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Dear Dr. Sellers:

The Moffitt Cancer Center ("Moffitt") External Advisory Committee (EAC) returned to Tampa on February 6-7, 2018 to review progress since the successful competitive renewal of the CCSG in 2016, and the start of the new grant period in February 2017. Moffitt enters the cycle with eight new EAC members (Drs. John Buatti, Corey Casper, Wally Curran, Karen Knudsen, Elizabeth Platz, Charlie Rudin, Celette Skinner, and myself) selected to address the evolving science of the Center and 2 new members (Dr. Dexter Frederick, Ms, Peggy Sherry) to specifically focus on the particular needs of the catchment area. The meeting began with a review and orientation to the Center over dinner, with the following day dedicated to future strategic opportunities that will address the summary statement critiques.

Overview and Summary
The NCI review panel merit score for the Center was a solid "Outstanding" at 25. While this was down somewhat from the prior review, the site visitors provided very strong and positive summary statements reflecting the progress Moffitt has made, as well as supportive comments regarding additional research opportunities and collaborative coordination: "*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*." As the only NCI designated Center, Moffitt remains solidly in the forefront of centers in Florida, providing a unique and valued state resource.

In the interim, progress has been substantial: grant funding has increased; recruitments- both junior and senior- have been of very high quality and clearly add to the science of the center; new leaders have been identified, installed and have emerging impact; new initiatives have been carefully considered; volumes and clinical trial accrual continue to rise (1100 accruals to clinical intervention trials); and the institution is embarking on its next strategic plan. Institutional and state

support is substantial, and philanthropic attainment has increased substantially. The normal tide of member turnover has been met with strong institutional response with targeted recruitments both completed and planned.

Variations in program review in the summary statement seem to relate mostly to presentation and perception of programmatic impact parameters since all have evidence of substantial progress, funding, collaboration and translation. While the discussion of programs during the EAC did emphasize attention to the catchment area, this was not a deficiency noted at review. Rather, the review noted: "*Overall, the depth and breadth of research at Moffitt Cancer Center and demonstrated impact on the catchment area meets the criteria for comprehensive status.*" But, given the attention to addressing catchment area in the current CCSG Funding Opportunity Announcement and the study section's current review expectations, the EAC noted that this has increased in importance. The EAC members encouraged the center leadership to attend to the impact on the catchment area (and vice versa) of science in each program. For example, integration of the new Moffitt practice at Memorial Hospital (MH) in Hollywood, FL into the geographic patient distribution will need some thought. Since MH is a limited scope network-like site, the entire population of that county need not be part of the primary catchment area, but the center might consider how and when to expand services and research in that geographic area.

Some accomplishments of special note include the expansion and success of the Office of Innovation and Industry Alliances. This is quite exceptional, and although not considered peer reviewed funding, it has provided substantial access to novel therapeutics and technology, as well as serving as an outlet to aggressively license intellectual property (IP). To demonstrate scientific impact of these alliances, Moffitt could track the origins of this IP, and the consequent impact including further sponsored research, new resulting peer review funding, investigator-initiated trials (IITs), career support including training opportunities, and other measures. The EAC applauded the very thoughtful approach towards improving clinical trial activity, begun in 2014, and now categorized by careful monitoring of IITs (based on three categories), and ongoing institutional-wide attention to the importance of clinical trials. Leadership has productively managed the previous reviewers' perception of Dan Sullivan's "over commitment." Further, the distribution of clinical research oversight from Dan Sullivan to three additional members and senior staff is a further demonstration of remarkable institutional commitment.

All new leaders presented to the EAC. They are impressive and add considerable depth and breadth to the research mission of the center. Newly recruited Associate Center Director (ACD) of Population Science, Dr. Shelley Tworoger, has substantial accomplishments to lead this effort and to assist in greater focus on the catchment area. Newly appointed ACD of Data Science, Dr. Dana Rollison, provided a very coherent plan for a significant uptick in support for data analytics that cuts across all programs and that will support initiatives in cancer care research. Further, Dr. Geoff Duyk's appointment as chair of the Research Committee of the Moffitt Board offers top of class expertise to expand the institution's engagement and strategic positioning with industrial partners at all levels. Finally, the continued investment in Total Cancer Care (TCC), commercial pharma, and data and -omic analytic entities, provide Moffitt national leadership in efforts to coordinate large data sets for scientific discovery and clinical benefit.The Moffitt leaders asked the EAC members for their assistance in ensuring that the key critiques in the summary statement were being addressed. The EAC concurred with the Center's assessment, and determined that concerns at the level of institution, program, shared resources and clinical research are being addressed. But the members noted that this is a moving target, and catchment and training are emerging as new aspects of increased attention and expectation.

Moffitt has grown significantly in the past several years, aided by an innovative marketing and public relations program. Moffitt requested guidance on the best strategies to communicate growth. The leaders outlined a number of thoughtful strategies to keep up with rapid growth in the areas of data management, clinical trials, and expanding catchment-related research. It seems reasonable to be forthright regarding these challenges and progress-to-date at the next submission.

The leaders also sought advice on developing expectations for research growth. All programs have active expansion and recruitments underway, with strong institutional support. They will benefit from the next MCC scientific strategic plan currently in development, links to the Centers of Excellence, and attention to catchment area needs by disease and special populations. Many centers utilize "cross-cutting" themes to show evidence of integration, but program leaders will benefit from considering these approaches collectively as well as strategic visioning within their individual programs.

Clinical Science

Dr. Sullivan reviewed the clinical research elements and how they were reviewed in the CCSG renewal. The Protocol Review & Monitoring System (PRMS) was judged as "Acceptable," and the Clinical Protocol & Data Management (CPDM) infrastructure was judged as "Outstanding." There will be center-wide benefit in adding additional basic scientists and population scientists to the Scientific Review Committee, which is underway now. Both Drs. Sellers and Sullivan described a strategic plan developed in conjunction with a four-person external advisory board to improve clinical trial enrollment. This 36-point plan was developed in 2014 and executed over a three-year period. At the point of the current EAC, 31 of 36 items have been completed, and the remaining five elements are ongoing processes. One of the primary goals of this strategic plan was to enhance the culture and motivation of faculty, staff, and community to focus their efforts on therapeutic trial enrollment. This initiative has been successful in that annual therapeutic enrollment has been increasing over the past three years, with increases from 870 to 932 to 1099. While improving, the ratio of this enrollment to the new cancer patients currently seen at Moffitt is relatively low. This has led to the drafting of a second focused Accrual Improvement Plan, which was shared with the EAC. Review of this draft plan found it to be very pragmatic and covering many of the potential obstacles and opportunities related to successful clinical trial enrollment.

There are several highly qualified new leaders in Clinical Science at Moffitt presented to the EAC, and Dr. Sullivan's "retirement" from his role as M2Gen Chief Medical Officer has afforded him more opportunity to focus on his leadership of Moffitt's Clinical Science efforts.

Enrollment of minority patients requires specific and intentional planning and MCC leadership has had consistent and proactive efforts in this area for at least ten years. As a result, the enrollment of Latino or African American patients is congruent with the ethnic and racial proportion of cancer in the catchment area. However, a proactive plan to monitor and improve upon that performance should be discussed at the next meeting.

Areas of opportunity for increased therapeutic enrollment to consider include:

1) Greater engagement in the NCTN. It is unusual for an NCI-designated CCC with a large and growing patient population to be as unengaged in the NCTN as Moffitt. It is unusual for a center like Moffitt not to have applied for an NCI LAPS U10, and the EAC members noted that this does not conflict with Moffitt's goal of having more IITs. While Moffitt is active in the ETCTN, greater engagement would provide career opportunities in NRG, SWOG and other research bases for a diverse group of Moffitt faculty.2)
2) Leverage the ORIEN opportunity. Moffitt is a founding member of ORIEN and recognizes the opportunity to conduct clinical trials within ORIEN. Moffitt has taken a leadership role in

creating a facile infrastructure to support clinical trials, including an agreement among all centers to use the same IRB and common contracting. Indeed, it has been approved by the NCI to host a single Scientific Review Committee for trials conducted within ORIEN. The EAC looks forward to hearing how this develops and benefits clinical trial accrual.

3) Additional trials engagement. Moffitt is encouraged to continue the conscious effort to develop a clinical trialist phenotype for non-medical oncology Moffitt faculty, such as surgical subspecialists, imagers, radiation oncologists, and other specialists.

Data Science

Since the CCSG review, Dr. Dana Rollison was appointed as the first ACD of Data Science. Development and inclusion of a Senior Leader in this area recognizes the prominent role of data in accelerating biomedical research and Moffitt's particular strengths and leadership in this area. In addition to recognizing Dr. Rollison's leadership in driving inter-programmatic research in the quantitative sciences, this builds a stronger academic home for faculty, and clear responsibility for expanding expertise in alignment with the research strategic plan. Dr. Rollison continues to report to Dr. Sellers as Vice President and Chief Data Officer, so this structure ensures strong institutional alignment and powerful ability to leverage Moffitt investments to support the hospital and clinics in a way that maximizes benefit to the research mission.

The EAC members strongly supported development of this new role, which is important and necessary. This provides a more prominent position within the CCSG. The EAC recommended clarifying and potentially expanding the interaction of this role with the members. The EAC is very supportive and looks forward to additional achievements in this important area.

Population Science

Most faculty in the Health Outcomes and Behavior (HOB) and Cancer Epidemiology (CE) Research Programs reside in the Population Science Division, now led by Dr. Shelley Tworoger, who came from Harvard in 2017, replacing Dr. Paul Jacobsen. Dr. Tworoger presented a coherent and compelling vision for population science research at Moffitt, one which included health behavior and patient reported outcomes in the overall understanding of host macro-environment and tumor-microenvironment. Her vision provides direction for continued success and positive growth in the HOB and CE Programs.

Health Outcomes & Behavior Research Program

The Health Outcomes & Behavior (HOB) Research Program, ably-led by Dr. Tom Brandon, was rated as "Outstanding" in the 2016 CCSG renewal. For at least the last three CCSG cycles, HOB has consistently performed quite well, and has been a standout program. The current well-earned "Outstanding" rating is actually a downgrade from the "Exceptional" rating in the prior cycle. The program currently has 25 members, 5-10 of whom are from the University of South Florida (USF) (and therefore their grants are not credited in the official funding base). The program has four aims surrounding prevention/detection, quality of life, cancer care delivery, and health disparities. The CCSG review panel criticized diminished NCI funding and reduced accrual to interventional studies.

Since the site visit, several important faculty and leadership losses, including Drs. Paul Jacobsen (ACD of Population Science), Benjamin Djulbegovic, and Gwendolyn Quinn (Scientific Director of the Survey Methods Core), have led this otherwise historically very strong program to seek advice regarding whether to deepen current strengths in tobacco control, quality of life and health disparities, or aggressively broaden into cancer care delivery research. HOB has commitment for at least five, and perhaps as many as six to seven new recruits in the time until the next renewal cycle. With the considerable time and energy necessary for recruitment, but given that there are

only three years before the next renewal, the EAC recommended that this program attempt both strategies, aggressively reconstituting the membership by deepening its strengths in Aims 1, 2, and 4, while at the same time continuing to search for an accomplished leader in cancer care delivery research. While the EAC members recognized that cancer care delivery research is a very difficult area in which to recruit because of a low supply/high demand imbalance, they suggested highlighting the value-added selling points that Moffitt can use to attract candidates. For example, Moffitt collects PROs for all new patients as part of clinical care under the governance of the Enterprise-Wide Analytic Strategy. Second is the support of the Collaborative Data Services Core (directed by Dr. Travis Gerke, overseen by Dr. Rollison as ACD), which provides concierge service around access to the Health and Research Informatics platform, which includes over 600,000 patients seen at Moffitt since Cerner was implemented as the Electronic Health Record. There is an opportunity to potentially offer both a program co-lead position to a senior recruit, as well as leadership of a new Department of Cancer Care Delivery Research. Although some candidates might see the focus of a free-standing cancer center as a limitation for implementation/dissemination and care delivery research, others would view this as an asset, which can be emphasized in recruitment.

Funding has dropped a bit in the last year, with sun-setting of some grants led by Dr. Jacobsen, who was recruited last year to head a branch at the NCI. Also, grants led by members with primary appointments at USF are not counted as part of the funding totals, although they contribute to the program's impact and depth. Several Moffitt HOB investigators have R01s and two recently submitted R01 applications scored in the 8th percentile. The previous review noted that accruals to HOB trials had declined, but this is due to the waxing/waning nature of five-year intervention trials in which most accruals occur within the first two years and then subjects continue to be followed through the end of the trial.

The EAC noted several exciting opportunities for HOB members to collaborate with members of other programs. For example, members could initiate closer ties with the Chemical Biology & Molecular Medicine (CBMM) and Immunology (IMM) programs to ensure that a range of useful patient-reported outcomes (PROs) are collected for enrollees of all clinical trials, with data made available for analysis. With CBMM, IMM, and Cancer Biology & Evolution (CBE) faculty, members could collaborate to facilitate systematic collection of PROs in clinic and to combine electronic health record (EHR) data with PROs collected through surveys for subjects enrolled in HOB studies. This would foster expansion of services offered through the Survey Methods Core (SMC). Capability to enroll, collect data, intervene, and follow subjects through longitudinal studies is the "new wave" of outcomes and behavior research and Moffitt can be a leader if it expands the excellent but more traditional survey methodology into this more innovative space. Such research will fit nicely with the recent investment in big data capabilities and the HOB's interest in expanding Cancer Care Delivery Research as well as provide support to other research programs, particularly CE, and enhance clinical trials.

The EAC had extensive discussion regarding whether Cancer Care Delivery Research should be a separate aim within HOB or a cross-cutting focus that is relevant to current Aims 1 (prevention/early detection), 2 (QOL), and 4 (health disparities). Program leaders may want to consider focusing on developing more evidence-based approaches for delivering cancer care in each of these areas rather than conceptualizing Cancer Care Delivery as a separate aim (and academic group).

Cancer Care Delivery is a large area of research; it can be defined in different ways and with different foci. Cancer Care Delivery Research is often associated with system-level research – several people mentioned research conducted by integrated systems such as Kaiser Permanente

– but that may not be the focus at Moffitt. The EAC recommends that the HOB program carefully define the type of Cancer Care Delivery Research aligning with the program and then work toward proposing research and recruiting faculty that align with that focus. This should be conducted in concert with other programs (e.g., CE) that touch upon Cancer Care Delivery Research and the Clinical Trials Office. The EAC members recommend that Moffitt select the approaches for delivering cancer care for which HOB should generate evidence – e.g., clinical decision making, reducing financial burden, and evidence-based clinical practice. The members recommended that Moffitt consider whether to develop a group that uses local data to generate evidence or hire faculty experts in using existing large data sets or some combination of both. It will be important to make a case for what investigators will be able to study at Moffitt that cannot be done as well in other kinds of cancer centers and to consider what type of Cancer Care Delivery Research will best address catchment area specific needs. These clarifications will likely guide program planning and recruitment.

Cancer Epidemiology Research Program

The Cancer Epidemiology (CE) Research Program is led by Dr. Peter Kanetsky, an outstanding and relatively recent recruit to Moffitt for a Program with a long and successful history. The overall goal of the Program is to reduce cancer burden by identifying determinants of disease development, progression and outcome, and to translate these findings to successful prevention interventions. The program has three focused aims: 1) Examine the association of inherited susceptibility biomarkers with cancer risk, progression, and outcome; 2) Identify and test acquired biomarkers that predict cancer risk, progression, and outcome; and 3) Investigate promising approaches for the prevention, detection and control of cancer. These aims remain highly relevant and the program is appropriately populated with members, including three new senior and four new junior recruits, to address them.

The Program received an “Exceptional” rating in the 2016 review, with praise for the recruitment of a new leader, exceptional science, a strong publication record, and solid grant funding. Scientific accomplishments that were highlighted included numerous infection-related cancer projects (HPV natural history and vaccine studies as well as viral etiologies of skin cancers) and the inherited susceptibility to cancers, including brain and ovarian cancers and melanoma. No notable weaknesses were articulated.

Dr. Kanetsky provided an update demonstrating exceptional productivity since the grant submission. Peer reviewed funding was stable from the time of submission ($5M), and there were 180 publications. Of note, the proportion of intra- and inter-programmatic publications was cited at ~19%. The Program membership has been dynamic, with the recruitment of senior faculty with expertise in the epidemiology of ovarian and breast cancer, clinical trial analysis, and statistical genomics and the loss of a senior genetic epidemiologist. The highlighted scientific achievements were quite exciting, including contributions to the genomic drivers of testicular cancer, evaluating the contribution of pain medications to brain tumors, and describing the protection of the HPV vaccination afforded through oropharyngeal antibodies in middle-aged men.

Looking ahead, the Program described two goals to accomplish prior to renewal in 2021: increasing base funding, and “continuing forward momentum” (with a focus on clinical epidemiology, radiomic research, and health disparities). It seeks to achieve this through recruitment of junior faculty, and possibly a program co-leader.

The EAC members found the presentation of the Cancer Epidemiology Program to be focused and quite exciting, and the work outlined will put the Program in strong shape for the competitive renewal. Some specific areas to address are outlined below:

1) The third aim of the Program reads a bit generic and weak, and it will be important to increase the specificity of the aim in the coming years.
2) The degree of intra- and inter-programmatic publications seems somewhat low (and is "significantly" lower than what was reported in the 2016 grant submission) and should be re-evaluated given the enthusiasm expressed for inter-disciplinary research at the EAC meeting.
3) Peer-reviewed funding for the Program is flat, especially considering the net addition of several faculty members; Dr. Kanetsky articulated a plan to address this, including an open recruitment for an assistant/associate member in breast or hematologic cancer or with expertise in clinical epidemiology, immunology, or metabolism (who would transfer in or seek funding). Dedicating cancer center pilot funding to CE program priority areas (specific aims and cancer center-identified catchment area cancer problems) with the greatest potential for grant funding is one strategy. As mentioned at the visit, all Program Leaders receive innovation funds to support priority areas.
4) Some of the areas that were highlighted in the 2016 summary statement and in Dr. Kanetsky's presentation are not emphasized in the future directions. As examples, there are exceptional opportunities to explore more deeply the immunology and expanded use of the HPV vaccine (and other viruses associated with cancer), and the opportunities afforded by the deeper analyses of inherited genetic contributions to cancer.
5) The proposed recruits do not particularly play to the strengths of existing faculty at Moffitt, and also may not be aligned to the disease burden in the catchment area (see item 1 below).

Dr. Kanetsky requested guidance in prioritization of faculty growth areas. EAC recommendations include prioritizing growth areas to those that deepen within CE and its interactions with other programs. Examples may include focusing faculty recruiting in areas relevant to uptake of HPV vaccine (across CE and HOB); natural and vaccine effectiveness for prevention of HPV infection; and treatment of HPV+ lesions (across CE and IMM). Other recommendations include aligning faculty recruitment to catchment area problems. For example, breast cancer (a common cancer in the catchment area and everywhere in the US), has only one CE member with a primary research focus (although four faculty have a history of research on this cancer). The EAC members were thus supportive of recruitment of another breast cancer epidemiologist who could compliment the strength of a recent recruit in the clinical faculty and would be responsive to an important disease in the catchment area. Given the high proportion of older adults in the catchment area, consider recruitment in relevant epidemiology substantive areas such as CHIP epidemiology (given MDS treatment research focus at Moffitt).

The EAC also discussed whether or not a co-leader should be appointed. At present, Dr. Kanetsky is the sole leader. The EAC recommended analysis of the need for a co-leader, along with definition of the separate roles of co-leaders, beyond simply research complementarity (unless the disciplines represented in the program were so disparate that a single leader may not be able to appropriately mentor all faculty). However, the EAC noted that, if the program foci do expand, a co-leader might be an excellent advancement.

Chemical Biology & Molecular Medicine Research Program

The Chemical Biology & Molecular Medicine (CBMM) Research Program represents a revision and realignment of the previous Experimental Therapeutics program; its current incarnation was first reviewed in the most recent competitive renewal. The program was restructured in part in response to prior reviewer concerns regarding overlap between the former Experimental Therapeutics and

Molecular Oncology and Drug Discovery programs. The program has strong leadership in Drs. Eric Haura and Saïd Sebti, both well-established investigators with complementary expertise in basic, translational, and clinical research. The goal of the program is to integrate chemical biology and systems biology technologies to develop new therapeutic approaches.

Criticisms of this program in the last competitive renewal included concerns regarding the diffuse nature of the stated Specific Aims, modest numbers of high impact publications with first and/or senior authorship at Moffitt, a recent decline in therapeutic clinical trials accruals, and limited examples of successful translation of laboratory science of the program into clinical testing.

The team has begun to address each of these concerns. The program Aims have been revised to focus on inhibition of cancer-specific signal transduction pathways, and updated data demonstrates substantial recovery in the pace of clinical trial accrual. There are examples of substantial publications in the past year, including the work of Dr. Uwe Rix defining novel secondary activities of ceritinib – an approach that can be more broadly applied to repurposing of other drugs – and a second example from Dr. Nupam Mahajan defining epigenetic mechanisms of acquired therapeutic resistance in prostate cancer with clear translational implications.

Opportunities for the program include consideration of additional focused multi-investigator grants (P01, SPORE, or other mechanisms). The leaders may consider more substantial revision of the Aims to capture the role of the program in prioritizing research directions – there is great science across the research participants in this program and it may help, in describing the program, to better define how the program structure adds value to what would otherwise be going on without programmatic designation. Examples of added value could include strategic investment in particular areas of interest, describing a clear programmatic role in prioritizing translational opportunities at Moffitt, and promoting team building toward collaborative multi-investigator grant submissions.

The recent competitive renewal may have underrepresented the actual translational impact of this program. The EAC members encouraged the program to recognize and highlight additional examples of clinical translation including from discovery research in other programs and even from outside the institution, for example when science within this program is contributing to defining novel potential applications of existing targeted inhibitors.

Immunology Research Program

The Immunology (IMM) Research Program received an “Excellent” rating at the last site visit, with a number of strengths but also some noted weaknesses. There are three aims: 1) Advance and translate T cell therapy; 2) Define molecular and cellular mechanisms of innate and adaptive immunity in cancer; and 3) Prevent graft-versus-host disease without interfering with anti-cancer effects.

The CCSG reviewers commented on the solid mix of basic and clinical investigators who have a strong cancer focus and impactful clinical studies. Strength was also noted in a T32 regarding the excellent mentorship within this program. The presentation highlighted the role of the Program Co-Leaders in mentoring junior faculty through grant writing and manuscript review. Finally, eight out of 13 new recruits have some grant funding. In addition, the reviewers noted multiple areas of strength including collaborative teams across IMM and the Immune and Cellular Therapy clinical services; high impact publications; strong focus on translational science and clinical outcomes using immunotherapeutic agents; high core usage; and strong collaborative activities. On the other hand, reviewers commented on a suboptimal R01 funding base, and missed opportunities to collaborate with others.

Some improvements have already been partly addressed since the recruitment of Dr. Jose Conejo-Garcia. NCI funding and NCI peer reviewed grants have risen to approximately $1.7 million (M) from the $1.14 M cited in the last review, and DOD and Stand Up to Cancer grants have also been funded. Since the site visit, peer review funding has increased by a factor of 2.7 and total funding by 3.7X (remarkable year over year growth). However, since the previous drop in funding was noted twice in the CCSG review, and the EAC noted the three-year duration of the SU2C cancer grant at a previous meeting, the IMM program as a whole has to push hard for both cancer-related and, more importantly, NCI funding.

Another critique focuses on inter-programmatic collaboration. This should already have been remedied due to the large number of immunotherapeutic trials representing collaboration with CBMM, and IMM members should be strongly encouraged to interact with investigators in other programs. Other potential areas of inter-programmatic collaboration include the study of mucosal immunity from HPV vaccination, which was highlighted in the Cancer Epidemiology presentation. This is an area that is primed for peer-review funding. It was encouraging to learn that there has already been a joint IMM-CE retreat and the leaders of the two Programs have pooled their innovation funds to spur additional inter-programmatic pilot projects.

Another major challenge noted by the site visit review was the loss of Dr. Jeff Weber. Additionally, two valuable founding/longstanding members, Drs. Julie Djeu and Claudio Anasetti, are retiring. These represent significant losses in seniority that need to be filled with outstanding candidates. To address this, Dr. Conejo-Garcia has already recruited an R01-funded and energetic investigator, Dr. Paulo Rodriguez, and additional recruitment is ongoing.

Overall, the IMM program has unique strengths in advancing immunotherapy and cell-based therapy at Moffitt. It is laudable that 14 immunotherapy trials are ongoing that recruited 258 patients for trial activities. This is supported by an outstanding Immunotherapy working group and the Immune and Cell Therapy (ICE-T) service, both led by Program member Dr. Fred Locke, who shortly after the EAC meeting was announced as IMM Co-Leader of IMM. The IMM faculty should be encouraged to collaborate with members of CBMM and other research programs to expand clinical trials and grant support. In addition, there should be a clear leadership structure to set priorities since these trials are expensive and need to be prioritized. A major challenge in the next term will be to increase funding and to recruit up to six IMM positions, including some senior scientists. However the EAC has confidence that Dr. Conejo-Garcia together with senior IMM members will guide the IMM program towards an upward trajectory. In addition, Cancer Center Leadership is driving recruitment of the next Chair of BMT, ensuring that hire has a strong research portfolio. Finally, the EAC recommended that the program continues on the strength of both adaptive and innate immunity in cancer, but Co-Leaders refocus the aims with fresh goals that will likely be greatly advanced due to recent and new recruits. These new goals may include the molecular understanding of immunoresistance, for example. In addition, the program may want to broaden the GVHD aim to include studying other facets of immunotoxicity, such as from checkpoint blockade and CAR T-cells.

Cancer Biology & Evolution Research Program

The Cancer Biology & Evolution (CBE) Research Program, led by Drs. Elsa Flores and Robert Gatenby, received a merit score of “Excellent to Outstanding” at review. Dr. Flores was a new leader introduced at the site visit. Comments noted that CBE was innovative, cutting edge and novel, with successful transdisciplinary collaborations across math, physics, evolutionary and cancer biology, multi-PI grants and an expectation that new discoveries would impact cancer prevention and tumorigenesis, although the EAC would add, therapeutic decision making and

clinical outcomes. Concerns were that the complexity of analytics might fail in its level of high impact discovery and thus was “nascent” and that “endpoints remain unmet.”

In the interim, the program continues to advance. CBE now includes over $7 M in peer reviewed funding; has initiated clinical trials in which trial design for drug exposure in prostate cancer is determined by modeling response linked to concepts of evolutionary biology; and has excelled in its rather unique expertise in Darwinian dynamics and adaptation strategies that can be both modeled and tested in biological and human systems. Programmatic efforts to link disciplines, increase training, host “mixers” for cross-disciplinary science, and integrate clinical collaborations are exactly how a program of this sort drives mutual benefit. The EAC members wondered whether the uniqueness of this program could be complex for CCSG reviewers and whether this might be improved by clearly describing the connectivity from model to biology to human application back to improving the model and pointing out the challenges and impact of these translations. Since many centers are using such modeling to track genetic mutational subclonal tumor evolution and response to therapy, this could be more overtly linked to the portfolio. While all of the new projects are quite exciting, the leaders will need to demonstrate innovation in model development, design and translational impact for this program to move up in review.

The interdisciplinary efforts should be noted, including the undergraduate and graduate course work, T32 application, well received international conference sponsorship, involvement of clinical investigators, new projects in adaptive therapy, immune-oncology trials and asymmetric game dosing. Likewise, the links to biological tumor and tumor model data will help refine the evolutionary systems biology towards broader applicability. The EAC recommended that the Program (leaders and members) work together to define metrics of success and engage in annual goal setting centered on two major areas: integration of disciplines, and clinical trial activity. Developing a clearly articulated set of metrics for success will be of benefit to the program. It was also recommended to identify clinical issues that can be addressed through the unique expertise of the CBE program. Finally, Program leaders should be prepared to articulate how CBE research addresses (at least in part) the needs of the catchment area, as aligned to the new guidelines.

Developmental CCSG Programs

Dr. John Cleveland, ACD of Basic Science and with significant cancer center leadership experience, was recruited to Moffitt in 2014. He presented two potential CCSG research programs that were introduced in the last renewal as goals for the current cycle: *Cancer Metabolism and Metabolic Therapy* and *RNA Biology and Medicine*. The existing strengths of each of these areas were well articulated, as were the challenges for creating one or both of these themes as new research programs given subsequent changes in the NCI guidelines.

The EAC was enthusiastic about Moffitt expanding the research and necessary infrastructure for both areas. However the EAC did not identify a compelling reason to create new CCSG research programs in either domain. Two alternative strategies discussed were either to create a center for metabolic research and/or RNA biology within Moffitt as a trans-programmatic effort or to focus on expanding the focus of one or both of these themes within the existing programs. The NCI Centers Branch’s stated emphasis on having fewer, stronger research programs in CCSG-funded centers lends support to either alternative approach.

The EAC advised against having a stand-alone Metabolic Clinic within Moffitt as opposed to embedding metabolic assessments and metabolic interventions in the existing clinics. There was also EAC interest in linking in the fledgling Moffitt research activities related to the microbiome to its metabolic research.

Center of Excellence in Infection Research in Cancer (CIRC)
The Center of Excellence (CoE) in Infection Research in Cancer (CIRC) was first established in 2012 and is led by Dr. Anna Giuliano. CIRC is one of four Centers of Excellence at Moffitt, and its stated goal is to "elucidate the role of infectious agents in the etiology of cancer and translate this knowledge into novel and effective strategies for the prevention and treatment of cancer." Aside from leaders being funded as Staff Investigators, the Centers of Excellence were not reviewed individually in the 2016 CCSG Summary Statement, although the work within the CIRC was highlighted with much enthusiasm in the evaluation of the Cancer Epidemiology Program.

Administratively, the CIRC reports to the ACD of Translational Science, Dr. Jim Mulé, and has "approximately 30" engaged faculty across all of the CCSG programs. The CIRC also has "several" working groups. It receives modest financial support, inclusive of support for administrative assistance, partial salary support for the Director, and small funds for seminar series and retreats.

Scientifically, the activities of the CIRC are centered around viruses that cause cancer, specifically HPV and HCV. The HPV research is outstanding, and Dr. Giuliano's projects to examine oropharyngeal immunity after HPV vaccination in men could potentially be paradigm shifting, especially a proposed large Phase 3 study to determine whether the HPV vaccine reduces detection of high-risk HPV strains in the oropharynx of middle-aged men. Additional work on barriers to HPV vaccine uptake is nascent, but also promising. Less developed but also of great potential is a project to examine the prevalence and natural history of HCV infection in the USF Health System and at other institutions in the state.

The CIRC would seem to be an ideal place to recruit additional faculty to work within both the Cancer Epidemiology and Health Outcomes & Behavior Research Programs. CIRC's projects have the potential to grow into many new fields of research with the input of new junior faculty. Specifically, recruitment of a scientist with expertise in immunology, epidemiology and vaccine development and implementation, or an infectious disease clinical trialist, could lead to strong NIH grant support and important scientific advances. Similarly, an investigator with experience in vaccine uptake and awareness could address both HPV vaccine uptake in the Moffitt catchment area, but also lay the groundwork for assuring the uptake of the HPV vaccine in men, if the upcoming study of immunity in this population shows positive results. Finally, adding a scientist with experience in behavioral approaches to improve adherence to cancer screening through viral detection (HPV / HCV) could build on a promising relationship with USF. Despite a relatively low HIV prevalence in its catchment area, Moffitt should consider increasing its focus on HIV-associated malignancies. NCI contributes nearly 20% of the $1 billion NIH AIDS research budget, and there are many calls out for supplements to the P30 award to increase research activities in this field. Consider contacting the Office of HIV-Associated Malignancies at NCI for more information.

A Center of Excellence must actually demonstrate its excellence with definable metrics. Although there is little doubt that the work of the CIRC is outstanding, metrics for success, growth or attrition should be formally articulated. If / when excellence is indeed demonstrated, further financial investments in the CIRC could lead to significant growth of Moffitt and further recognition of the MCC as a leader in infection-associated cancer prevention and treatment.

Center for Evolutionary Therapy (CET)
Dr. Alexander (Sandy) Anderson leads the Center for Evolutionary Therapy (CET) CoE. This new center creates a unique milieu of investigators from mathematical oncology, evolutionary biology, cancer biology, oncology, epidemiology, behavior (e.g., risk prediction, decision-making) and imaging. The participants have been highly successful in developing high impact papers and in

developing unique concepts associated with novel investigator initiated trials. The CoE challenges some basic tenets of clinical oncology that can be rigorously tested although the metrics for this are in development. The important next hurdles for the CET will be expansion into relevant biologic and clinical models with appropriate biomarkers, spanning genomics, radiomics, metabolic markers etc. The future is bright and targeting some additional models and metrics for development and translation will be helpful to its growth. This involves extensive discussion among the multiple disciplines noted previously.

Center of Excellence (CoE) in Lung Cancer
The Lung Cancer COE is a cross-disciplinary center established in 2010 and is currently led by Dr. Eric Haura. Dr. Haura is well positioned to lead this center, with active engagement in both laboratory-based discovery and translational clinical research domains. This center serves as a magnet for disease-focused philanthropic gifts, and provides flexible funding for high priority initiatives in lung cancer research. These funds have been effectively deployed to support expansion of proteomic and metabolomic research in lung cancer, areas of particular innovation and strength at Moffitt. These funds have also been used to fund key research staff, and to prime new pilot projects in lung cancer that can support the application for external peer-reviewed grants.

Lung cancer is identified as a high priority within the Moffitt catchment area. Targeted investment in this area through the CoE mechanism is appropriate. Impact of these philanthropic funds is being carefully tracked, to the benefit of the center and to provide return-on-investment feedback to the contributing donors.

There were no major concerns with the Lung CoE as currently structured. A minor concern is commitment of Dr. Haura as the director of the Lung CoE, while also serving as CBMM Co-Leader. As currently structured, it appears that the administrative burden of directing the Lung CoE is quite manageable, and Dr. Haura's research expertise nicely encompasses both of these domains. Over time as the Lung CoE and the CBMM Research Program grow with additional recruitment, it may be appropriate to identify distinct leaders for these two important initiatives.

Center of Excellence (CoE) Melanoma and Non-Melanoma Skin Cancer
The Melanoma and Non-Melanoma Skin Cancer CoE has been led by Dr. Keiran Smalley since 2016. The activities of the center initially centered around the Melanoma and Skin SPORE, which will be resubmitted in May of 2018, but are now expanding into other areas, including uveal melanoma and leptomeningeal disease. Projects in the SPORE for the upcoming renewal include: 1) IMiDs and anti-PD1 therapy based on preclinical data that IMiDs alter T-cell metabolism; 2) the p53 family of genes and squamous cell cancer of the skin; 3) a proteomics approach to target NRAS+ melanoma, and 4) a single cell RNA sequencing project to look at melanoma cell diversity within tumors.

In addition, the CoE is expanding to include studies of CNS metastases, in collaboration with the neuro-oncology group. These studies will include evaluation of tumor cells by single cell RNA-seq from the CSF of patients with leptomeningeal disease. In addition the group is collaborating with Dr. Bill Harbour at the University of Miami to study uveal melanoma, which continues to have a dismal outcome.

The CoE concept is an outstanding vehicle for fund raising and performing multidisciplinary research. Recommendations include:

1) Moffitt should enhance the existing TCC protocol and infrastructure with surgeons, pathologists and laboratory personnel to systematically and methodically capture and bank tumor tissue from patients before therapy, on therapy, and at the time of progression.
2) It will be important to raise more funds to support more innovative pilot projects. This will help enable future grants, as well as entrepreneurial activities.
3) The leaders should continue to mentor young faculty in conducting multidisciplinary translational research, as well as in grant-writing, leadership, understanding intellectual property and entrepreneurship, and strategies to interface with the biotech and pharma industry.

Shared Resources

Gene Targeting

Dr. Florian Karreth presented the developing Gene Targeting shared resource. The core is newly operating with current/planned services including generation of genetically engineered mouse strains; colony establishment and maintenance; and embryonic stem cell (ES) services (ES derivation/targeting and CRISPR). There are 10 ongoing projects, and 10 planned projects thus far. Future plans call for rolling out the core on a wider basis, optimizing ES services, and providing a range of educational services.

Dr. Karreth was recruited to Moffitt in 2016 as Assistant Member. He is enthusiastic and well-trained, having worked in the laboratories of Drs. Erwin Wagner, Dave Tuveson, and Pier Pandolfi. He has already been recognized with a funded NCI K22 grant.

This core provides key transgenic services that are widely used in current cancer and non-cancer science, and the EAC was supportive of the core. However, there was a concern that the narrow scope of current efforts could hamper review for CCSG support. The members recommended including patient-derived xenograft (PDX) and organoid models and they also encouraged efforts to include more immunologic models.

Survey Methods Core

The Survey Methods Core (SMC), now under Interim Director Dr. Shelley Tworoger, was rated "Exceptional" in the 2016 review. Its three aims (consult on use of quality survey tools; multi-modality survey services; qualitative methodology) have been well met; however the core has seen a recent downturn in utilization, and most users are from one program (HOB). This has led the Moffitt leadership to establish a task force to review the SMC. This will include conducting an environmental scan of other similar cores at other Centers, and assessing whether a restructuring or reorganization should be considered. Some preliminary thought has been given to expanding services to include novel data collection methods, Apps for mHealth and eHealth research, and expanded support for interventional trials. Additional consideration is being given to leveraging cores with expertise in these areas (Cancer Informatics and Collaborative Data Services Cores). The results of the environmental scan and self-study are not yet complete, so the EAC is not in a position to make firm recommendations at this time. The members recommended that this be discussed at the next meeting, if not sooner, when the optimal structure and function of this highly successful core can be considered more fully.

Biostatistics and Cancer Informatics

The EAC conducted a focused review of the Biostatistics and Cancer Informatics Cores. Overall, the members were very pleased with Moffitt's emphasis on the quantitative sciences and institutional commitment to improving team science collaboration and the quality of research

produced. Both cores function well and exhibit a solid record of interaction between the quantitative scientists and researchers. The faculty financial model based upon percent effort and a transaction-based model for staff has always worked well. The cores are highly productive, with a strong track record of grant applications and published papers.

The new chair of the Department of Biostatistics and Bioinformatics, Dr. Brooke L. Fridley, is an outstanding addition. Prior to joining Moffitt Cancer Center, Dr. Fridley directed the Biostatistics and Informatics Shared Resource for the NCI designated University of Kansas Cancer Center, as well as the Kansas-INBRE Bioinformatics Core. Her research, which had a very productive start while on faculty at the Mayo Clinic, focuses on the areas of statistical genomics, molecular epidemiology of cancer, cancer genomics, and pharmacogenomics. She has extensive experience as both a PI and a collaborating statistician, particularly in the design and analysis of genomic studies involving multiple types of -omics data (e.g., genotypic, DNA methylation, mRNA expression, copy number). Thus, in the era of big data, Dr. Fridley is a top-notch choice to lead the department.

The EAC members recommended that the existing Biostatistics and Cancer Informatics cores be merged to a single quantitative sciences core, under the overall scientific leadership of Dr. Fridley. On the most recent CCSG renewal, both the Cancer Informatics and Biostatistics cores were scored as "Outstanding;" a single merged core would likely be scored as "Exceptional." Additional leadership of distinct areas will likely be necessary, but with the merging of expertise, it may be along the traditional biostatistics/bioinformatics division, or it may materialize in other sections within the larger core. The EAC also recommended that the core consider expanding the infrastructure to ensure access of members to a broader range of publicly available datasets. For example, the core may wish to consider creating a local repository with instances of these datasets, to facility member access. Other focus areas that were discussed included pragmatic trials, real-world data, TCC/ORIEN, and learning health systems; these directions are strongly encouraged.

Community Engagement and Outreach

Brian Springer, ACD of Research Administration, presented an overview of Community Outreach and Engagement (COE), focusing on the catchment area, research strategies in the catchment area, and leadership structure. This area has continued to grow in importance. While it was not scored separately in the last review, most of the comments were strongly positive and supportive of Moffitt's efforts in the 15-county west central Florida catchment area. Key specific catchment area needs (lung cancer, skin cancer, HPV immunization) have been addressed through targeted Centers of Excellence. Moffitt has been generally successful overall in accruing race/gender/ethnicity representative populations to interventional clinical trials. The Tampa Bay Community Cancer Network continues as a robust resource for engaging the greater community in both research and outreach activities.

Moffitt has established a working group to define catchment area needs. Several unique needs have developed since the prior review, for example relocated populations (approximately 300,000) from Puerto Rico after Hurricane Maria. Strategies to build research have included use of internal developmental funds, collaborations with the Florida Academic Cancer Centers Alliance, and emphasis on minority accruals. The EAC strongly encouraged these important activities.

The EAC recommended that Moffitt re-evaluate the current catchment area, particularly with the growth of Moffitt's affiliations and partnerships. For example, substantive relationships in other parts of the state might more effectively be called a "secondary catchment area." The members also recommended that each research program specifically articulate catchment area activities and results, and emphasize the relevant activities in each clinical area as well. It will be important to

develop specific metrics for success to demonstrate impact. The EAC members reviewed and discussed extensively a number of potential leadership structures for this area, for example appointing a distinct Associate Center Director (ACD) of Community Outreach and Engagement, or having this be a component of another ACD's portfolio. There are several different types of models in practice. The EAC recommended reviewing the responsibilities of each of the ACDs to assess the optimal structure for oversight of these key activities.

Cancer Research Career Enhancement and Related Activities

Dr. Julie Djeu, who has served as Moffitt's founding Associate Center Director of Education and Training, recently announced her retirement. The EAC members lauded Dr. Djeu's many accomplishments as she gave an overview of the area now called Cancer Research Career Enhancement and Related Activities. Since the last review, Drs. Djeu and Ken Wright have developed an Education Council that provides comprehensive oversight of educational activities from high school to junior faculty, from research to clinical areas, and from Moffitt to regional and global communities. The Education Council is made up of key leaders from across the institution. Dr. Djeu described programs in each area, including a High School Internship in Mathematical Oncology; the Summer Program in Advancement of Knowledge (SPARK) and the Dartmouth Spring Course in Math Oncology (both undergraduate); and Cancer Biology, Medical Physics, and Systems Biology PhD programs. Programs focusing on postdoctoral trainees, underrepresented populations, and unique internships were also highlighted. Moffitt operates several T32s (2), R25s (2), and K/F grants (6). A number of other T32 submissions are currently planned or are underway based around Moffitt strengths (infection research, precision medicine, mathematical oncology, immunotherapy).

The EAC noted Moffitt's success to date in educational efforts. With this now being a separately scored area, the members recommended several ways to further improve. Developing additional peer-reviewed funding will be helpful, as well as better outcome tracking for the nearly 2,000 trainees per year. It will be helpful to highlight strategies to transition junior trainee grants to R funding, and to increase the number of K awards. This may require expanding the infrastructure supporting educational activities.

In summary, the EAC members are enthusiastic about Moffitt's achievements to date, and positive trajectory. The goal of the time until the next CCSG renewal should focus on expanding strengths and demonstrating impact through clear metrics of success. Thank you for a well-organized and extremely productive visit. The EAC members look forward to reviewing your continued progress next year.

Sincerely,

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