitoring, and closing poorly accruing trials. The SRC will need to broaden its membership to include a greater number of experienced clinical investigators as well as include basic scientists, radiologists, and pathologists to provide basic and translational research expertise. It will be important to continue to carefully monitor the progress of the PRMS as volume and workload expands with the continued growth of the clinical research efforts. Finally, the issue relating to overlap of commitment of both Dr. Sullivan and Dr. Lush in both PRMS and CPDM needs to be considered. The overcommitment of Dr. Sullivan is especially relevant since this same issue had been raised at the previous CCSG site visit.

Personnel: The PRMS core is directed by Dr. Sullivan who is a physician-scientist with both early phase clinical trial expertise and drug discovery expertise. He is well-funded, well-published and an

ideal physician to lead this core. Dr. Lush has expertise in oncology clinical pharmacology and perfectly complements Dr. Sullivan's expertise.

Assessment: Approval.

Minority Report: Based on the significant issues as outlined above, a minority group of the Site Visit Committee felt that, when taken together, these sufficient weaknesses raised serious concerns as to the true effectiveness of the MCC PRMS. As such, this group voted for Conditional Approval of PRMS.

Budget: The budget is recommended as requested.

SENIOR LEADERSHIP

DESCRIPTION (provided by applicant): The Senior Leadership team is comprised of the Center Director and six Associate Center Directors (ACDs) (Fig. 5), who comprise the Research Executive Committee (REX). There are specific responsibilities assigned, but unlike most Cancer Centers there is no 1:1 alignment of Programs to ACDs. This is by design, and reflects the fact that all programs: (i) have physicians and conduct trials; (ii) are multidisciplinary; (iii) have educational components; and (iv), benefit from the input of expertise of each of the ACDs. Thus, there is collective ownership of the programs. REX meets weekly for one and a half to two hours, along with frequent in-person and e-mail communication in-between, plus occasional off-site retreats. All offices are within a five-minute walk. The Senior Leaders are all highly productive, seasoned scientist; together they have more than 110 years of Cancer Center leadership experience.

CRITIQUE: The goal of Moffitt Cancer Center Senior Leadership is to support the Director's vision by providing the support and infrastructure to drive collaboration and maximize the quality of the science conducted by the five research programs. The current Senior Leadership include all well-funded, strong leaders. Together the Senior Leadership works to coordinate the leadership and vision of the Moffitt Cancer Center and develops and implements a strategic plan to conduct bench to community scientific discovery.

At the past review, it was clear that the Moffitt Cancer Center had a very impressive and rapid development in a short time. Over the current funding period, this rapid growth has been sustained and the Program has significantly matured in its depth and breath. Senior Leadership is credited with this rapid and sustained growth. Over the past 15 years, Moffitt Cancer Center has become a leader in translational research and biobanking. There are numerous instances where the Senior Leaders played an important role in strengthening the programs as well improving programmatic focus. Senior Leadership includes:

Center Director and Principal Investigator, Thomas A. Sellers, PhD, MPH, has a 23-year NCI funding history and has secured over $45 million in peer-reviewed extramural grant support as PI or Co-PI. He also authored publications in the *New England Journal of Medicine*, *JAMA*, *Nature Genetics*, and *JNCI*. Dr. Sellers has served on NCI-A and on the External Advisory Committees for 26 Cancer Centers. Dr. Sellers has contributed substantially to the strong and effective leadership of the Moffitt Cancer Center and sustained growth.

Associate Center Director, Basic Science, John L. Cleveland, PhD, was recruited as ACD of Basic Science in early 2014 from Scripps Research Institute in Florida. His research focuses on the molecular pathogenesis of cancer, target discovery and drug development; he has four R01 grants, and has authored over 200 publications. Dr. Cleveland is a strong new addition to the Moffitt Cancer Center and is highly qualified.

Associate Center Director, Population Science, Paul Jacobsen, PhD, was appointed as successor to Dr. Sellers in 2012. Dr. Jacobsen's research focuses on using knowledge from the behavioral and social sciences to promote reductions in cancer risk, early detection, and improvements in quality of life following cancer diagnosis. He is PI of an NCI R25, R21, ACS project and has authored more than 250 peer-reviewed journal articles. Dr. Jacobson is a strong and effective leader.

Associate Center Director, Clinical Science, Dan Sullivan, MD, has served as ACD of Clinical Science since 2005. Dr. Sullivan has expertise in hematologic malignancies and has served as Principal Investigator of the N01-CM-62208 Southeast Phase 2 Consortium (SEP2C; MCC, Vanderbilt, Emory, UNC and VCU) from 2006 to the present, as well as a Co-PI of the NCI UM1 Grant with Princess Margaret Cancer Centre. He currently holds four NCI grants (R01, N01 Phase 1 contract, UM1 subcontract, PACHE grant Co-PI) and has authored more than 130 peer-reviewed journal articles. Dr. Dan Sullivan is also Interim CPDM Medical Director of CRS and oversees many aspects of PRMS. The over-commitment and multiple roles of Dr. Sullivan had been raised at the time of the previous CCSG review; this issue was not entirely resolved through the written document or at the site visit.

Associate Center Director, Translational Science, James Mulé, PhD, was named ACD of Translational Science in 2010. He focuses on translational research studies in cancer immunotherapy for melanoma. He has published more than 165 articles in the areas of cancer vaccines and cancer immunotherapy and is an NCI-NIH funded investigator continuously for more than 20 years. Dr. Mulé is highly qualified and an effective leader.

Associate Center Director, Education & Training, Julie Djeu, PhD, was named founding ACD of Education & Training in 2013. Dr. Djeu has 40 years of experience in tumor immunology. She currently holds two peer-reviewed grants (DOD, NCI T32) and has authored more than 220 peer-reviewed papers. Dr. Djeu has been a driver for innovation, growth, and cohesion of the Moffitt Cancer Center. She is to be commended for her vision and hard work; her efforts have paid off extremely well for the Moffitt Cancer Center.

Associate Center Director, Research Administration, Brian Springer, MHA was appointed founding ACD of Research Administration in 2013. Mr. Springer has more than 18 years of experience in NCI Cancer Center central administration at three previous Comprehensive Cancer Centers. He has served as a leader on the Executive Committee of the Cancer Center Administrators Forum (CCAF), the Steering Committee of the Association of American Cancer Institute's Clinical Research Initiative (AACI CRI), and Co-Chair of the National Cancer Institute Phase 2 Working Group to streamline the Cancer Center Support Grant application.

In summary**,** this is a strong group of well-funded leaders who have lead the sustained growth of the basic, translational, clinical, and population research mission of the Moffitt Cancer Center. Senior Leadership has been effective in setting a future vision for advancing goals and policies relevant to the Moffitt Cancer Center. They have also been highly effective in establishing a biobanking program and numerous other very strong core resources and translational research programs. However, there was some unevenness in the programs. During the site visit there was confusion about the decrease in clinical trials accrual that was not entirely clarified. While Senior Leadership was highly effective in articulating a scientific vision, they were less effective (lack of granularity) in articulating a vision for translating discovery to the catchment area. There was concern that the demographics of the study population in the catchment area were never clearly delineated. In addition, there was very little discussion on the cancers that disproportionately impacted the minority populations.

Assessment: Outstanding merit.

Budget: The budget is recommended as requested.

PLANNING AND EVALUATION

DESCRIPTION (provided by applicant): Dr. Thomas Sellers utilizes internal and external advisory groups to facilitate strategic planning, monitoring, and evaluation of Moffitt Cancer Center (MCC) cancer research activities. These processes have been critical to development of Moffitt 3.0 and the Research Strategic Plan (RSP). The goals of Planning & Evaluation are to: 1) develop, implement, and review a dynamic strategic plan; 2) utilize external experts to evaluate progress and future research priorities; and 3) operate an effective planning and evaluation infrastructure that enhances efficiency and stimulates collaboration, innovation, and strategic growth. Internal and external advisory groups provide guidance and recommendations. The Research Executive Committee (REX, which functions as the CCSG Senior Leadership) is comprised of the Center Director and the six Associate Center Directors (ACDs) and is the primary decision-making group of the Center. REX led development of the RSP, with the vision “to be the leader in understanding the complexity of cancer through team science and applying those insights for human benefit.” Progress in achieving the RSP is reviewed by REX and the groups described below. External planning and evaluation utilizes annual meetings of the External Advisory Committee (EAC), supplemented by focused external reviews (e.g., external shared resource consultants and clinical research advisors). The Scientific Leadership Committee (SLC) at MCC functions similarly to a traditional executive committee at other centers; membership includes REX, research program leaders, and Center of Excellence directors. The SLC provides primary review of programs, shared resources, and clinical trials and includes four standing subcommittees, each chaired by a different ACD: 1) Membership Committee (MC, review of new and ongoing members for cancer focus and scientific productivity); 2) Core Leadership Committee (CLC, shared resource reviews, chargebacks, assessment of member needs); 3) Clinical Research Action Committee (CRAC, clinical research standards and trial portfolio); and 4) Innovation & Technology Committee (ITC, new technologies and tools). In addition, MCC supports seminars and retreats at the program, division (basic, clinical, and population science) and center-wide levels to ensure full membership engagement in planning and evaluation. An annual scientific symposium and Business of Biotech events bring together members, staff, and external collaborators to develop the collaborative research central to CCSG Programs.

CRITIQUE: The MCC has continued a strong trajectory of scientific, clinical and translational research and clinical service over the last funding cycle. In addition, the MCC makes major contributions to the health and public education in its region and is a national leader in innovative research and outreach programs. A rigorous and robust planning and evaluation process is used to develop and implement a strategic plan. Two internal committees, an External Advisory Committee (EAC), and *ad hoc* advisors provide guidance to the development of the Cancer Center.

Dr. Sellers reorganized the leadership committee structure in response to the previous review that noted an appearance of overlap between governance committees.

At the senior leadership level, the Research Executive Committee (REX), composed of the Center Director and the six Associate Center Directors, meets weekly to plan, evaluate, and monitor research activities and progress toward meeting strategic goals.

The Scientific Leadership Committee (SLC) includes senior leadership, research Program Leaders, and Center of Excellence Directors. It meets quarterly to evaluate progress in major areas related to the Cancer Center Support Grant, including research programs, recruitment, membership, shared resources, clinical research activities, interdisciplinary and transdisciplinary collaboration, new technologies and training, and education activities. The four subcommittees of the SLC oversee specific domains and this organization appears effective in promoting and sustaining an environment conducive to collaborative and innovative research.

Finally, regular research program meetings and numerous scientific retreats and symposia provide forums to promote collaboration and innovation.

The Cancer Center's External Advisory Committee has 14 members, with expertise matching to the major Moffitt Cancer Center's research areas.

The EAC is an experienced group led by Dr. James Willson, Director of the University of Texas Southwestern Simmons Comprehensive Cancer Center. The other members are appropriately chosen as leaders in their respective areas of cancer research and/or leadership, and have expertise in the major research themes of this Cancer Center. The EAC meets annually, and there was documented evidence that the advice provided is appropriately considered and applied. *Ad hoc* consultants have also played an important role in the planning and evaluation process. Nationally and internationally recognized experts in chemical biology, immunology, population sciences, health disparities, clinical trials, and administration have been engaged as *ad hoc* consultants during the most recent grant period, and their recommendations led to significant restructuring of the organization and realignment of scientific programs.

A strategic planning process is described, and the strategic plan is appropriately targeted as a three to five year plan, given the exigencies in current funding and science environment. Strategic objectives are to: 1) foster collaborative research; 2) expand the MCC innovation portfolio; and 3) diversify the research funding portfolio. The plan serves as a guide in their decision-making.

In conclusion, the Planning and Evaluation process for the Moffitt Cancer Center is well organized and provides strong internal mechanisms to support the Cancer Center in making substantive contributions across the spectrum of cancer research, prevention and treatment.

Assessment: Exceptional merit.

Budget: The budget is recommended as requested.

DEVELOPMENTAL FUNDS (including staff investigators, where appropriate)

DESCRIPTION (provided by applicant): CCSG Developmental Funds are critical for realizing the Research Strategic Plan (RSP). These investments support RSP elements emphasizing integrative science, innovation, and collaboration. In the previous renewal, MCC requested and was recommended to receive $400,000 per year in Developmental Funds for pilot projects and shared resources. However, after administrative reductions only $75,000 in CCSG developmental funding was available over the five-year period. These funds were leveraged with significant institutional funds to support pilot projects, which was ultimately the only category for which CCSG Developmental Funds were used. This CCSG investment returned more than $20 million in subsequent peer-reviewed funding and 54 publications. Future plans are to support collaborative pilot projects and invest in a novel mechanism to foster innovation in MCC cores over the next project period. MCC requests $190,000 for Developmental Funds to: 1) Foster innovative science through the support of collaborative pilot projects; and 2) Facilitate and Encourage Core Innovation. MCC will continue to recruit new faculty, allocate discretionary "pre-pilot" funds for Program Leaders, and provide bridge funding for members; however this will be institutional support, and no CCSG funding is requested in these categories at this time.

Staff Investigators: MCC's Centers of Excellence (CoE) build and foster transdisciplinary collaborations across all Research Programs based on areas of institutional strength that align with the needs of the catchment area. Staff Investigators lead each CoE, with the expectation that they bring together members from across all Research Programs to enhance discovery and translation through interdisciplinary and transdisciplinary team science. MCC has four CoEs, each led by a Staff

Investigator, who reports directly to the Associate Center Director (ACD) of Translational Science. The four Staff Investigators, all of whom are accomplished, senior scientists, are: 1) Kieran Smalley, PhD, who leads the Melanoma CoE; 2) Eric Haura, MD, who leads the Lung Cancer CoE; 3) Anna Giuliano, PhD, who leads the Center for Infection Research in Cancer; and 4) Robert Gillies, PhD, who leads the Center for Imaging and Technology. MCC requests Staff Investigator support of 1.20 calendar months (10%) for the CoE Directors, partially supported by the CCSG ($44,725).

CRITIQUE: In the previous renewal, Moffitt Cancer Center requested and was recommended to receive $400,000 per year in Developmental Funds for pilot projects and shared resources. However, after administrative reductions, only $75,000 in CCSG developmental funding was available over the past cycle. These funds were leveraged with significant institutional funds to support pilot projects. Overall, almost $5M in institutional funds was invested in pilot projects, yielding 54 publications and over $20M in grants, representing a significant return on investment.

In the current application, Moffitt Cancer Center requests $150,000 for pilot projects, $40,000 for core innovation, and $44,725 for Staff Investigators annually. Funds for pilot projects will be used to support the goal to enhance team science. One Team Science award, for an interdisciplinary or transdisciplinary collaboration of at least two members from different programs or disciplines, will be awarded annually from this source.

$40,000 annually is requested to establish and provide new service lines in shared resources to meet the needs of member investigators. These will be selected by the Moffitt Cancer Center Innovation and Technology Committee, which was established to evaluate the need for new service offerings.

Partial Staff Investigator support at $44,725 annually is requested for four senior scientists to lead Centers of Excellence. All are accomplished investigators who will work with Research Program Leaders and Associate Center Directors to build and foster transdisciplinary collaborations across the Cancer Center. The Staff Investigators will report to the Associate Center Director for Translational Research and will work to enhance discovery, translation, and address needs of the catchment area.

There is a clear institutional commitment as evidenced by the substantial funds allocated for pilot research, and the considerable investment in core development over the past funding cycle. The new Collaborative Data Services Core is an example of its effectiveness in using developmental funds to foster innovative research. The addition of the support for the Centers of Excellence will further MCC's ability to foster transdisciplinary collaborative research across all of its programs.

Assessment: Exceptional merit.

Staff Investigators: Approval.

Budget: The budget is recommended as requested.

ADMINISTRATION

DESCRIPTION (provided by applicant): Moffitt Cancer Center Administration includes the Research Executive Committee (REX), Scientific Leadership Committee (SLC), and Research Administration. REX establishes the overall scientific direction of the Center through strategic planning investment, evaluation, and nimble, coordinated activities that take advantage of unique opportunities or that address problems. Research Administration operationalizes and supports this vision. REX members include the Center Director and the six Associate Center Directors (ACDs) of Basic, Clinical, Population, and Translational Sciences; Education & Training; and Research Administration. This committee meets weekly for one and a half to two hours. This frequency ensures that activities related to recruitment, research development (including the Grant Review Committee, GRC), planning, space,

academic affairs, and policy are rapidly addressed, while fostering a highly collaborative and integrated culture. The REX members are all highly productive scientists and leaders; collectively they have more than 110 years of Cancer Center leadership experience. SLC includes REX plus Program Leaders and Center of Excellence (transdisciplinary interest groups) Leaders. This group advises the Director and REX, with subcommittees for shared resources (Core Leadership Committee, CLC), member evaluation (Membership Committee, MC), clinical science (Clinical Research Action Committee, CRAC), and technology transfer/development (Innovation & Technology Committee, ITC).

CCSG Research Administration is composed of 68 (only 2.6 FTE requested) staff members that support Moffitt's 142 Members, 698 other staff, and 13 shared resources. Reporting to the ACD of Research Administration, the administrative unit includes three Senior Directors, five Directors, four Managers, and their teams. Administration assists the Center Director in the ongoing research strategic planning and evaluation process; regular member and staff communications; faculty recruitment; shared resource oversight, including chargebacks, performance review, and user satisfaction; managing the $145 million annual budget, including philanthropic funds; awarding and monitoring more than $2 million in annual institutionally-supported developmental awards; managing and implementing MCC policies for 333,000-sf of dedicated research space; conducting the quarterly membership review and monitoring process; and arranging and documenting approximately 150 Center meetings and retreats per year. The current budget requests for Senior Leadership and Administration are $174,034 (9% of CCSG budget) and $153,888 (8% of CCSG budget), respectively. Collectively this represents less than 0.3% of the overall institutional research budget.

CRITIQUE: The Administration supports the Director's vision by providing the support and infrastructure to drive collaboration and maximize the quality of the science conducted by the five research programs. The specific aims for the administration are to: 1) manage and track the research strategic plan, 2) foster member and team science, 3) communicate Center activities and research opportunities, and 4) provide overall Center management functions.

Administration is under the leadership of Brian C. Springer, MHA, who joined Moffitt Cancer Center in 2013 as Associate Center Director and Vice President of Administration. This position was created in response to the previous critique, which recommended the formal recognition of the ACD of Administration as a member of the senior leadership. Mr. Springer oversees a broad administrative structure, which includes the CCSG.

Over the last cycle, Administration has focused on streamlining and improving support functions, along with building a support structure to foster mentorship and succession planning. Among the achievements of Administration are: developing and tracking the 2013-2018 Research Strategic Plan; designing and implementing a Clinical Research Action development plan; enhancement of shared resources through adoption of a more rigorous review and monitoring process and implementation of a new laboratory information management system; expansion of the administrative database to create links to OnCore and to improve and expand reporting; and supported the implementation of a new institutional pilot program.

Brian Springer, Center Associate Director for Research Administration, is one of six Associate Directors that comprise the senior leadership of the Moffitt Cancer Center (Research Executive Committee, or REX). This group meets weekly, with frequent communication among the leaders between meetings. He works closely with the CCSG Director and the ACDs on all planning and evaluation, priority setting, resource allocation, and policy development activities.

In his role as ACD for the Administration, Mr. Springer directs and oversees all research operations, research development, space, shared resources, human resources, information technology, and grant pre-and post-award. He provides executive administrative leadership of Clinical Protocol & Data Management and Protocol Review & Monitoring System activities.

Under Mr. Springer's leadership, the Administrative Core has advanced steadily toward creating a supportive infrastructure that makes use of information technology developments in multiple areas. These activities are carried out in conjunction with careful planning, and are consistent with the overall strategic vision of the Cancer Center. There is a commitment to continuous improvement and a strong service orientation among the staff. They are attentive to the demands placed upon the leaders and members and develop strategies to facilitate their efforts. A career ladder has been developed, giving staff opportunities to grow and develop and providing support for succession planning.

All CCSG responsibilities are met effectively. The membership database and review process is substantive, with a membership policy addressing the oversight, eligibility, benefits, responsibilities and appointment process. Annual reviews of all members evaluate continued cancer focus and funding. Administration manages all activities related to the CCSG application, including planning and development, coordinating the participation of all scientific leadership.

All research space is allocated by the Center Director, and the Administration supports the annual review process that is based on established criteria (awards, expenditures, indirect costs, and funded FTEs per sf).

The Cancer Center offers ten key developmental funding opportunities annually; the process of announcement, review and award is managed by the Administration.

Support for all external advisory and internal leadership is enhanced with broad communication to the membership. Templates have been developed to document specific action items and target dates for their completion.

Frequent communication with the membership is provided through a weekly electronic newsletter, and funding opportunities are published in a monthly electronic newsletter.

Activities for trainees are supported by the Administration. A Research Services Specialist organizes the Grand Rounds calendar, processes all trainees for graduate, undergraduate, and summer students, and provides support for the T32 training grants.

In summary, the support provided to the membership by the Administrative Core is significant. The staff is cohesive and dedicated to continually improving processes. The Administration supports all of the Cancer Center's initiatives effectively. Their capacity to provide timely and accurate information enables enhanced monitoring and assessment, strengthening the capacity of leadership to make strategic adjustments as needed.

Personnel: In addition to support for the Associate Center Director for Research Administration, partial support is requested for six additional individuals whose roles are critical for the CCSG. Staff and roles are listed below.

Lowell Smith, MA, Senior Director, Business and Communication: 3.0 calendar months, 25% effort, partially funded by the CCSG.

Christine O'Connell, MMSc, FABC, Senior Director, Laboratory Research Operations and Shared Resources: 3.0 calendar months, 25% effort, partially funded by the CCSG.

Edward Seijo, MS, FABC, Director of Translational Sciences & Biorepository Shared Resources: 3.0 calendar months, 25% effort, partially funded by the CCSG.

John Schatzle, PhD, Director of Basic & Population Shared Resources: 3.0 calendar months, 25% effort, partially funded by the CCSG.

Maureen Ahearn, Senior Research Administrator: 3.0 calendar months, 25% effort, partially funded by the CCSG.

Debbie Magley, Research Services Administrator: 3.0 calendar months, 25% effort, partially funded by the CCSG.

All are well qualified for their positions.

Assessment: Exceptional merit.

Budget: The budget is recommended as requested.

ESSENTIAL CHARACTERISTICS

Physical Space: (Exceptional merit) Moffitt Cancer Center (MCC) has two campuses (Magnolia and McKinley) and research space at three other locations. The space available at MCC has expanded considerably with a brand-new 208,000 square foot (sf) outpatient building that opened on the McKinley Campus in November 2015. Center Director, Dr. Sellers, has complete authority and control over 333,000 sf of dedicated research space. Recent additions and renovations on the Magnolia Campus include a 1,400 sf institutionally supported radiochemistry facility that opened in 2014 and a renovation of 11,000 sf in the Moffitt Research Center in January 2015 to relocate and expand space for three CCSG-supported core facilities. At the site visit, it was disclosed that there is a plan to build a new research building on the Magnolia campus, which will be adjacent to the current research building, and funds have been secured for the construction. MCC's space and physical facilities appear to be adequate and appropriate to its identity, objectives, and activities.

Clinical research space at the MCC is located at both campuses and a satellite location known as the Moffitt International Plaza. Eleven Shared Resources are housed in two buildings on the Magnolia Campus. Wet and Dry Laboratory Space, Administration, Radiochemistry Facility, Vivarium, Glass Wash Facility, Biomedical Library, and Computer/Network support are also located on the Magnolia Campus. Services and resources at the McKinley Campus include a Biorepository, Cell Therapies Core Facility, and Molecular Diagnostic Laboratory. Based on the information provided in the application, the access to shared resources and other services and resources for MCC members is reasonable.

Overall, the physical space at MCC is exceptional. It would be helpful to develop/strengthen mechanisms to facilitate the integration of the two campuses and three other locations, as physical distance in a multiple-campus system can impact the efficiency of collaboration and communication.

Organizational Capabilities: (Outstanding merit) During the previous project period, the roles of CEO and Center Director were divided. Dr. Thomas Sellers was named Center Director in July 2012, and reports to the CEO, Dr. Alan List. Dr. Sellers has oversight and authority over the entire MCC research enterprise, and is one of the six-member CEO cabinet. They appear to have a strong working relationship. One minor concern is a lack of description of how decisions are made.

The Senior Leadership team, named the Research Executive Committee, consists of the Center Director and six Associate Center Directors. This committee drives the research strategic plan. The Associate Center Directors have considerable research and leadership experience. A unique feature is that all MCC Programs have physicians in their membership and conduct translational clinical trials. The Senior Leadership Committee meets quarterly and consists of all Program Leaders and Center of Excellence Leaders. Six new Program Leaders were added in the previous period, and two were

introduced at the site visit. There is a question how well they are working together. All of the Research Programs are multidisciplinary and meet individually and jointly. Most of the Programs focus on cancers that have a high incidence in the catchment area.

A new Institutional Strategic Plan for fiscal years 2014-2018 was developed. A Research Strategic Plan, which provides research-specific goals and strategies, was finalized for the July 2013-June 2018 period. It fosters team science, puts an emphasis on enhancing scientific innovation and diversifying research support. This document serves as the guide for recruitment, program development, and research development funds.

There is a dedicated effort and unified corporate structure consisting of the Cancer Center, Cancer Hospital/Clinics, Moffitt Medical Group, Moffitt Foundation, and M2Gen to provide strong organizational capabilities to oversee and coordinate clinical care and prevention.

In regard to Education and Training, Dr. Djeu was appointed as Associate Center Director of Education and Training in 2013. The educational and training programs are offered to high school students, fellows, and junior faculty. Research and career development opportunities are discussed.

Transdisciplinary Collaboration and Coordination: (Outstanding merit) Moffitt Cancer Center uses a series of collaborative strategies to facilitate institutional based transdisciplinary collaboration and coordination that focuses on the principal that multidisciplinary teamwork fosters optimal outcomes. The Cancer Center, as well as the hospital, promotes multidisciplinary collaborations that is built into the criterion and expectations by which faculty members are evaluated. The MCC utilizes a number of mechanisms to enhance transdisciplinary collaboration, including: (1) Research Executive Committee (REX); (2) Scientific Leadership Committee (SLC); (3) Targeted Recruitment; (4) Physical Space; (5) Communications; (6) Secondary Academic Appointments; (7) Total Cancer Care; (8) Seminars and Meetings; and (9) Pilot Funding.

There is a high level of transdisciplinary and translational collaborations among members of the basic, clinical, and population science programs. The MCC has 24 multi-investigator grants and a relatively strong inter- and intra-programmatic publication record. There are 11 multi-investigator grants in the MCC. Overall, the intra- and inter-programmatic interactions provide significant value to the cancer-related scientific activities, although the intra-programmatic productivity of the IC Program needs improvement. There are a number of mechanisms that MCC has implemented to promote collaborative interactions, which are anticipated to further impact the collaborative interactions.

The institutional commitment to transdisciplinary and translational collaborations in the MCC appears to be extremely strong. The MCC differing programs have a great deal of intra- and inter-programmatic interactions that appear to be driven by a series of initiatives most of which are outlined in the overview. The program members are clearly incentivized by these initiatives, to develop and complete collaborative projects as well as funding through P, U, and multi-project grants. These include, but are not limited, to a lung cancer SPORE (P50 CA119997), led by Dr. Eric Haura (CBMM), an NCI melanoma research SPORE (P50 CA168536) grant that was originally led by Dr. Jeffrey Weber and is now led by Dr. Vernon Sondak (IMM), an NCI Physical Science Oncology Center (PSOC, U54 CA143970) led by Dr. Robert Gatenby (CBE), a U01 prostate cancer aggressiveness (U01 CA151924) led by Dr. Alexander Anderson (CBE), an NCI CNPII U54 grant that has provided funding and expansion of the Tampa Bay Community Cancer Network (CA153509) led by Drs. Cathy Meade and Clement Gwede (HOB), and a U19 initiative on Post-GWAS Follow-Up Studies led by Drs. Sellers (CE) Monteiro, Chen, Permuth, and Phelan (all CE) to identify susceptibility loci for epithelial ovarian cancer and determine the biological and functional significance. This initiative lists a total of 2430 publications, of which approximately 1/3 are intra-institutional collaborations and 1/3 are inter-institutional collaborations.

Transdisciplinary Collaboration and Coordination was rated as outstanding in the last CCSG site review and during the most recent cycle this appears to continue to be one of the major focus and strengths of the MCC. In summary, Transdisciplinary Collaboration and Coordination has clearly met the goals set forth five years ago and seems well placed to make additional advancements in the next five year cycle.

Cancer Focus: (Exceptional merit) The MCC has a very high cancer focus. It is a free standing Cancer Center with the singular mission of preventing and curing cancer. MCC has 5 research programs all focused on cancer with a distinguished membership of scientists who are well regarded for their research on cancer. It is very active in both basic and translational cancer related studies with over 2400 cancer related publications during the last funding period. MCC has focused on clinical trials in disease sites that are in the top 10 by death rate in Florida. There are active basic and clinical projects for treating melanoma, lung cancer, and hematologic malignancies. MCC enrolled 11,851 participants on interventional trials and 250,147 outpatients on non-interventional trials during the previous funding period. A concern is that NCI peer reviewed funding, while substantial, has decreased significantly from 52.9 million in the last funding period to $22 (71.5% of $39.7 million). However, MCC has formed strategic partnerships and research agreements to capture $4.6 million from non-peer reviewed sources and $21.4 million from industry with the goal of working to minimize the budget constraints of NCI.

Institutional Commitment: (Exceptional merit) The MCC is a free standing 501(c)3 not-for-profit institution that is focused on cancer research and cancer patient care. Dr. Sellers holds a strong leadership position in the research institute and is involved in all major decisions. He has authority over cancer research activities including membership, space allocation and budget control. The MCC research institute provides the facilities needed to support the mission of the MCC. The institution provides approximately $40M annually to the Cancer Center in operational funds, $17 million in administrative and facilities support and an additional $13M in philanthropic support. There is a team science policy in place at the MCC.

Center Director, Dr. Sellers, has authority over more than $6M in available support through the Moffitt Foundation and these philanthropic funds come primarily from two events: (1) the Magnolia Ball; and (2) Miles for Moffitt run. The institution provides an additional $2M per year for “Distinguished Moffitt Scholars.” There is also philanthropy 13 million dollars last year in funds from the Moffitt Foundation ($13.0M) as well as $36.1 million in yearly state funding. These funds provide all research leaders at MCC, i.e., the Director, ACDs, Program Leaders, Center of Excellence Leaders, and Department Chairs, $100K per year for support cancer research related efforts. In addition, starting in 2015 the Foundation launched a Comprehensive Campaign to raise $300M and $80M has been raised to date. There is also a clear commitment to the necessary space so as the funded investigators will be successful, a very strong five year record of Faculty Recruitment, as well as support for team science as shown by funding from multiple funding for pilot studies, as well as P, U, and other multi-investigator, multi-project grants.

Overall, the institution is highly supportive of the Cancer Center.

Center Director: (Outstanding to Exceptional merit) Dr. Sellers, PhD, MPH, oversees the scientific and clinical mission of the Moffitt Cancer Center, and also serves as one of six Executive Vice Presidents of the free-standing Cancer Center. Dr. Sellers devotes a significant fraction of effort (50%) to the Center, as appropriate, given his authority and responsibilities. With the other EVPs and the CEO, Dr. Sellers oversees major decisions associated with research, the hospital, outpatient clinics, and the Moffitt Foundation. Dr. Sellers reports to the CEO, giving strength to the position of the Center Director.

Total research support is ~$145M per year, and Dr. Sellers holds primary authority over >$6M from the Moffitt Foundation. Dr. Sellers also has primary authority over ~333K sq. ft. of research space, and has

direct responsibility for recruitment and appointment of all PhD scientists to the Divisions of Basic Science and Population Science. It is stated that Dr. Sellers partners with Dr. Letson for recruitment of physician scientists, but the nature of this partnership was not well articulated.

Credentials of the Cancer Center Director are impressive. Dr. Sellers is an accomplished population scientist with a substantial background of success at the NCI. He has been funded for >23 years, is PI of NCI supported U19 and R25 grants, and has contributed to >320 publications. Dr. Sellers has substantive experience in Cancer Center leadership (at Mayo Cancer Center and Moffitt Cancer Center), and has served in high level positions at NCI (including Parent Committee A, the NCI Board of Scientific Counselors, etc.). Dr. Seller is leading his Cancer Center by example, which is an asset for this Center as it strives to achieve strategic goals.

As evidenced throughout the application, Dr. Sellers harbors the prerequisite experience, skills and institutionally-granted authority to successfully lead the Cancer Center forward, and has assembled an expert team of Associate Directors to lead the Center.

BUDGET RECOMMENDATION

The site visit team did not make any reductions from the total direct costs of the CCSG. In total direct costs, the current budget is $1,782,013 (from Data Table 5); requested budget is $1,918,736 (from Face Sheet); and the recommended budget is $1,918,736. The site visit team recommends that the budget be evaluated by the NCI Subcommittee A, as needed.

The NCI Subcommittee A concurs with the site visit team’s recommendation and recommends $1,918,736 in direct costs.

The budget tables that follow are provided as informational item only. The official recommendation for support is provided under the heading, RECOMMENDED BUDGET/NCI SUBCOMMITTEE A, after the NCI IRG, Subcommittee A (parent committee) meeting.

COMMITTEE BUDGET RECOMMENDATIONS/SITE VISIT TEAM’S RECOMMENDATIONS

The table below summarizes the estimated effects on the original amounts requested by the applicant of implementing the budgetary changes recommended by the reviewers and summarized in the Budget section(s) of the Summary Statement above. The table below does not take into account either additional information that may be provided by the applicants in response to administrative requests for updates or additional administrative changes that may be required to meet Institute funding policies, either or both of which may result in a significantly different final recommended budget figure. Consequently, applicants should make no inferences from these figures about what the final budget might be should an award be possible.

	First Year Requested Direct Costs $	First Year Recommended Direct Costs $
SENIOR LEADERSHIP	207,578	207,578
PROGRAM LEADERSHIP (including other budget categories, where appropriate)	143,067	143,067
PLANNING AND EVALUATION	40,000	40,000
DEVELOPMENTAL FUNDS (including staff investigators, where appropriate)	234,724	234,724
ADMINISTRATION	120,344	120,344
Analytic Microscopy Core	58,212	58,212
Biostatistics Core	127,251	127,251
Cancer Informatics	111,130	111,130
Cell Therapies Core	73,451	73,451
Chemical Biology Core	59,436	59,436
Collaborative Data Services Core	70,214	70,214
Flow Cytometry Core	41,340	41,340
Image Response Assessment Team	62,921	62,921
Molecular Genomics Core	74,844	74,844
Proteomics Core	74,695	74,695
Small Animal Imaging Lab Core	56,806	56,806
Survey Methods Core	31,401	31,401
Tissue Core	125,304	125,304
CLINICAL PROTOCOL & DATA MANAGEMENT (CPDM)/ CLINICAL TRIALS OFFICE & DATA AND SAFETY MONITORING		
Clinical Protocol and Data Management	160,016	160,016
Data and Safety Monitoring		
PROTOCOL REVIEW AND MONITORING SYSTEM	46,002	46,002

SUMMARY OF RECOMMENDED BUDGETS/SITE VISIT TEAM'S RECOMMENDATIONS

Budget Categories	YEAR 19 $	YEAR 20 $	YEAR 21 $	YEAR 22 $	YEAR 23 $
Salary, Wages and Fringe Benefits	1,688,736	1,688,736	1,688,736	1,688,736	1,688,736
Equipment					
Travel					
Participant/Trainee Support Costs					
Other Direct Costs (excluding Consortium)	230,000	230,000	230,000	230,000	230,000
Consortium Costs					
Direct Costs	1,918,736	1,918,736	1,918,736	1,918,736	1,918,736
Indirect Costs	1,313,555	1,313,555	1,313,555	1,313,555	1,313,555
Total Costs	3,232,291	3,232,291	3,232,291	3,232,291	3,232,291

RECOMMENDED BUDGET/NCI SUBCOMMITTEE A *

Budget Categories	YEAR 19 $	YEAR 20 $	YEAR 21 $	YEAR 22 $	YEAR 23 $
Total Direct Costs	1,918,736	1,918,736	1,918,736	1,918,736	1,918,736
Total Costs	3,232,291	3,232,291	3,232,291	3,232,291	3,232,291

* The official recommendation for support is indicated under the heading, RECOMMENDED BUDGET/NCI SUBCOMMITTEE A. (This information may differ from the amounts in the tables, COMMITTEE BUDGET RECOMMENDATIONS/SITE VISIT TEAM'S RECOMMENDATIONS and SUMMARY OF RECOMMENDED BUDGETS/SITE VISIT TEAM'S RECOMMENDATIONS.) Appropriate escalation factors may be added in the event of an award.

Footnotes for 2 P30 CA076292-19; PI Name: SELLERS, THOMAS A

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER
Subcommittee A - Cancer Centers
National Cancer Institute Initial Review Group
NATIONAL CANCER INSTITUTE
Dr. Thomas Sellers (2 P30 CA076292-19)
NCI-A RTRB-C (E1) Work Group# 1
05/11/2016 - 05/13/2016

CHAIRPERSON(S)

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PROFESSOR OF COMPARATIVE PATHOBIOLOGY;
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National Cancer Institute Initial Review Group
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NCI-A
08/11/2016

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