SUMMARY STATEMENT

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(Privileged Communication)

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Principal Investigator

WEINER, GEORGE J.

Applicant Organization: UNIVERSITY OF IOWA

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

Meeting Date: **12/03/2020**
Council: **JAN 2021**
Requested Start: **04/01/2021**

RFA/PA: **PAR20-043**
PCC: **2IMD**

Project Title: **Cancer Center Support Grant**

SRG Action: **Impact Score:28**
Next Steps: **Visit https://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**
Age: **1A-Children, Adults, Older Adults, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
21	1,764,344	2,725,914
22	1,764,344	2,725,914
23	1,764,344	2,725,914
24	1,764,344	2,725,914
25	1,764,344	2,725,914
TOTAL	8,821,720	13,629,570

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: The overall mission of the Holden Comprehensive Cancer Center (HCCC) at the University of Iowa (UI), the only NCI-designated cancer center in Iowa, is to decrease the pain and suffering caused by cancer in Iowa, surrounding communities, and around the world through improved cancer prevention and treatment based on three interdependent missions of research, clinical service and education.

In this Cancer Center Support Grant (CCSG) competing renewal application, support is requested for four Research Programs; Shared Resource Management; nine Shared Resources; Cancer Research Training and Education Coordination; Community Outreach and Engagement; Clinical Protocol and Data Management; Protocol Review and Monitoring System; Developmental Funds; Leadership, Planning, and Evaluation; and Administration.

Cancer Genes and Pathway (CGP) Research Program, rated excellent, is led by two well-qualified investigators─Dr. Dawn Quelle, who is driving the research on endocrine tumors and signaling pathways, and Dr. Michael Tomasson, a physician scientist recruited to enhance translation aspect of the CGP program. This program's overall funding is strong, and it has solid productivity in terms of publications. Notable program research includes the strong work on T cell responses to DNA damage and the study of BRAF resistance mechanisms. It also provides unique expertise and animal model systems to the HCCC research. Its work on DNA damage/repair and genome stability forms a strong foundational science, but translation of this fundamental science to more clinical aspects could be further enhanced. In the current project period, the program has enhanced its cancer focus and some examples of research taken through the translation pipeline were presented. In addition, strong collaborations evidenced by a high rate of collaborative publications as well as development of collaborative grants is noted. However, although the program is moving in the right direction, it has not reached its maximum effectiveness and levels of innovation and impact of the CGP program research could be improved. The program's future direction could be more strategic and intentional in thematic development and there are some missed opportunities in addressing the catchment area needs, considering the CGP expertise in DNA repair mechanism and lymphoma biology as well as the unique environmental risk factors of the HCCC catchment area. Overall, the CGP program is a solid, excellent research program.

Experimental Therapeutics (ET) Research Program, rated outstanding to excellent, is led by two highly collaborative investigators─Dr. Aliasger Salem, who has expertise in drug formulation and nanotechnology, and Dr. Bryan Allen, a new leader with expertise in translational research and clinical trial development. In the current project period, the program has increased the activities to enhance translational collaboration and advance drugs through the pipeline to clinical trials. Multiple scientific accomplishments of the ET program include new mechanistic understanding of breast cancer stem cells, lead compounds identified by high-throughput screening, and development of some novel cancer therapeutics. In particular, the work on the TLR9 agonists documents the movement of the basic science research findings to clinical trials. The program has well-defined intra- and inter-program activities and productive collaborations are demonstrated by the number of collaborative publications and multi-investigator grants. While the ET program is improving overall and its future goals and focus on the catchment area priorities are satisfactory, its research still appears more technology-driven and rather incremental and opportunities exist in enhancing innovation and pushing science and translation through long-term strategy. Only 10% of the program publications are in high-impact journals and there is limited evidence of paradigm-shifting research or impact of clinical trials on changes to patient care. In addition, overall translation pathways in terms of preclinical evaluation and drug discovery could be better defined.

Free Radical Metabolism and Imaging (FRMI) Research Program, rated excellent to outstanding, is led by two investigators with complementary expertise—Dr. Douglas Spitz, a well-recognized investigator in studying oxidative stress in cancer biology and therapy as well as radiobiology, and Dr. Yusuf Menda, a recently recruited medical imaging expert. The FRMI program is a cornerstone program of the HCCC with free radical metabolism and imaging components. Its free radical component under the exceptional leadership of Dr. Spitz is quite strong and there is evidence of moving preclinical hypothesis to clinical studies. The work on ascorbate demonstrates the impact of the interaction between basic and clinical investigators. However, while the program is moving in the right direction by including imaging component, it is not as strong as the free radical component due to lack of innovation and clearly articulated vision beyond its role in complementing the redox metabolism aspect of this program. This weakness is somewhat mitigated by Dr. Menda's description of a vision to expand radionuclide-based theranostics in the next project period at the site visit. An additional weakness is that the program has not fully realized the potential of tumor genomics and epigenetics in complementing the research done in this program. Overall, this program has a good representation from the entire cancer center, and strong integration and more innovation and vision could enhance the future growth of this program.

Cancer Epidemiology and Population Science (CEPS) Research Program, rated excellent to outstanding, is led by two investigators with complementary expertise—Dr. Charles Lynch, an epidemiologist, and Dr. Richard Hoffman, an internist. The CEPS program's innovation reflects participation in long-standing national research programs and consortia, including the NCI SEER Program. The strengths of this program include its impact on improving HPV vaccination rates locally and nationally and its important work in the area of tobacco use and cessation, cancer screening, and cancer etiology research focusing on risk factors including environmental exposures. The collaborative nature of this program is evident with high rates of intra- and inter-programmatic publications. However, full cancer relevance of the funding from the NIEHS on environmental toxicology is not well clarified and the decrease in overall cancer-relevant peer-reviewed funding is of some concern. There are opportunities to translate observations from the program's catchment area research for an impact on reducing the cancer burden and cancer disparities.

These four research programs are supported by nine shared resources (SRs) managed by the Shared Resource Management (SRM), which is rated excellent. The SRM has done a good job in establishing the User Advisory Committees and conducting surveys for feedback. The major restructuring of biobanking efforts through the BioMER Shard Resource have been impressive and three SR directors holding NCI R50 grants speaks to the quality of the SRs. However, the overall organization and management system appears somewhat complex with unclear decision-making processes and authority due to joint management with the institution. Despite this, the SRM appears reasonably effective in ensuring that HCCC members' needs are addressed and implementing changes in response to user feedback. Some areas for improvement are related to the lack of tracking system across the SRs, lack of detailed description about the User Advisory Committees, the potential issue of inadequate HCCC representation for the jointly managed SRs, and lack of clear plans to give priority access to SRs for cancer center members. In addition, the effectiveness of the recently implemented distribution of the bioinformatics embedded in other SRs is yet to be evaluated.

Biospecimen Procurement and Molecular Epidemiology Resource (BioMER) and Biostatistics Core (Biostats) are each rated outstanding to exceptional; High-Throughput Screening Core (HTS), Radiation Free Radical Research Core (RFRRC) and Viral Vector Core (VVC) are each rated outstanding; Population Research Core (PopRC) is rated outstanding to excellent; Flow Cytometry

Core (Flow) and Genomics Shared Resource (GSR) are each rated excellent; and Central Microscopy Research Facility (CMRF) is rated very good. In general, these SRs provide effective and essential support for HCCC research and their leadership and staff members have appropriate expertise and extensive experience for their roles.

The Cancer Research Training and Education Coordination (CRTEC), rated outstanding to exceptional, is led by a highly qualified and well-funded associate director (AD), Dr. Jon Houtman. The CRTEC activities are facilitated by the Office of Cancer Career Enhancement and Training (OCCET) for educating and training diverse trainees at all stages of training from high school students through faculty members. Educational programs are very well planned and strong, and they are available for students, researchers, clinicians, staff and community providers. Examples of integrating the input from the Community Advisory Board are also presented. However, the CRTEC's weakness is related to the measures of success due to lack of tracking of the past trainees. But a tracking system has just been initiated and the CRTEC is overall very strong.

Community Outreach and Engagement (COE), rated excellent, is led by Dr. Elizabeth Chrischilles, an expert on patient-centered cancer outcomes and comparative effectiveness research. The COE has a strong team with impactful program. It has made outstanding progress in assessing and monitoring the HCCC catchment area need by leveraging the Iowa Cancer Maps Initiative that was created to identify geographic patterns in cancer incidence. The COE is strong in regulation and policy areas mostly in population science and there is a focus on rural cancer control. In addition, its notable strength is the relationship between the HCCC and the Iowa Cancer Consortium (ICC)─the cancer control partnership for Iowa─that has had a positive impact on the catchment area through a variety of state-wide initiatives. However, it is unclear how the Community Advisory Board (CAB) and ICC work together to identify priorities in the catchment area. Specific examples of initiatives in response to the CAB feedback were not clearly described. In addition, there are still opportunities for the COE to catalyze catchment area-relevant research in basic science research programs as well as to improve efforts to increase under-represented minority representation in HCCC's clinical trials. In addition, there is some concern about the bandwidth of the AD of COE, Dr. Chrischilles, who also serves as the AD of population sciences, to oversee this important initiative. There is also a need to track and respond to actual data on metrics to evaluate COE's success

Clinical Protocol and Data Management (CPDM), rated very good to excellent, provides support for HCCC investigators through Clinical Research Services (CRS) and Data and Safety Monitoring (DSM). The CRS is well organized with well-described emphasis on increasing phase I trials and it has grown substantially by developing new capabilities. It has fully implemented OnCore in the current project period. While a 25% increase in number of trials is reported, there appears to be a lack of aspiration to do better. The areas for further improvements include overall accruals to treatment trials and trial activation time. The Data and Safety Monitoring (DSM) Plan, using risk-based monitoring, is acceptable. Inclusion of Minorities, Inclusion of Women, and Inclusion of Individuals Across the Lifespan in Clinical Research are each acceptable. Protocol Review and Monitoring System (PRMS) is satisfactory, with a large and well-organized process through disease-specific Multidisciplinary Oncology Groups (MOGs) and Trial Resource Evaluation Committee (TREC) for the first stage of scientific review and the Protocol Review and Monitoring Committee (PRMC) for the second stage. However, the specific description of the MOGs are lacking and there are issues with the PRMC quorum and still weak standards for accrual monitoring. It is also unclear how clinical research relevant to the catchment area is developed by the MOGs and then prioritized.

Developmental Funds is rated outstanding to excellent. The main investment areas are recruitment of both senior and junior faculty with a priority given in the areas that align with the HCCC strategic needs and seed grants using two different mechanisms, Oberley Awards to support innovative research concepts and Mezhir Awards to catalyze transdisciplinary team science that leverage matching institutional funds. These pilot funds are focused on catchment area issues with over 13-fold return on investments. However, a few reviewers question the rationale for proposing Dr. Maria Spies, whose expertise is in DNA repair basic science area, as a staff investigator in consideration of the HCCC's existing strength in DNA repair area.

Leadership, Planning, and Evaluation is rated outstanding. The HCCC has a strong and experienced leadership team that has been working well together. They are well qualified and very engaged in providing collaborative leadership for all aspects of the HCCC. The strategic planning process is comprehensive and rigorous with input from the External Advisory Board as well as Community Advisory Board. The new strategic plan is somewhat lacking on metrics for evaluating success. The process leading to the decision to eliminate the bioinformatics shared resource and replace it with a distributed model were not clear, nor was the process for evaluating the success of this new model. Similarly, metrics to evaluate the outcome of the protected time of clinicians for research as well as a specific plan for sustaining the protected time are not well described. In addition, there is some concern about the dual role for Dr. Elizabeth Chrischilles as AD of Population Science and AD of COE, specifically that she may be too overcommitted to be effective in both roles.

Cancer Center Administration, rated outstanding, is generally strong and meet all expectations of the CCSG. The Administration staff are well qualified with extensive experience for their respective roles. It has effectively represented the HCCC and provided oversight of the CCSG application process. While improvements made on data reporting in the current project period are evident, they are dependent on institutional reporting tools and there are opportunities for augmentation of information and reporting systems with the capability to capture cancer center-specific data fields and fulfill HCCC reporting requirements. A proactive role in providing ongoing Administration infrastructure support to new programmatic center initiatives, such as obesity/cancer, would benefit further the strategic advance of center plans. Clear metrics to show how Administration supports and informs the strategic planning and evaluation activities are lacking

The six Essential Characteristics are met. Transdisciplinary Collaboration and Coordination and Center Director are each rated exceptional, Cancer Focus is rated outstanding, Organizational Capabilities and Institutional Commitment are each rated outstanding to excellent, and Physical Space is rated excellent to outstanding.

Overall, as the only NCI-designated cancer center in Iowa, the HCCC is meeting all expectations of a CCSG-supported cancer center. It is conducting transdisciplinary research, next generation of cancer researchers are being trained, and its highly collaborative research programs are making solid progress. Under the strong, experienced leadership and unwavering commitment of the Director, Dr. George Weiner, the HCCC is doing overall a strong job with some exemplary scientific research and the CCSG adds strong value to the center's accomplishment. It is evident that the HCCC has an important and essential role in Iowa and it is in a unique position to capitalize on its unique catchment area populations. However, the HCCC has not reached its full potential yet and there are some missed opportunities. It is overall lacking impact and innovation in the development of scientific themes; shared resources are variable in quality; more efforts are needed in addressing its catchment area needs that

have been recognized; and clinical trials need improvements in moving forward. Overall, this application is rated excellent to outstanding and support for five years is appropriate.

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OVERALL DESCRIPTION (provided by applicant): Holden Comprehensive Cancer Center (HCCC) at the University of Iowa (UI) is the only NCI designated cancer center in the state of Iowa, a highly rural state that serves as the HCCC catchment area. The nearest Comprehensive Cancer Centers are approximately 200 miles away. The HCCC leverages its highly collaborative culture to advance transdisciplinary, collaborative cancer research that is particularly relevant to the people of Iowa. This includes basic cancer research, a strong portfolio of translational multi-investigator grants including two Specialized Program of Research Excellence (SPORE) P50 grants, a new NCI P01 and a growing portfolio of early phase clinical trials including studies based on basic science emerging from the HCCC. The HCCC functions administratively as a matrix Cancer Center with 170 Center members from seven UI colleges. Examples of transdisciplinary scientific advances include fundamental research into DNA repair, multiple promising early phase clinical trials based on laboratory advances made at the HCCC in the areas of toll-like receptor 9 (TLR9) agonists and pharmacologic doses of ascorbate, innovative studies in theranostics, and extensive molecular epidemiologic studies in lymphoma that have changed clinical practice. The members of the HCCC have $23.4 million in direct annual cancer-related, peer-reviewed, external research support. Of this, $11.0 million comes from the NCI. In the last funding cycle, HCCC members published 1,102 peer-reviewed cancer-relevant publications, with 76% involving intra-, inter-, or multi-institutional collaborations. The HCCC is organized into four research programs. Cancer Genes and Pathways (CGP) is the basic science program of the HCCC. Experimental Therapeutics (ET) and Free Radical Metabolism and Imaging (FRMI) are translational programs and Cancer Epidemiology and Population Science (CEPS) is a population science program. Support is requested for administration, evaluation and planning, clinical protocol development and monitoring, protocol review and monitoring and nine shared resources including Biostatistics, Central Microscopy, Flow Cytometry, Genomics, High Throughput Screening, Biospecimen Procurement & Molecular Epidemiology, Population Research, Radiation Free Radical Research and Viral Vector. The HCCC has a robust Community Outreach and Engagement effort focused on unique disparities in Iowa, such as rurality, obesity, HPV vaccination, that facilitates bidirectional interactions between the HCCC and the people of Iowa. It leverages the resources of the Iowa Cancer Consortium (ICC) and research infrastructure that extends into the community. It also has a comprehensive Career Enhancement (CE) Program. In summary, the HCCC provides a collaborative environment, infrastructure and resources to strengthen all aspects of interdisciplinary cancer research taking place at UI. The HCCC is requesting Cancer Center Support Grant (CCSG) funding and renewal of its status as an NCI designated Comprehensive Cancer Center.

OVERALL CRITIQUE:

Criterion Scores:

	Significance	Investigator	Innovation	Approach	Environment
Reviewer 1	2	2	3	2	3
Reviewer 2	2	1	2	2	3
Reviewer 3	2	2	4	4	2

The Holden Comprehensive Cancer Center (HCCC) at the University of Iowa (UI) is a matrix cancer center which received its initial NCI CCSG and comprehensive status in 2000 under the directorship of Dr. George Weiner, who has been the HCCC Director since 1999. In this competing renewal application for a CCSG, five years of support are requested for four Research Programs; Shared Resource Management and nine Shared Resources; Clinical Trials Office; Protocol Review and

Monitoring System; Cancer Research Training and Education Coordination; Community Outreach and Engagement; Leadership, Planning and Evaluation; Administration; and Developmental Funds.

The overall mission of the HCCC is to decrease the pain and suffering caused by cancer in Iowa, surrounding communities, and around the world through improved cancer prevention and treatment base on three interdependent missions of research, clinical service, and education. The mission is pursed via three aims. Aim 1 is to support a culture of excellence and transdisciplinary collaboration in cancer research, Aim 2 is to translate cancer research advances from the laboratory to the clinic and the clinic to the laboratory, and Aim 3 is to strengthen bidirectional interactions with the people of Iowa to reduce the burden of cancer in the state.

Peer-reviewed cancer-relevant funding for the HCCC is approximately $21.5 million in direct costs. Transdisciplinary collaboration is evident with an impressive rate of collaborative publications (76% of 1,102 publications) with 23% intra-programmatic, 21% inter-programmatic, and 57% inter-institutional collaborations. The HCCC defines its catchment area as the entire state of Iowa, a population of approximately 3.18 million of which 36% live in rural areas. Iowa has a high mortality rates for obesity-related cancers, there are important rural and racial/ethnic cancer disparities, and cancers related to environmental exposures are a high priority. It is noted that the HCCC is working in partnership with the Iowa Cancer Consortium to advance community outreach and engagement. The HCCC has 131 full and 39 associate members and it continues with the same four research program structure, including Cancer Genes and Pathways, Experimental Therapeutics, Free Radical Metabolism and Imaging, and Cancer Epidemiology and Population Science Research Programs.

The Cancer Genes and Pathways (CGP) Research Program, rated excellent, is led by Dr. Dawn Quelle, an expert in cancer cell biology who plays a key role in driving investigations on neuroendocrine tumors, and Dr. Michael Tomasson, a physician scientist with a focus in cancer genetics and translational research in hematologic malignancies. This basic research program has 42 full and nine associate members from five colleges and 17 academic departments. It has approximately $6.97 million (direct costs) in peer-reviewed cancer research funding. The three aims of the CGP program focus on cancer genetics and genomics, signaling and pathways within the malignant cell, and tumor extrinsic factors. In the current project period, the CGP program members have generated 384 peer-reviewed publications with 22% intra-programmatic, 30% inter-programmatic, and 54% inter-institutional collaborative publications. The CGP program provides solid, contemporary basic science studies in support of the mission of the HCCC. Its strengths include the continued productive scientific output; improvements in cancer focus and collaborative activities, including new multi-investigator program grants; and enhanced efforts towards translation. Program strengths in the area of the DNA damage/genome stability, neuroendocrine biology, and immune cell signaling have led to new scientific synergies within CGP and across the programs and are providing avenues for translation. However, there remain some weaknesses related to program breadth, lack of a clear vision for future thematic development, and somewhat moderate scientific impact. Greater clarity on how the “hand-off” of research discoveries happens and what role this program plays in prioritizing research findings for translation is needed. In addition, the program’s future direction could be more strategic and intentional and there are missed opportunities in addressing the catchment area needs.

The Experimental Therapeutics (ET) Research Program, led by Drs. Aliasger Salem and Bryan Allen, is rated outstanding to excellent. This translational research program has 28 full and 16 associate members from five colleges and 17 academic departments. Overall peer-reviewed funding remained the same from the previous funding cycle, approximately $2.69 million (direct costs), while the

percentage of NCI funding increased from 50% to 75%. The ET program has three aims: 1) Identify potential new cancer targets and develop novel cancer therapy approaches, 2) conduct pre-clinical evaluation of promising new therapeutic leads, and 3) translate promising leads to early phase clinical trials. In the current project period, the ET program members have generated 316 peer-reviewed publications with 24% intra-programmatic, 43% inter-programmatic, and 42% inter-institutional collaborative publications. The program activities and productive collaborations leading to clinical trials have been increased. Although the program is moderate on innovation and lacking clearly defined long-term strategies to bring therapeutics to clinical application, there has been significant improvement in investigator-initiated trials (IITs) and identification of new lead drug candidates based on the information of the early translational pipeline provided at the site visit. Significant scientific advancements and translation of research findings have been made in each of the three aims, but they have not been paradigm shifting or resulted in changes to standard of care practice that improved cancer patient outcomes.

The Free Radical Metabolism and Imaging (FRMI) Research Program, led by Drs. Douglas Spitz and Yusuf Menda, is rated excellent to outstanding. This translational research program has 33 full and five associate members from two colleges and nine academic departments. It has approximately $3.19 million (direct costs) in peer-reviewed funding. It has two aims (Aims 1 and 2) focused on free radical metabolism and two aims (Aims 3 and 4) focused on imaging. In the current project period, the FRMI program members have generated 235 peer-reviewed publications with 32% intra-programmatic, 35% inter-programmatic, and 54% inter-institutional collaborative publications. The FRMI is directed by two strong leaders with synergistic strengths. Much of the featured science is strong, spanning fundamental science to translation and clinical studies with several clinical trials. The clinical trials help extend the fundamental science of this program to the clinic in a robust manner. Overall value added between the program and the center is outstanding and well documented. Its weaknesses are largely related to a less clear vision articulated for the imaging component of the program, and a lack of innovation in the imaging studies over the current project period. There are also some concerns about its overall relevance to cancer biology, with some links to other aspects of cancer biology being underexplored. However, a new program co-leader with expertise in medical imaging was recently appointed with an interest in radionuclide-based theranostics that has potential to re-invigorate innovation in the next project period.

The Cancer Epidemiology and Population Science (CEPS) Research Program, led by an epidemiologist (Dr. Charles Lynch) and an internist (Dr. Richard Hoffman), is rated excellent to outstanding. This population science research program has 28 full and nine associate members from six colleges and 17 academic departments. It has approximately $3.61 million (direct costs) in peer-reviewed funding. The CEPS program adds significant value to the cancer center. Strengths include important collaborative research in cancer etiology, cancer screening, and patterns of care. The CEPS members serve as co-investigators on multi-investigator grants led by other program members, including the NCI Lymphoma SPORE, and Dr. Lynch serves as PI of the NCI SEER and related projects. A hallmark of the CEPS program is that its members are highly collaborative; 24% of the CEPS publications are intra-programmatic,18% are inter-programmatic, and 63% are inter-institutional collaborations. However, there are some weaknesses. Overall funding has decreased since the last review. In addition, the weakness noted in the previous review that few (if any) funded projects leveraged research based on the Agricultural Health Study still remains. The cancer focus of some toxicology publications, despite these grants being counted as 100% cancer related, is unclear and the research relevant to the catchment area appears to be primarily descriptive, with notable exceptions including the work on improving HPV vaccination rates. Overall, the program is strong with strong

leadership, but important opportunities that remain are to expand CEPS member-led cancer-focused grants and high-impact publications.

The Shared Resource Management, rated excellent, meets the scientific needs of the HCCC members. The overarching goal of the shared resources is to provide essential technological support and expert advice to enhance the effectiveness and positive impact of HCCC research. Shared resources are managed by the HCCC leadership as well as collegiate and university administration. Overall, the management of shared resources is appropriate and seems to be working. Nine shared resources (SRs) are proposed by the center for CCSG support. As a testament to the strength and innovation of the HCCC SRs and its core leadership, three HCCC SR directors have received NCI R50 awards. User Advisory Committees guide each SR and member needs are assessed through annual user surveys. However, the mechanisms to ensure accessibility (location, space, proximity, priority) were not clearly articulated. In addition, it is somewhat unclear how user services and performance metrics are exactly tracked. A lack of priority access for cancer center members, while not considered by Shared Resource Management to be a problem, is a weakness. Questions were raised around restructuring of the previous Bioinformatics Core that has been changed to a distributed model of bioinformatics support in other shared resources. This is a relatively recent restructuring and anecdotal evaluation has been positive. The shared resources of the HCCC are rated as follows: Biospecimen Procurement and Molecular Epidemiology Resource and Biostatistics Core are each rated outstanding to exceptional; High Throughput Screening Core, Radiation Free Radical Research Core, and Viral Vector Core are each rated outstanding; Population Research Core is rated outstanding to excellent; Flow Cytometry Core and Genomics Shared Resource are each rated excellent; and Central Microscopy Research Facility is rated very good.

Cancer Research Training and Education Coordination (CRTEC), led by the Associate Director of Career Enhancement, Dr. Jon Houtman, is rated outstanding to exceptional. The career enhancement activities at the center are very strong with programs in place for community outreach; undergraduate, graduate, and medical training; and post-docs and faculty development. There is also good focus with respect to the catchment area on outreach to more rural populations in addition to the efforts to improve underrepresented minority representation in cancer research activities. Dr. Houtman was appointed as the director of these activities with appropriate time commitment and support. In fact, he appears to provide exceptionally strong leadership, and is developing plans to address lack of tracking data, with a software-based system to be implemented for this task. However, it is surprising that there was a lack of past tracking data beyond the past year given the educational nature of the institution, and that new systems have not yet been implemented. This minor weakness notwithstanding, in general, the CRTEC aspect of the center is noted to be very strong.

The Community Outreach and Engagement (COE), led by Dr. Elizabeth Chrischilles, Associate Director of COE, is rated excellent. There is a strong team that has made excellent progress in assessing and monitoring Iowa cancer burdens and providing education and outreach activities to reduce the catchment area cancer burden. Through its relationship with the Iowa Cancer Consortium (ICC), HCCC COE has had a positive impact on the catchment area through a variety of state-wide initiatives. However, weaknesses include the need to enhance its efforts to increase minority representation in HCCC’s clinical trials, the absence of targeted efforts to reach underrepresented minorities who are noted as a growing population in Iowa, missed opportunities for engagement of basic scientists in catchment area-relevant research, and specific examples of initiatives in response to CAB feedback were not clearly described. Overall, there is a need to track and respond to actual data on tangible metrics to evaluate COE’s success.

The Clinical Protocol and Data Management (CPDM) is rated very good to excellent. CPDM is generally well organized and has shown substantial growth over the current funding period. In addition to full implementation of OnCore, CPDM has grown significantly in support of the Center's desire to provide a unique clinical trials portfolio for the residents of Iowa, including phase 1 trials and research studies focusing on rare cancers. However, there are several weaknesses, including questions about overall adequacy of accruals to treatment trials, room for improvement in trial activation time, issues with accrual standards, and how clinical research relevant to the catchment area is prioritized. Data and Safety Monitoring (DSM) is acceptable. Frequency of review is dictated by assignment of risk level (1-4), with the highest level (4) being studies supporting IND applications. Risk levels are defined in the DSMP and are assigned by the study PI in consultation with the DMSC during protocol development. The PI is ultimately responsible for attribution of adverse events, and it was clarified at the site visit that these attributions are reviewed for consistency by the DSMC. The DSMC should have full authority to halt or close a trial for data and safety reasons without requiring PRMC action, while accruals (scientific progress) is the purview of the PRMC and not the DSMC. At the site visit, it was clarified by the HCCC Director that the DSMC has full authority to suspend or close a trial, independent of the PRMC. The components─Inclusion of Minorities, Inclusion of Women, and Inclusion of Individuals across the Lifespan in Clinical Research─are each acceptable. Although the percentage of women in trials has been consistently low, strategies to address this issue are provided. Protocol Review and Monitoring System (PRMS) is satisfactory. The PRMS and corresponding committee of the HCCC is well structured and functions appropriately together with the Multidisciplinary Oncology Groups (MOGs) to assess scientific quality of proposed clinical trial protocols, and to monitor accrual progress and trial scientific relevance. Some areas for improvement include increasing the size of a PRMC quorum and tightening criteria for judging accrual progress.

Developmental Funds is rated outstanding to excellent. Developmental Funds have supported pilot projects that have had a high rate of return on investment. The funds have been appropriately distributed across basic, clinical and population studies. Developmental funds are also used for recruitment of both senior and junior faculty and have been appropriately prioritized to attract individuals with expertise in areas lacking within the HCCC strategic plans and scientific leadership. The strategic use of Developmental Funds will continue to build on strengths of the institution and aid with major strategic directions in the center. However, a minority of reviewers question the rationale for proposing Dr. Maria Spies as a Staff Investigator in terms of strengthening cancer-related science because her expertise is in DNA repair, the area of existing strength of the HCCC.

Leadership, Planning and Evaluation is rated outstanding. The HCCC has a very strong and experienced leadership team with a history of working well together. The rigorous strategic planning process sought input from a wide range of stakeholders and there is evidence for key accomplishments aligned with the strategic plan. Opportunities include separation of the role of AD for Population Science from the AD for COE and tighter data-driven evaluation processes.

Cancer Center Administration is rated outstanding. HCCC Administration effectively addresses all CCCG expectations for infrastructure support of the Center’s research mission. Evidence of improvements made during the current project period is apparent. The Administration relies on a number of institutional tools for transactional and financial reporting that are proving sufficient for center use, but their adaptation to capture HCCC-required metrics, as well as linking information maintained in separate institutional information systems, needs to be pursued. As a matrix center, HCCC has established effective relationships led by the Administration to secure substantive input into

responsibilities retained by institutional and/or departmental lead units. Given the proven capabilities of the Administration, a proactive role in providing ongoing Administration infrastructure support to new programmatic center initiatives, such as obesity/cancer and theranostics, would further benefit the strategic advance of center plans.

Six Essential Characteristics of a cancer center are fulfilled. Physical Space is rated excellent to outstanding. HCCC has a distinct physical identity on the UI Iowa City Campus, with facilities that span the scope of its mission and a notable more than doubling in research space in the last five years. Research space appears to be ample to support ongoing cancer research, with expansion of clinical research space in the current period. While the Director and Dean addressed the “collaborative space model” satisfactorily, the footprint under the Director’s control remains small. As space is reassessed annually by an institution-level committee, with new space assigned by the Dean, HCCC participation in that review process should be codified so that its benefit from recent decisions is sustained going forward. Research, clinical, shared resource, and administrative space are situated within an accessible central campus cluster, with continuing reliance on additional departmental sites in the School of Public Health accommodate HCCC population science-related activities.

Organizational Capabilities is rated outstanding to excellent. HCCC effectively engages its members in cancer-relevant activities and includes appropriate oversight and governing processes. Creating an independent role for the Associate Director for COE would heighten HCCC members’ engagement in catchment area-relevant research. Improved delineation of tangible metrics of success would not only strengthen evaluation processes but also enable course corrections to enhance HCCC’s research infrastructure. Pursuit of new Center initiatives would benefit from clearer delineation of the administrative organization that is advancing their consideration.

Transdisciplinary Collaboration and Coordination is rated exceptional. The HCCC is doing very well in promoting transdisciplinary collaboration through a number of mechanisms in place to improve collaboration between basic, clinical and population scientists. Efforts have been made over the current project period to strengthen the Multidisciplinary Oncology Groups (MOGs) and various research programs. Most MOGs have members in all four research programs and hold symposiums and retreats. A Cancer Center annual retreat, joint program retreats, weekly grand rounds, and inter-institutional conferences are also held to foster transdisciplinary research. The success of these clear efforts to promote collaborative transdisciplinary research is documented by multiple-investigator grants as well as the rate of collaborative publications. Overall, no major weaknesses were noted in this essential characteristic.

Cancer Focus is rated outstanding. The HCCC maintains a clear cancer focus in its program emphases and initiatives. Over the current funding cycle, careful review of the membership, publication and funding policies and revision of program aims has served to tighten the focus. There has been a steady increase in accruals to cancer clinical trials across the spectrum of early phase, therapeutic and non-therapeutic interventional and observational. Investigator-initiated treatment trials have doubled since 2015 and now make up 44% of therapeutic accruals. Through the leadership of the Iowa Cancer Consortium and partnership with several funded NCORP sites, the HCCC extends its reach throughout Iowa to serve as the nexus for cancer research and education. Overall, cancer focus is strong with some residual issues regarding the robustness of the processes used and the questionable cancer relevance of certain grants.

Institutional Commitment is rated outstanding to excellent. The HCCC parent institution has fulfilled significant prior institutional commitments and proposed further increases in resources over the next project period. The HCCC Director has substantial authorities that cross usual departments and holds positions and leadership in significant institutional decision-making forums. Center membership is under the director's authority and participation by the matrix center in joint faculty recruitments has been apparent. Application of clinical facilities to research priorities is apparent. The director's authority over philanthropic support is impressive, and a modest commitment to reinvestment of clinical margin is evident. Much of the HCCC membership is in space that undergoes annual institutional review, and the ability of the current center leadership to influence those considerations needs to be codified to assure its sustainability going forward. At the individual faculty level, HCCC future plans would benefit from strong assertion in policies at the institutional level for clinician participation in clinical trials, a commitment to clinician scientist research, and recognition of team science in promotion and tenure decisions.

Center Director is rated exceptional. Dr. George Weiner is the founding director of the HCCC. He is an accomplished and effective director with broad based local, state, and national experience, expertise, and leadership that substantially enhances the UI HCCC.

In Summary, the HCCC fulfills all the requirements of a cancer center and serves its catchment area well. It has notable strength in multidisciplinary collaboration demonstrated by the level of collaborative publications and grants and demonstrates activities across the cancer research continuum. Clear examples exist of basic science discoveries that have entered the translational pipeline and there is evidence of practice changing clinical research and areas where population research has changed public policy. Continued growth of transdisciplinary research and new cancer-focused educational and training programs are indications of a center on the rise. The HCCC is guided by strong and experienced leadership and supported by effective Cancer Center Administration. However, there is unevenness in the quality of the research programs as well as shared resources and the scientific impact could be stronger through more innovation. While the HCCC has clearly defined the problems relevant to its catchment area, there are some missed opportunities to address the unique problems identified in Iowa such as exposure to agriculture chemicals and radon. In addition, the center's response to the low number of women in clinical trials as well as disparities in care and access for growing numbers of minorities in Iowa has been slow. In addition, the infrastructure for obtaining metrics for evaluation is weak or lacking. Nevertheless, the value added by the CCSG to the HCCC's accomplishments in effectively serving the population in the state of Iowa is apparent and, under the strong leadership of Dr. Weiner, the HCCC has the opportunity to move to the next level in the next project period. Overall, this application is rated excellent to outstanding and support for the requested five years is appropriate.

IRG NOTE: In response to the Site Visit Report, written comments were received from the principal investigator in a letter dated October 28, 2020. 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 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: ACCEPTABLE
(Also, see the heading, Data and Safety Monitoring)

DATA AND SAFETY MONITORING PLAN: ACCEPTABLE

INCLUSION OF WOMEN PLAN: ACCEPTABLE
(Also, see the heading, Inclusion of Women in Clinical Research.)
The state of Iowa has a population that is 50.2% women and the percentage of women seen at the HCCC for evaluation and/or treatment is 49.9%. Despite these statistics, the percentage of women in interventional treatment, interventional, and non-interventional trials is 40.5%, 45% and 48%, respectively. It is of concern that these percentages have been consistently below 50% with the exception of 2017. Though these declines are attributed to the closure of high-accruing breast and gyn-onc trials with concordant increased enrollment in prostate cancer trials, analyses/monitoring or strategies are provided to address this problem.

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

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN PLAN: ACCEPTABLE
(Also, see the heading, Inclusion of Individuals Across the Lifespan in Clinical Research.)

VERTEBRATE ANIMALS: ACCEPTABLE

ADDITIONAL REVIEW CONSIDERATIONS

COMPREHENSIVENESS:
The UI HCCC is the only NCI designated comprehensive cancer center for the state and people of Iowa, its catchment area. The four HCCC research programs span basic, translational and clinical cancer research, along with extensive population science and community outreach and engagement. There is a strong commitment with infrastructure and resources that enables cancer education, training, and career enhancement. These educational, basic, translational/clinical, and population science/outreach components integrate in the center, as evidenced by a high level of interactivity with high percentages of intra- and inter-programmatic and inter-institutional publications, two NCI SPORE programs in Lymphoma (with Mayo Clinic-Rochester) and Neuroendocrine Tumors, a recently awarded collaborative P01 grant, and collaborator activities within the ICC across the state. Pipeline structures, such as PACT, move fundamental discoveries in the CGP and FRMI programs into ET for translation, and MOGs have broad based interdepartmental membership that includes basic science and CEPS representation. This cross-disciplinary approach broadly and bi-directionally disseminates information on catchment area and community focused priorities to center membership. Working with its community partners including and beyond the ICC, the HCCC has identified main and in some cases unique (e.g. agricultural toxic exposures) cancer burdens in its catchment area and is responding to these burdens effectively by institutionalizing mechanisms that guide research to these community priorities. Support for the HCCC mission gains added strength from committed faculty who train and educate biomedical scientists and health care professionals for the future.

Assessment: SATISFACTORY

RESOURCES SHARING PLANS

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

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

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

ADDITIONAL REVIEW CRITERIA

RESEARCH PROGRAMS

CANCER GENES AND PATHWAYS RESEARCH PROGRAM

DESCRIPTION (provided by applicant): Research in the Cancer Genes and Pathways (CGP) program focuses on defining essential molecular and biological mechanisms underlying tumor pathogenesis and successful therapy. The primary goal of this basic science program is to discover, characterize, and validate new tumor alterations (genetic, molecular and cellular pathways) to fuel translational cancer research that will lead to improved cancer patient outcomes. This is accomplished through three overlapping research aims centered on the study of 1) structural and functional genetic and nuclear alterations that promote tumorigenesis, 2) intrinsic cellular processes and pathways that drive malignant transformation and tumor progression, and 3) tumor extrinsic factors, such as immune cells and environmental carcinogens, that contribute to cancer development and suppression. Key scientific achievements over the prior funding period include defining the role of RAD52 protein in damaged DNA repair and genome stability, identifying metastatic gene signatures and druggable pathways driving neuroendocrine tumor (NET) pathogenesis, and deciphering fundamental mechanisms by which external mechanical forces influence tumor cell metabolism. CGP membership includes 42 full and nine associate members spanning seventeen departments across four colleges. Annual direct cancer-relevant peer-reviewed funding in the last budget year was $6.7 million with $1.2 million from the NCI. CGP members are highly collaborative, having authored or co-authored 384 cancer-related peer-reviewed publications in the past four years, with 22% (n= 85) intraprogrammatic, 30% (n= 117) interprogrammatic, and 54% (n= 206) inter-institutional publications. 57 manuscripts appeared in high impact journals (Impact Factor >10). Productive intra/interprogrammatic and multi-institutional groups are leading investigations that reflect the breadth of CGP research, including advances in mechanisms of DNA repair and genome instability, genetic and molecular events underlying blood cell transformation, animal tumor model development, druggable pathways in sarcoma, novel targets and therapies for NETs, G-protein signaling in breast cancer stemness and metastasis, immune cell activation and the tumor microenvironment, carcinogenic effects of Iowa environmental toxins, and drug resistance in melanoma. In the context of the CCSG, CGP is the basic science foundation that is guided by and drives translational oncology through its partnership with other Holden Comprehensive Cancer Center (HCCC) programs. This is exemplified by CGP member direction of tumor procurement, CGP provision of integral genomic, immunological, and bioinformatics support for clinical studies involving colleagues in all four HCCC programs, the outstanding number of

interprogrammatic publications, and key leadership roles of CGP members on a U01 and two NCI SPORE grants.

CRITIQUE: The CGP program focuses on defining essential molecular and biological mechanisms underlying tumor pathogenesis and successful therapy. Research is organized around three broad goals: 1) to define nuclear alterations (genetic/epigenetic/structural) changes that promote tumorigenesis, 2) to determine the cell intrinsic processes and pathways that drive cancer, and 3) to define tumor extrinsic factors (immune, environmental, physical) and therapies in cancer development and cancer suppression. The program consists of 42 full and nine associate members across 17 departments and five colleges at the UI and serves as the main basic science program for the center. The program members currently hold $6.97 million (direct costs) in cancer-relevant peer-reviewed funding, including $1.4 million from the NCI. Publications are strong but mostly of moderate impact. It would seem that the research questions and level of innovation, while strong, could be higher. An important strength is the high degree of intra-programmatic (22%), inter-programmatic (30%) and inter-institutional (54%) publications. Overall, 284 publications (74% of total publications) from CGP members were collaborative. This represents an improvement over the last funding cycle and is an indication that program activities are stimulating new synergies.

The CGP program continues along a trajectory of basic science discovery. New findings on the role of RAD52 in the resolution of stalled replication forks is leading to important insights into the unique vulnerabilities among BRCA-deficient breast cancers and a new multi-PI R01 project. Unique Sleeping Beauty (SB) mutagenesis screens are identifying novel mechanisms of drug resistance. CGP members have played a central role in the neuroendocrine tumor (NET) SPORE, leading two of the four projects. Their work has provided important insights into malignant peripheral nerve sheath tumors (MPNSTs), including the identification of RABL6A-RB1 and preclinical studies revealing a unique sensitivity to CDK4/6 inhibition. Important insights have been made into the genetics and pathogenesis of pancreatic and small bowel NETs including the identification of a parallel role for RABL6A in PP2A-AKT-mTOR signaling that drives pancreatic NET pathogenesis, which can potentially help advanced NET patients who develop mTOR inhibitor-resistant tumors through PP2A reactivation strategies. Additional studies have identified a gene signatures of metastatic pan-NETS. Studies identifying a key role for TRAF3 signaling in B-cell survival are innovative and present opportunities for lymphoma and other B-cell malignancies. In addition, there are discoveries that decreased CD8 T cell-mediated antitumor immunity induced by a surgical sepsis event influences tumor development and responses to checkpoint blockade. Overall, the science is strong but for the most part it is not paradigm-setting and thus has not penetrated the highest impact journals.

In the current project period, CGP program has strengthened its cancer focus through a membership overhaul and collaborative activities have significantly increased as reflected in strong intra- and inter-programmatic publications. Areas of programmatic strength and cohesion have emerged; research into DNA damage/repair and genome instability is a clear strength, with scientific findings and emerging multidisciplinary activities, including the acquisition of a new NCI MPI R01 grant around RAD52 synthetic lethality in BRCA1 breast cancers and several co-investigator awards. Multi-investigator and transdisciplinary efforts across programs have also improved with CGP program members playing important roles in the NET and Lymphoma SPOREs. Finally, the impact of the CGP in driving activities in other programs was raised, with examples of basic science moving to translation, including a study of immune response to epigenetic modulators in sarcoma being translated in collaboration with ET program members.

The HCCC provides considerable value to CGP; over the current funding cycle CGP program benefitted from the investments in shared resource development (e.g., HTS) and the recruitment of four new faculty. Pilot awards have stimulated new intra- and inter-programmatic activities, some of which have been leveraged towards new grants, including the multi-PI grant on RAD52 in genome stability. The CGP program adds value to the HCCC by providing unique expertise; generating model systems for cancer research; participation in MOGs; and providing leadership of multi-PI grants, including two SPORE, NCI U01, and several multi-PI R01 grants. CGP program has developed novel preclinical and cancer animal models that are important avenues for ongoing target validation studies, including the development of new preclinical models of pancreatic and small bowel NETs, a novel pig model of NF1 deficiency that recapitulates the features of MPNSTs and melanoma, bioluminescent mouse models of metastatic pancreatic NETs, and patient-derived small bowel NET spheroids.

CGP program aims/goals, while revised, remain relatively broad and there is some question as to whether the program as currently configured is poised to reach its maximal effectiveness. Each aim shows productivity and strength, but the program has not fully realized the potential of the synergy between faculty represented in each aim. Future plans are laudable and include moving into obesity as a risk factor and recruitment of a tumor immunologist to enhance the potential for translation. While logical extensions of center-wide goals, the vision for where this program is going thematically was less clear. In this regard, the plan for future program development could be more strategic and intentional with regards to thematic development.

Importantly, basic science discoveries ripe for translation have begun to emerge, and an increased emphasis on novel therapeutics and/or biomarker development is earmarked as a future goal. CGP program members sit on the MOGs, but how the MOGs have specifically guided this program research activities is unclear. Several examples of successful cross-programmatic interactions with ET program were described at the site visit. Still, greater clarity on how the “hand-off” of research discoveries happens and what role this program plays in prioritizing research findings for translation is needed. Furthermore, although admittedly a basic science program, program efforts to understand and address cancer problems relevant to the HCCC catchment area are not readily apparent. Given the program’s expertise in DNA repair mechanisms and lymphoma biology, and the unique environmental risk factors of the catchment area, this seems a missed opportunity.

Program Leader(s): The CGP program is aptly led by Drs. Dawn Quelle and Michael Tomasson. Dr. Quelle, who has led the CGP program since 2009, is an expert in cancer cell biology. She plays a key role in driving investigations around NETs as the PI on the NET SPORE among other center-wide and national leadership roles. Dr. Tomasson was recruited to IU in 2016. He is a physician scientist with a focus in cancer genetics and translational research in hematologic malignancies. He also serves as the clinical director of malignant hematology/oncology and bone marrow transplant, providing an important link to translational outlets for the program activities. How the program leaders work together to guide program development, in particular around Aim1, and their vision to enhance program cohesion was not entirely clear. Although some concerns were raised over the current gap in funding for both leaders, these concerns were mitigated by their track record and significant and complementary leadership experience each brings to the program. They are well positioned to move the CGP program forward.

Assessment: Excellent merit

Budget: The budget is appropriate as requested.

EXPERIMENTAL THERAPEUTICS RESEARCH PROGRAM

DESCRIPTION (provided by applicant): Research in the Experimental Therapeutics (ET) program focuses on identification, development and testing of new cancer therapeutics. This is accomplished through three overlapping specific aims centered on 1) identifying potential targets and discovering therapeutics leads, 2) conducting preclinical evaluation of promising new therapeutic approaches, and 3) evaluating innovative and promising agents, combinations, and approaches to monitoring response in clinical trials. ET investigators are highly collaborative. Key scientific achievements of ET investigators over the prior funding period include identification of novel therapeutic targets in endometrial cancer and myeloma, nanoparticle based drug development, cancer immunotherapy based on toll-like receptor (TLR9) agonists, use of pharmacologic ascorbate to enhance the efficacy and reduce the toxicity of both chemotherapy and radiation therapy (in collaboration with the FRMI Program), and expansion of investigator-initiated and Phase I capabilities including trials of intralesional therapy. There are 28 full and 16 associate members of ET including laboratory-based, translational and clinical investigators spanning 13 departments across five colleges. Annual total peer-reviewed cancer direct costs in the most recent budget year was $2.7 million ($1.9 million from the NCI). Additional funding included $3.8 million for non-peer-reviewed research projects. ET members are highly collaborative having authored or co-authored 291 cancer-related peer-reviewed publications in the past five years, with 24% (n= 69) intraprogrammatic, 43% (n= 124) interprogrammatic, and 42% (n= 123) interinstitutional publications. Twenty-nine manuscripts appeared in high impact journals (Impact Factor ≥10).

CRITIQUE: The ET program is a long-standing program that identifies, develops, and tests new cancer therapeutics. In addition to developing their own therapeutics, this program serves as a venue. The membership of the program has changed from 48 (31 full and 17 associate members from 10 departments and three colleges) to 44 members (28 full and 16 associate members from 14 departments and five colleges), which is a slight decrease in number but an increase in the multi-disciplinary nature. It has maintained the $2.69 million (direct costs) in funding from the previous project period and now has more than 76% from the NCI. ET program produced 291 peer-reviewed publications, of which 29 were in high-impact journals (Impact Factor ≥10) and 24% represent intra-programmatic, 43% inter-programmatic, and 42% inter-institutional collaborations. The program is supported by $3.8 million in non-peer-reviewed funding, which is reduced from the $10.5 million in the previous funding cycle. In the current project period, program activities to support translational collaboration and advancing drugs through the pipeline to clinical trials has been increased. The regular inter- and intra-program activities are well defined. At the site visit, reasonable future goals and focus on catchment area priorities were presented.

Scientific accomplishments from Aim 1 include mechanistic studies that led to a drug combination clinical trial in Ewing Sarcoma, new mechanistic understanding of breast cancer stem cells, identification of NEK2 and CD24 as therapeutic targets in myeloma, and identification of new molecularly targeted lead compounds through high-throughput screening. The example of TLR9 agonists documents movement of research findings from basic science through clinical trials. Additional scientific accomplishments relevant to Aim 2 include development of nanoparticle delivery strategies to improve paclitaxel therapy and to deliver targeted agents that this group identified for endometrial cancer. Aim 3 has developed infrastructure for studies of intralesional therapy with immunostimulatory agents to support 14 clinical trials with 153 patients accrued. Additional clinical trials are studying epigenetic modifications of tumor suppressor genes to increase drug sensitivity, use of nicotinamide

riboside to reduce taxane-induced neurotoxicity, and use of GC4419 to reduce grade 4 mucositis incidence and duration in head and neck cancer patients treated with radiation and cisplatin. Examples of productive collaborations with each of the other programs is described. Collaborations with the FRMI include multiple clinical trials, high-impact publications, and a P01 grant.

In order to increase the level of programmatic activity and connection with other programs, the new program leader, Bryan Allen, MD, PhD, established a weekly translational research conference with the FRMI program and multiple ET program-sponsored meetings and retreats. Meetings and workshops with other programs to support collaboration have been well attended and productive with new funding (an R37 grant) and a new collaboration (NEK2 modulation during immune checkpoint blockade in multiple myeloma and other malignancies). The HCCC Pipeline for Accelerating Cancer Therapeutics (PACT) mechanism developed at the last review now has been extensively utilized by ET program members for efforts that have led to clinical trials.

The program has a P01 grant focused on ascorbate in multiple cancers, a SPORE focused on lymphoma, and 4 multi-investigator grants. Nine of the 12 MOGs are led by ET members which shows benefit of the program to the cancer center. Two ET members lead the PACT, which assists investigators in bringing their drugs to clinical trial. Productivity in terms of high-impact journal publications and new or renewed grant funding from ET-supported programs is evident. Research includes cancer control and quality of life. The program has effectively utilized shared resources. The cancer center has provided support in the form of shared resources, seed grant funding, funding for external speakers, and, in combination with the university, three start-up packages for new recruits. The program has supported translation of basic science discoveries into clinical trials. ET members are involved in two cancer center SPOREs (lymphoma and NET) and multi-investigator grants.

The external funding is modest considering more than 42 investigators in the program. The overall translational pathways are not well defined. The preclinical evaluation and drug discovery parts are somewhat disjointed without a well-defined, long-term strategies. While program activities have increased, they are still only moderate. Only 10% of the publications were published in high-impact journals (Impact Factor ≥ 10) and there was limited evidence of paradigm-shifting research or impact of clinical trials on changes to patient care.

Program Leader(s): Bryan G. Allen, MD, PhD, took on the role of ET program co-leader in 2019. He is well qualified for this role, with expertise in translational research and clinical trial development. His expertise in free radical biology provides an avenue for collaboration with the FRMI program. Aliasger Salem, PhD, has been an ET program leader for the past five years. He provides expertise in drug formulation and nanotechnology. Both leaders are highly collaborative. They meet annually with each program member to discuss research efforts, current plans and career goals.

Assessment: Outstanding to Excellent merit

Budget: The budget is appropriate as requested.

FREE RADICAL METABOLISM AND IMAGING RESEARCH PROGRAM

DESCRIPTION (provided by applicant): During the past two decades a significant body of evidence has shown that metabolic oxidation/reduction reactions represent a significant underlying mechanism

contributing to promotion and progression of malignancy, as well as a therapeutic target for selectively sensitizing cancer cells to therapeutic interventions and protecting normal tissues from conventional cytotoxic therapies. Evolving in parallel has been the recognition that advanced medical imaging techniques, measuring metabolic changes in cancer versus normal tissues before and during therapy show great promise in allowing non-invasive quantitation and monitoring of fundamental differences in cancer cell metabolism to improve cancer therapy. The overarching hypothesis in the Free Radical Metabolism and Imaging (FRMI) program is that cancer cells exist in a chronic state of metabolic oxidative stress that represents a significant underlying mechanism contributing to promotion and progression of malignancy as well as a therapeutic target for sensitizing tumor cells to therapy as well as protecting against normal tissue injury. Furthermore, functional imaging techniques measuring metabolic changes in tumors versus normal tissues have shown great promise as predictors and biomarkers that can be used to improve cancer therapy. The diverse membership of this unique program includes 33 full members and five associate members representing two colleges and nine departments. These investigators work together to take full advantage of the convergence of the science in these two related disciplines for developing a mechanism based biochemical rationale for new image-guided cancer therapies and diagnostic/prognostic tools. FRMI members are highly collaborative. During the last period of support, 83% of a total of 235 cancer relevant publications were collaborative including 75 (32%) intraprogrammatic, 83 (35%) interprogrammatic and 127 (54%) interinstitutional publications including 17 in high impact (Impact Factor >10) journals. Program member cancer research was supported by $3.7 million of direct peer-reviewed funding including $2.1 million of NCI funding in the last year of CCSG support. Productive intra/interprogrammatic and interinstitutional groups are leading advances in the development of pharmacological ascorbate as an adjuvant to cancer therapy supported by a new NCI P01, superoxide dismutase mimetics for protection of normal tissues toxicities, and peptide-targeted, radionuclide-based theragnostic treatments.

CRITIQUE: The FRMI program is focused on understanding how oxidation/reduction reactions contribute to cancer progression and impact toxicity of therapy. It is based on the concept that oxidative stress contributes to the promotion and progression of malignancy and represents a therapeutic target for sensitizing tumor cells to therapy and for protecting against normal tissue injury. FRMI program research includes development and application of novel functional imaging techniques that measure metabolic changes in tumors versus normal tissues and can be used as both predictors and biomarkers to improve cancer therapy. This program also aims to develop theranostics to image and treat cancer. The FRMI program has four aims: Aim 1 is to characterize fundamental differences in cancer cell redox biochemistry that impact on cell signaling, genetics, and epigenetics in cancer biology and therapy; Aim 2 is to develop and test redox active cancer therapeutics based on fundamental metabolic differences between cancer cells and normal tissues; Aim 3 is to explore novel metabolic imaging technologies to improve and predict patient outcomes to cancer therapy; and Aim 4 is to develop theragnostic and other approaches to integrate functional imaging and cancer therapy. There were 235 publications listed, including a subset (17) in journals with impact factor 10 or greater. FRMI program members have been collaborative; 83% of cancer-relevant publications were collaborative, including 75 (32%) intra-programmatic, 83 (35%) inter-programmatic, and 127 (54%) inter-institutional publications. FRMI program member cancer research is supported by $3.2 million of peer-reviewed funding, although some program investigators lack cancer-related support. Work in this program is relevant to the HCCC catchment area, and use of shared resources by the FRMI members is well documented.

During the current project period, the FRMI program has made improvements in several areas, including enhanced team science and increased tissue procurement. The program has representation from clinical and basic scientists; has a track record of interaction evidenced by collaborative

publications and funding; and is advancing discoveries from the laboratory to clinical trials. The program investigators from multiple departments clearly work well together based on collaborative publications and joint funding. The program has exceptional leadership, particularly Dr. Douglas Spitz, who is directly involved in much of the most impactful work from this program and leveraging his clear expertise in free radical biology to test novel and interesting hypotheses in many of the projects. He also has helped guide some vision for the entire program, including articulating the relevance of imaging to translate redox aspects of the program. Of note, this program has a record of moving projects from pre-clinical hypotheses to clinical trials, most evident in the work on ascorbate, demonstrating impact of the interactions between basic and clinical scientists.

The future directions are for the most part extensions of ongoing work and largely built on the strength of redox biology in the center. The main weaknesses of the program are related to the imaging component, where lack of innovation in the approaches used is noted. The overall vision of the imaging component of the program, particularly as it extends beyond its role in complementing the redox metabolism aspects of the program, were also less well articulated in the application. A new co-leader of the program, Dr. Yusuf Menda, an expert in medical imaging, was recruited. During the site visit, he expressed a vision to expand radionuclide-based theranostics going forward and it is hopeful that the new leadership in imaging will reinvigorate innovation in the imaging part of the program over the next project period. Additional weakness is that overall relevance to cancer biology of some aspects are still developing, and the program has not fully realized the potential of tumor genomics and epigenetic in complementing science done in this program.

Program Leader(s): Dr. Douglas Spitz is a well-established investigator studying the role of metabolic oxidative stress in cancer biology and therapy as well as radiobiology. His seminal work on the characterization of superoxide dismutases and responses to oxidative stress makes him ideally suited to help oversee the development of this program. He is also the director of the Radiation and Free Radical Research Core and an NCI-funded T32 entitled Free Radical and Radiation Biology Program for students and postdocs. He is also involved in pre-clinical and clinical trials which proves strong support for helping translation of basic finding into the clinic. Dr. Yusuf Menda was appointed co-leader of FRMI in 2019 following the retirement of Dr. Michael Graham. Dr. Menda is a physician-scientist, professor and division chief of Nuclear Medicine in the Department of Radiology, with a primary research focus in targeted radiotherapy of malignancies with radiopharmaceuticals and clinical applications of novel PET radiopharmaceuticals and pharmacokinetic analysis. He is well suited to help drive new radiotheranostics and functional imaging. These two leaders, together with their nicely synergistic expertise, provide strong leadership to the program.

Assessment: Excellent to Outstanding merit

Budget: The budget is appropriate as requested.

CANCER EPIDEMIOLOGY AND POPULATION SCIENCE REEARCH PROGRAM

DESCRIPTION (provided by applicant): The Cancer Epidemiology and Population Science (CEPS) research program focuses primarily on cancer in Iowa, the Holden Comprehensive Cancer Center (HCCC) catchment area, while recognizing that its impact extends well beyond the state. The primary goal of the CEPS is to conduct population-based research that improves our understanding of cancer etiology, morbidity, and mortality in order to explore interventions for reducing cancer incidence and

mortality and improving quality of life for cancer survivors. This is accomplished through three related research aims centered on 1) cancer etiology, 2) primary and secondary cancer prevention and 3) cancer health care services and outcomes. Recent influential CEPS publications have addressed lymphoma, chronic lymphocytic leukemia, contralateral breast cancer, pancreatic and breast cancer survival, stress, and end-of-life issues, as well as United States Preventive Services Task Force recommendations for cancer prevention and screening. CEPS membership includes 28 full and nine associate members spanning 17 departments across five colleges. Annual total direct funding for peer-reviewed research in the last budget year was $4.3 million with $1.5 million from the NCI. CEPS members are highly productive, having authored or co-authored 372 cancer-related peer-reviewed publications since 2016, and highly collaborative, with 24% (n=91) intraprogrammatic, 18% (n=70) interprogrammatic, and 63% (n=235) interinstitutional publications. Fifty-two of these publications appeared in high impact journals (Impact Factor >10). Successful intra/interprogrammatic and multi-institutional collaborations are generating important cancer-related advances in knowledge about pesticide and polychlorinated biphenyl exposures; lymphoma, sarcoma, and cancers of the breast, ovary, and colorectum; HPV-related cancer and vaccination; multimorbidity science; cancer screening; and tobacco cessation.

CRITIQUE: The primary goal of the Cancer Epidemiology and Population Science (CEPS) research program is to conduct population-based research that improves understanding of cancer etiology, morbidity, and mortality in the HCCC catchment area. This is accomplished through three research aims: 1. To conduct etiologic research on genetic, environmental, lifestyle, and contextual risk factors for cancer; 2. To enhance primary and secondary cancer prevention through research exploring issues such as tobacco use, radon exposure, screening, HPV vaccine uptake, and behavioral changes; and 3. To evaluate cancer health care services and outcomes to better understand the effects of biobehavioral factors, patterns of care, treatment delivery, treatment decision making, prognostic factors, and rurality on cancer outcomes. This established program is co-led by Dr. Charles Lynch, an epidemiologist, and Dr. Richard Hoffman, an internist.

CEPS membership includes 28 full and 9 associate members spanning 17 departments across five colleges. These include two new faculty recruits during the current cycle (Drs. O'Rorke and Watkins) with a plan to recruit a senior level cancer epidemiologist to succeed Dr. Lynch who plans to retire in the upcoming cycle. These members hold a total of $3.61 million in peer-reviewed funding (direct costs). NCI funding has increased, as has overall funding from the last review which was $3.45 million in cancer-related funding as calculated using current funding metrics.

The CEPS member-led (PI or MPI) portfolio of active grants includes four R01 (3 NCI), 1 PCORI (ending 9/2020), an NINR P20, and an NIEHS P30 and several NIEHS P42 grants. CEPS members serve as co-investigators on additional multi-investigator grants led by other program members, including the NCI Lymphoma SPORE. Dr. Lynch also serves as PI of the NCI SEER and related projects and Dr. Link is PI on two subcontracts from the Mayo Clinic for an NCI U01 grant (both ended earlier this year). The scientific achievements of CEPS are represented in 372 peer-reviewed publications during the current grant cycle, with 52 published in high-impact journals (Impact Factor > 10) although one publication noted as a high-impact publication is in the Journal of Cancer Education which has an impact factor of 1.6. CEPS members are highly collaborative; 24% of publications are intra-programmatic,18% are inter-programmatic, and 63% are inter-institutional. Collaboration is a hallmark of this program.

With regard to cancer research led by investigators, the application highlights interest in collaborative research and CEPS-led grants and publications represent a relative minority among the program's overall contributions. With respect to cancer focus, a sizable proportion of peer-reviewed funding is in the area of environmental toxicology. However, the cancer focus of the NIEHS grants (rated as 100%) is not entirely clear and was not sufficiently clarified at the site visit and there is also a concern about the relatively limited number of grants. The application notes that the NCI contract supporting the Agricultural Health Study (AHS) ended, while data analysis and training is ongoing, and a remaining weakness is related to few (if any) funded projects related to research based on the AHS. The overall financial investment in CEPS research was not noted, although it is mentioned that HCCC supported the Population Research Core (PopRC) and Iowa Residual Tissue Repository (RTR) (part of the Core) and provided support for the recruitment of one member (Dr. O'Rorke) and support for a leadership position for Dr. Vander Weg.

Many of the most innovative aspects of CEPS research are based on long-standing national programs such as SEER, the AHS, the Environmental Health Sciences Research Center (EHSRC), the Center for Health Effects of Environmental Contamination (CHEEC), the Center for Advancing Multimorbidity Science (CAMS), and their respective center grants. The Iowa Cancer Registry has been part of the NCI SEER program since its inception and was renewed in 2018 for 10 years. A number of significant publications were leveraged from the linked SEER-Medicare data. However, there is limited funding that has been leveraged from this resource and resulting publications. A long-standing research collaboration is with the Lymphoma SPORE which has been continuously funded since 2002 with Dr. Weiner and Dr. Witzig from Mayo Clinic as PIs. Drs. Link and Cerhan lead the epidemiology component of the SPORE, Lymphoma Molecular Epidemiology Resource (L-MER), which was initiated in 2002. This led to the Lymphoma Epidemiology and Outcomes (LEO) cohort supported by a U01 infrastructure grant. This was a new collaboration cited in the previous review. LEO expanded the accrual to six additional sites to increase ethnic diversity; however, the level of diversity for L-MER or LEO is not stated. From these projects, a number of articles have been published in high-impact journals. CEPS members also participate in the inter-institutional WECARE consortium, with a new R01 grant awarded to Dr. Lynch with the Fred Hutchison Cancer Center to study the molecular pathoepidemiology of contralateral breast cancer tissues.

The work on diet, obesity and cancer has been conducted through collaborations with the Women's Health Initiative and other cohorts within the PopRC. Other investigators within CEPS have several publications on HPV and cancer. Under Aim 2, work in the area of tobacco use and cessation is a strength of the program including intervention trials for which Drs. Katz and Vander Weg are lead authors. Likewise, Hoffman and colleagues have published important work on lung cancer screening. Dr. Levy leads an NCI-funded R01 project on the comparative effectiveness of immunochemical tests with optical colonoscopy. Under Aim 3, Dr. Chrischilles leads a breast cancer cohort study with a consortium of 10 medical centers focused on integrating electronic health record data with hospital cancer registries, leading to important collaborative papers on quality and coordination of care. Exciting work by Dr. Lutgendorf reveals novel findings on biobehavioral modulation of exosomes and the tumor microenvironment. Dr. Hoffman also led important work on treatment decision regret among prostate cancer survivors published in the Journal of Clinical Oncology. Notably, Dr. Curry plays a major role in establishing and publishing national cancer control-related guidelines.

The value added of CEPS to HCCC includes contributions to collaborative, catchment area-relevant population-based research, leadership of national initiatives, and seed grants provided via the Iowa Cancer Registry and other grants held by CEPS members. The program offers a variety of program-

related activities including quarterly luncheons to which CEPS members are invited and retreats. There is little indication of how many (if any) grants or publications have resulted from these activities and there is limited description of the activities/topics covered through these activities. It is unclear in the application how the program and program leaders catalyze and foster the research presented within the scientific accomplishments. Research of relevance to the catchment area appears to be primarily descriptive, with notable exceptions including the work on improving HPV vaccination rates. The value added by the HCCC to CEPS includes support for shared resources, seed grant funding, and new faculty recruitment.

A significant decline in colorectal cancer incidence (35%) and mortality (44%) was noted between 1990 and 2015; however, access to screening and care in rural communities remains a challenge that has been studied extensively by several CEPS members. There is little mention of interventions or other activities among members in the CEPS that have contributed to this reduction in cancer burden or the remaining challenges. Studies in the AHS and the Women's Health Initiative are notable and described as catchment area-related research; however, there are insufficient details on how this work has led to a change or implemented programs within the catchment area. One example is the work by Drs. Field and Lynch in 2012 to support a breathing easier video shared on the EPA and ICC website.

CEPS is planning three overarching initiatives for the next cycle. These include building data linkages within the SEER program to enhance population science infrastructure, strengthening molecular epidemiology capabilities including new biobanking shared resources and expansion of engagement in the Oncology Research Information Exchange Network (ORIEN), and expanding community-based research with a focus on rural populations.

Program Leader(s): The program is very capably led by Drs. Lynch and Hoffman who have complementary expertise. Dr. Lynch, an epidemiologist, has served since 1994 and recently announced his plan to retire. He has led the NCI SEER program and focuses his efforts on Aim 1 of the program. Appointed in 2015, Dr. Hoffman is Chief of General Internal Medicine and PI on a VA Office of Rural Health and is a co-investigator on an NCI grant. He focuses on Aim 2 of CEPS and these co-leaders work together to foster research under Aim 3. Together, they mentor trainees and identify new opportunities for collaborations and grants.

Assessment: Excellent to Outstanding merit

Budget: The budget is appropriate as requested.

SHARED RESOURCE MANAGEMENT

DESCRIPTION (provided by applicant): Access to effective, state-of-the-art Shared Research (SR) facilities to support experimental goals and projects is a critical need for cancer investigators performing basic, translational, and clinical research. The overall goal of the SRs supported by the Holden Comprehensive Cancer Center (HCCC) is to provide essential technological support and expert advice to enhance the effectiveness and positive impact of HCCC member research. These SRs also provide ongoing advice and education that encourages and facilitates investigator exploration of new developments in technologies, experimental approaches, and data analysis. Although focused upon SR-specific services and mechanisms to accomplish this goal, each SR is designed to achieve this objective. Leadership of the HCCC coordinates closely with collegiate and university administration to

ensure that the specific SRs most needed by HCCC researchers are accessible and adequately supported. Oversight is exercised by close and regular interaction of HCCC leaders with SR Directors and technical managers, feedback from HCCC member users, and advice from the HCCC External Advisory Board. This ensures clear understanding by the leadership of SR goals, challenges, and future directions, as well as appreciation by SR Directors of HCCC member needs, and how the SRs can best effectively address these needs. SR goals are addressed via three specific aims: 1) assure SRs have appropriate polices governing their use, including member accessibility, 2) monitor current and future needs of HCCC members, including appropriateness and quality of SR services, and access to technologies and expertise, and 3) work with HCCC members and the institution to identify and support new SRs, new capabilities for current SRs, and new approaches to optimize SR support for cancer research. The nine HCCC-supported SRs proposed for the requested funding period are Biostatistics, Central Microscopy, Flow Cytometry, Genomics, High Throughput Screening, Population Research, Radiation and Free Radical, and Viral Vector and the Biospecimens Procurement and Molecular Epidemiology Resource.

CRITIQUE: The overarching goal of the Shared Resource Management (SRM) is to provide essential technological support and expert advice to enhance the effectiveness and positive impact of HCCC research. Shared resources are managed by leadership of the HCCC as well as collegiate and university administration (HCCC is a matrix cancer center with a combination of directly managed SRs and jointly managed SRs). Oversight is exercised by close and regular interaction of HCCC leaders with SR directors and technical managers, feedback from HCCC member users, and advice from the HCCC External Advisory Board. There are three specific aims: 1) Assure that SRs have appropriate polices governing their use, including member accessibility; 2) Monitor current and future needs of HCCC members, including appropriateness and quality of SR services, and access to technologies and expertise; and 3) Work with HCCC members and the institution to identify and support new SRs, new capabilities for current SRs, and new approaches to optimize SR support for cancer research. HCCC currently has 11 CCSG-supported SRs and proposes nine SRs for support in the next funding period. Nine SRs are Biostatistics, Central Microscopy, Flow Cytometry, Genomics, High-Throughput Screening, Population Research, Radiation and Free Radical, Viral Vector, and Biospecimens Procurement and Molecular Epidemiology Resource. A new developing SR is Human Immunology Core (HIC). The HCCC SRs report through the AD for Basic Research, Dr. Gail Bishop, with the exceptions of Biostatistics and the Population Science Research Core that report through the AD for Population Science and Community Outreach and Engagement, Dr. Elizabeth Chrischilles.

The overall organization could be simplified and enhanced as there appear some circular/complex reporting and unclear authorities among the various decision-making bodies. How decisions are made in particular with regard to the jointly managed SRs is also unclear. For example, the makeup, roles and authorities of the User Advisory Committees (UAC) and how they interface with HCCC leadership are not entirely clear, and there is potential for inadequate representation on jointly managed SRs. Although aspects of oversight and authorities were unclear, the system appears to be effective in managing HCCC position and implementing change in response to user feedback and member needs.

Over the current funding cycle, HCCC and SR leadership orchestrated the restructuring of the institutionally managed Microscopy Core to eliminate fiscal inefficiencies and maximize member access. Bioinformatics SR has been reorganized from a distinct SR to a distributed model embedded in other SRs to allow for more focused specialization and closer interaction with distinct data types (e.g., genomics, image analysis, flow, and population databasing). This new distributed model of bioinformatics support appears to only recently been implemented and whether this will adequately

meet member needs remains to be seen. SR capabilities in small animal radiation, CRISPR/Cas9 and functional genomics, and high-throughput screening were expanded in response to growing member needs. Quality improvements have been made around the oversight and management of tissue procurement and use that should have a sustained impact on translational cancer research. Development of the Human Immunology Core is appropriate and aligns well with the research directions and needs of the center.

However, there are also some weaknesses. A lack of priority access for cancer center members, while not noted by the center to be a problem, raised some concerns; there is a lack of consistent, cohesive tracking system across the shared resources; and the role of SRs in member training and education is not well elaborated.

Leaders: Dr. Gail Bishop, who works within the University leadership with input from the cancer center leaders, facility managers, member users, and external advisory board to address research needs and administer core facilities that benefit the cancer research activities at the center. Drs. Bishop and Chrischilles participate in the respective committees of the SRs for which they are responsible. They are responsible for communicating the UAC reports to HCCC leadership and Research Executive Committee (REC), but their respective roles and authority to negotiate on behalf of the HCCC or to champion HCCC member needs to the institutional leadership were not immediately evident. If the SR directors are meeting directly with the REC on an annual basis to drive decision making, what role Drs. Bishop and Chrischilles have is unclear. How member needs and financial as well as other decisions are negotiated for jointly managed resources is not clear.

Assessment: Excellent merit

Budget: The budget is appropriate as requested.

SHARED RESOURCES

Biospecimen Procurement and Molecular Epidemiology Resource (BioMER)

DESCRIPTION (provided by applicant): The Biospecimen Procurement and Molecular Epidemiology Resource (BioMER) provides HCCC members with IRB-compliant, clinically annotated, quality-ensured biomaterials to facilitate research objectives. These materials include tissues which are distributed as fresh, frozen or paraffin-embedded specimens, and serum, plasma and germline DNA, all linkable to tumor samples and clinical data catalogued in coordination with the tissue. The BioMER uses a single unified biorepository consent that allows current and future use of tissue for research, permissions to link that tissue to clinical data, and to recontact the patient for additional studies. All newly diagnosed patients with appropriate histologies as selected by the investigators are approached for informed consent. Following enrollment, serum, plasma, buffy coat and peripheral blood DNA (at diagnosis and selected longitudinal time points) are collected, as is excess surgical tissue (tumor and normal) from resections and biopsies.

The BioMER also offers meticulous collection of longitudinal clinical data, linked as needed to biospecimens. BioMER staff abstract clinical information including tumor stage, histology, lab and imaging data, treatment modality, treatment response, events (progression, death) and comorbidities. In general, clinical information on each subject is updated 2x/year for three years, then annually.

Psychosocial data including quality-of-life analyses are collected longitudinally. The clinical data are periodically validated to enable their readiness for analysis without investigators needing to return to the medical record. The BioMER is responsible for providing a single point of entry for investigators requesting specimens for research use. The BioMER is vital to multiple projects that rely on biospecimens linked to clinical data and supports research in all four research programs.

CRITIQUE: The Biospecimen Procurement and Molecular Epidemiology Resource (BioMER) was established in 2018 as a result of a HCCC comprehensive review process with the goal of improving ability of the cancer center to distribute tissues and linked clinical data to enhance cancer research across the spectrum. This new shared resource was created from two cores in the prior submission: the Tissue Procurement Core and the Molecular Epidemiology Resource. One of the advantages of this new SR is to unify the HCCC's many biorepositories into a single unified process. The new "opt in" consent is called PERCH which stands for Patients Enhancing Research Collaboration at Holden. This consent covers current and future use of tissues for cancer research, permission to link clinical tissues to clinical data, and permission to recontact the subject for consideration of additional research projects. The cancer center uses a single workflow to access tissues from the surgical pathology suite and specimens that are available include fresh, frozen, and paraffin-embedded specimens.

The BioMER currently supports eight Multidisciplinary Oncology Groups (MOGs). Major roles of MER include obtaining clinicopathological, treatment, and outcomes information as well as project coordination. The BioMER also supports the HCCC's membership in the Oncology Research Information Exchange Network (ORIEN), which began in December 2017. To date, 250 patients had provided clinical data as well as tumor specimens for whole exome and RNA sequencing through ORIEN's Avatar program. The HCCC has also benefited from two novel original research awards to HCCC members from ORIEN.

FY19 data documents effective use of the BioMER services that processed over 54 requests for tissue and 51 requests for MER functions. The preponderance of users are cancer center members and there is evidence that tissues are primarily being utilized by peer-reviewed funded investigators. At the site visit, information about quality control was provided. It was also clarified that the data architecture for the MER was created in collaboration with the institution's Clinical and Translational Science Award (CTSA).

There is an executive committee that meets quarterly to set policy and provides oversight/governance. There is also a Biomarker Research Evaluation Committee that receives requests for tissue and/or clinical data and makes decisions about these requests based on resources and tissue availability. Future directions are presented including creating virtual consent processes and expanding engagement with the Avatar program.

Overall, the BioMER adds value to the cancer center by providing a host of tissues and/or clinical data to support research across the spectrum from clinical science to translational research to basic investigations. Committees are in place to evaluate and coordinate the services of this shared resource. However, many of the changes to this SR happened very recently, so the effectiveness of this SR in its new configuration has not yet been fully assessed.

Personnel: The BioMER is led by Dr. Carlos Chan, who is a board-certified surgical oncologist. He also received his PhD in biochemistry. He conducts basic and translational research in his own laboratory. He has experience in translational, clinical research and tissue procurement from his work

at the MGH. He is qualified to lead this shared resource. Dr. Michael Knudson leads tissue procurement within the BioMER.

Assessment: Outstanding to Exceptional merit

Budget: The budget is appropriate as requested,

Biostatistics Core (Biostats)

DESCRIPTION (provided by applicant): The Biostatistics Core (Biostats) is a centralized and dedicated resource structured to meet biostatistical needs of the Holden Comprehensive Cancer Center (HCCC). Quality biostatistical support promotes good study design, efficient use of resources, and effective analysis of data. Biostats provides such support in close collaborations with HCCC members, other shared research resources, and administration to advance the research and education missions of the HCCC. The comprehensive nature of Biostats assures cost-effective access to biostatistical support that includes study design and development; protocol review and study monitoring; research data management; statistical analysis and programming; analysis reporting and publication; methodological development; and education, training, and professional development. The primary resources of Biostats are the expertise and time of its biostatistician personnel. In order to meet HCCC biostatistical needs, Biostats includes personnel who have a wide range of expertise, including experimental design, clinical trials, statistical computing, spatially and temporally correlated data analysis, genetic and genomic data analysis, and Bayesian statistics. Personnel are active participants in multiple aspects of the HCCC. They serve on the HCCC Protocol Review and Monitoring Committee and the Data Safety and Monitoring Committee. Collaborations involve all research programs and close interactions with the Population Research Core, Biospecimen Procurement and Molecular Epidemiologic Resource, as well as the Clinical Research Services. Additionally, Biostats provided educational training and professional development. In summary, Biostats is a highly collaborative, productive, and integrated resource that is vital for the HCCC.

CRITIQUE: The Biostatistics Core (Biostats) is a centralized resource that provides quality biostatistical support and promotes good study design, efficient use of resources, and effective analysis of data. In order to meet HCCC biostatistical needs, Biostats's personnel provides a wide range of expertise, including experimental design, clinical trials, statistical computing, spatially and temporally correlated data analysis, genetic and genomic data analysis, and Bayesian statistics. They serve on the HCCC Protocol Review and Monitoring Committee and the Data Safety and Monitoring Committee. Collaborations involve all research programs and close interactions with the Population Research Core, and Biospecimen Procurement and Molecular Epidemiologic Resource as well as the Clinical Research Services. Additionally, the Biostats provides educational training and professional development. The Biostats has two specific aims: 1) Provide essential expert biostatistics consultation and support for optimal design; and 2) Evaluate data to provide the most appropriate statistical analysis, and the clearest presentation of data for manuscripts, proposal submissions, and reports. The Biostats shared resource team includes Brian J. Smith, PhD (CEPS); Gideon Zamba, PhD; and Patrick Breheny, MS, PhD. They are assisted by two MS staff, MS. Sarah Mott and Mr. Bradley Loeffler.

The Biostats has good productivity metrics. During the current project period, the Biostats supported a total of 359 new cancer-related projects, 94 (26%) of which involved study design and protocol development, and new and continued funding through biostatistical involvement in multi-project

program grants including NCI P50 Lymphoma SPORE, NCI P50 Neuroendocrine SPORE, NCI P01 on Pharmacological Ascorbate, and NCI Quantitative Imaging Network U01. This SR has, even though not part of the proposed aims, a strong education mission–formal courses (Biostatistics, Biostatistical Computing in R and SAS, and Machine Learning), SAS user group, and seminars; it mentored 91 trainees of HCCC members on 134 cancer research projects during 2015 to 2019 and mentored undergraduate students.

This SR supports analysis on a very long list of areas covered with a very short list of personnel. Very little details regarding performance metrics are provided, such as total number of hours and activities. For example, 26% of the projects involved study design and protocol development, but it is unclear what the other 74% of the projects were, hours per research program, what type of grants have been supported/developed (the number of R01, R21, P01 grants, etc.), and number and impact of the publications it supported. Although some of these metrics were provided during the site visit, it seems that the SR does not have a solid system to track usage and performance metrics.

The Biostats works with the Department of Biostatistics when they need to increase the capacity when funding levels of the cancer center members are maximized. Regarding future directions, it is not clear how the areas of spatial characteristics of cancer risk factors and outcomes, and statistical genetics and mediation analysis (causal inference) related to HCCC future direction.

In summary, the Biostats team is small but very effective in how they support cancer research and collaborate with other shared resources, in particular with the Population Research Core. These two SRs collaborate and work closely together as both SRs report to Dr. Chrischilles in her role as AD for Population Science and AD for Community Outreach and Engagement. One weakness is the lack of a solid tracking system given that very few metrics were provided in the application. This issue was common to almost all shared resources. In addition, it is not clear how the expansion in the proposed areas is aligned with the HCCC goals.

Personnel: Dr. Brian Smith has been the Director of the Biostats since 2006 and he is a strong leader for this SR. He is a member of the CEPS Program, the CEPS Leadership Committee, Population Research Core Advisory Committee, and Data Safety and Monitoring Committee. He is also Co-Director of the P50 UI/Mayo Lymphoma SPORE and the lead statistician on a U01 QIN grant and a P01 program project study of pharmacologic ascorbate. These numerous leadership roles allow him to provide integration of the Biostats efforts across the HCCC. It is unclear how Dr. Smith and Dr. Zamba, Biostats faculty biostatisticians, handle conflict as members/reviewers of DSMC when they provide support in trial design.

Assessment: Outstanding to Exceptional merit

Budget: The budget is appropriate as requested.

Central Microscopy Research Facility (CMRF)

DESCRIPTION (provided by applicant): The major goal of the Central Microscopy Research Facility (CMRF) is to provide high-quality microscopy services to cancer research projects, ensuring that Holden Comprehensive Cancer Center (HCCC) investigators have access to the latest instrumentation and techniques to enhance their work. The facility provides access to approximately $10 million in

equipment including light, confocal, and electron microscopy of a variety of different types. It also supports cancer researcher access to specialized staining and embedding of samples, negative staining, metallic coating, autoradiography, cryo-fixation, enzyme and immunocytochemistry, morphometry, stereology, X-ray microanalysis and microdissection. The facility is accessible seven days/week, 24 hours/day to trained investigators and staff. The CMRF is directed by Randy Nessler, who has 29 years of experience in this facility, and brings this tremendous experience and expertise to serve the research needs of HCCC investigators. The six full-time staff members have a combined total of +90 years of microscopy research experience, with many years devoted to cancer research.

CRITIQUE: The major goal of the Central Microscopy Research Facility (CMRF) is to provide high-quality microscopy services to cancer research projects, ensuring that HCCC investigators have access to the latest instrumentation and techniques to enhance their work. This SR provides access to approximately $10 million in equipment of a variety of different types including light, confocal, and electron microscopes. It also supports cancer researcher access to specialized staining and embedding of samples, negative staining, metallic coating, autoradiography, cryo-fixation, enzyme and immuno-cytochemistry, morphometry, stereology, X-ray microanalysis, and microdissection. This SR is accessible seven days/week, 24 hours/day to trained investigators and staff. The facility is close to the Cancer Center allowing ready access to the instruments. The CMRF plays a vital role for cancer research using modern cancer biology approaches; having ready access to modern fluorescence microscopy and EM techniques is crucial to achieve highly impactful discoveries in cancer biology.

The CMRF has two specific aims: (1) to support microscopy-based research of HCCC members including instrument and technique training; and (2) to continually enhance and upgrade equipment and capabilities, with all equipment under service contracts. CMRF personnel have extensive combined microscopy experience including specialized STED confocal/super-resolution microscopy, LCM, TEM, SCM, complete sample preparation, and full imaging analyses. CMRF offers a custom-built computer workstation for user image analyses and visualization. Examples of HCCC research facilitated by CMRF during the current project period include staining and imaging to support translational studies on melanocortin 1 receptor-targeted radiotherapy in metastatic melanoma (Schultz; FRMI); support of physio-chemical characterization of new nanoparticles used to treat serous uterine carcinoma in a preclinical xenograft mouse model (Leslie; ET); and a study of connections between TCA cycle and stress in the ER within tumor cells using TEM (Rutkowski; FRMI).

The use of this SR is well documented and the number of publications citing this facility was relatively high. Perusal of the published papers appears to indicate that most of the applications were fairly standard EM or immunofluorescence of confocal images of fixed tissue or cells.

In FY 2019, there were 269 CMRF total users, with 16% (44) from HCCC labs, and of these HCCC labs 31 (70%) had peer-reviewed funding. Future activities include a new three-year budget allotment of $100,000 per year for instrument acquisition from the UI Office of the VP for Research, with key upgrades of a TEM in year one and, in years two and three, purchase of a cryo-ultramicrotome, a vacuum evaporator, and two cryostats, respectively. A yearly user survey (In the last FY, there were 81 total respondents) assesses (1) accessibility, responsiveness of staff to investigator needs, affordability, and promptness of service; (2) shared resources at UI that would benefit from HCCC investment; and (3) how research would significantly benefit from new shared resources that are not currently available.

Staff and leadership stability with extensive experience and expertise is a strength of the CMRF. The offerings of services and instrumentation span a range of capabilities to support HCCC member

microscopy needs. Examples of studies supported add value to fundamental and translational science of the HCCC. Representation on the faculty advisory committee aligns with the needs of HCCC investigators and the broader life sciences community with the current and future capabilities of the CMRF. Some items to consider include adding or swapping in a faculty advisory committee member from an UI physical sciences or engineering department because of advances in microscopy in the physical sciences that spill into life sciences applications, such as light sheet microscopy. In the current project period, geology and physical sciences had different needs for microscopy and therefore the CMRF was relocated; however, physical science advisory input still seems desirable to add knowledge of coming advances in technology. Also, CMRF utilization by HCCC members appears modest, with fewer than one project per week in 2019 (44 projects/52 weeks). The staff size of the CMRF also appears quite robust, which may be necessary to span the required expertise and training offered by the CMRF. It was not detailed how many HCCC and other UI individuals were trained by the CMRF in the current project period, nor was it mentioned how instrument prioritization is resolved if/when time conflicts and competing priorities arise.

One major weakness is that the equipment described in the application is not state-of-the-art in this facility, which, while having STED, lacks any STORM, PALM, or SIM super resolution capabilities. The description in the application did not indicate that the facility has any live-cell image capabilities on their one confocal microscope. In addition, advanced techniques such as lattice light sheet, two-photon or intravital imaging are not represented. However, during the site visit, the CMRF Director, Mr. Randy Nessler, indicated that there is a plan to purchase a new confocal microscope which will have live cell and higher resolution capabilities. He indicated that the CMRF has a Total Internal Reflection Fluorescence (TIRF) microscope and also a new EM is arriving soon. He also indicated that the campus had a lattice light sheet instrument and he could direct interested researchers to this facility. Finally, he indicated that the facility had at one time two-photon capabilities, but this resource was underutilized and thus no longer available. Therefore, while the facility fills an essential need, it does not appear to be leading HCCC with new innovative state-of-the-art approaches. Ideally, this SR could be driving new discoveries and educating faculty on potential new innovative uses rather than polling faculty to request new approaches.

In summary, this is a standard microscopy shared resource that adds value for cancer center basic and translational studies. Opportunities exist for input from physical sciences and increased utilization by HCCC members. Recent updating of some equipment will help provide more up to date approaches, but the resource has not fully realized the goal of providing state-of-the-art innovative imaging approaches.

Personnel: The CMRF has six highly experienced staff members with extensive combined experience in microscopy. Its director, Mr. Randy Nessler, has over 29 years of experience in core management, overseeing associated technologies and techniques. He appears to bring adequate experience and expertise to serve the research needs of HCCC investigators. He participates in several microscopy professional societies and attends national and regional meetings yearly.

Assessment: Very Good merit

Budget: The annual CMRF operating budget is $1.23 million, with $49,000 (or 4.0%) coming from the CCSG for personnel and minimal supplies, 64% from chargeback of users, and 32% from other sources. The proposed CCSG budget for the next FY in the next five-year budget cycle remains similar.

$232,000 in total CCSG funds for small percentages of personnel and supplies are requested, which seems appropriate. The budget is appropriate as requested.

Flow Cytometry Core (Flow)

DESCRIPTION (provided by applicant): The Flow Cytometry Core (Flow) offers state-of-the-art instrumentation and consultation to cancer researchers. It also provides investigators with the current and effective data analysis software as well as secure data storage options. Basic and translational cancer research projects being conducted by Holden Comprehensive Cancer Center (HCCC) members take advantage of Flow's high-speed sorting, multi-parameter analysis, high efficiency purification of cell subsets. New equipment includes two five-laser Cytek Aurora spectral analyzers with a 96-well autosamplers that can perform up to 40 color analysis and cell sorting. Flow also offers training and assists investigators with software programs available for interpretation and analysis of data. Individual training of investigators and their laboratory personnel in use of the bench-top instruments is provided which allows trained personnel access to these instruments around the clock. Flow is in a constant process of developing new technology and services as requested and/or needed by HCCC investigators.

CRITIQUE: The Flow Cytometry Core (Flow) offers standard, high-end instrumentation and expertise in cell sorting, multi-parameter analyses, and high efficiency cell purification. Consultation services, data analyses software, and secure data storage are also offered. New equipment in the current funding cycle includes two (one operational, one just arrived) five-laser Cytek Aurora spectral analyzers with 96-well autosamplers for 40-color analysis and sorting. Training in bench-top equipment enables authorized users 24/7 access to these instruments. The Flow SR has three specific aims: (1) provide state-of-the-art flow cytometry instrumentation and consultative services, (2) provide current and effective data analyses software and secure data storage, and (3) provide flow cytometry educational resources for HCCC members. In Aim 1, this SR offers two five-laser Cytek Aurora spectral analyzers, two 11-14 color cell sorters in biosafety cabinets, a Luminex 200, a Miltenyi autoMACs, and four benchtop flow cytometers. Aim 2 lists computers with standard analytic software to support instruments offered in Aim 1. During the site visit, it was clarified that a FlowJo analytic software license permitted investigators to analyze collected flow data off site. Aim 3 describes web-available staining protocols, cell preparation, instrument descriptions, instrument scheduling, policies, services and fees, education resources, links to other tools, and available individualized education for benchtop flow cytometers and software usage. Examples of Flow support of HCCC research includes B cell clonality studies (Zhao; ET), TLR9 agonists on the immune responses to lymphoma (Weiner; ET), studies of self-renewal of hematopoietic and leukemic stem cells (Xue), and several other studies.

The Flow SR is jointly overseen and managed by the Carver College of Medicine (CCOM) and HCCC with a five-member faculty oversight committee that has been operating for 36 years and currently sets user fees, access policies, and operational guidelines. The committee meets regularly. Facility staff are available from 9 am to 5 pm (Monday through Friday), with after-hour operations for approved, trained members to benchtop cytometers. Rates are $40/h for HCCC and VA members and $57/h for everyone else. Utilization in FY 2019 was 192 total users, of which 82 (43%) were HCCC members, with 57/83 (69%) having peer-reviewed funding. A poster provided FY 2020 updated metrics, with 41% of users being HCCC members (52 total users).

A yearly user survey (81 total respondents in last FY) assesses (1) accessibility, responsiveness of staff to investigator needs, affordability, and promptness of service; (2) shared resources at UI that would benefit from HCCC investment, and (3) how research would significantly benefit from new shared resources that are not currently available. Future directions for Flow include installation of the second five-laser Cytek analyzer, purchased jointly with the VA; and submission of a S10 NIH instrumentation grant for an Amnis ImageStream cytometer and standard ongoing equipment and software updates.

A large number of publications that benefitted from Flow was provided in a table format at the site visit. However, detailed information was not provided regarding how many HCCC and other UI individuals were trained by Flow in the current funding period, nor was it mentioned how instrument prioritization is resolved if/when time conflicts and competing priorities arise.

In summary, this is an excellent shared resource with standard instruments and capabilities for the HCCC that adds value for cancer center basic and translational studies. Opportunities exist for increased utilization for its available capacity.

Personnel: The Flow Director, Dr. Zuhair Ballas, is a highly experienced immunologist who oversees a staff of three facility-dedicated technical support personnel. Dr. Ballas is supported by a Technical Director, Mr. Heath Vignes; a Flow Facility Research Specialist, Mr. Michael Shey; and a Flow Facility Research Professional, Mr. Thomas Kaufman. Dr. Ballas' research has been focused on NK cells in tumor surveillance, inflammatory disorders, and immunodeficiency. He has been the Flow Director since 1992.

Assessment: Excellent merit

Budget: The 2019 FY Flow operating budget is $417,000, with $59,000 (14.0%) coming from the CCSG for personnel and minimal supplies, 72% from chargeback of users, and 14% from other sources. For FY 2020 the metrics were similar with an operating budget reduced by 5.0% to $396,000. These lower numbers for FY 2020 likely reflect the COVID-19 pandemic and transient work slowdown or stoppages in spring 2020. The proposed CCSG budget for FY 2021 in the next five-year budget cycle remains similar. About $47,000 is requested for 4.2-month aggregate effort for SR director and two support staff. $273,000 total in CCSG funds for 5 years including supplies is the request. The budget is appropriate as requested.

Genomics Shared Resource (GSR)

DESCRIPTION (provided by applicant): The Genomics Shared Resource (GSR) provides a broad spectrum of services and resources designed to make the state-of-the-art techniques used in DNA sequence and transcript analysis readily available to the Holden Comprehensive Cancer Center (HCCC) laboratory and clinical research communities. The research-based services and resources of the GSR include: 1) DNA sequencing, including whole exome sequencing, 2) custom oligonucleotides, 3) DNA microarrays (Illumina BeadArray system), 4) real-time PCR, 5) molecular biology computing, and 6) genome, mRNA and single cell sequencing using next-generation sequencing (NGS) technologies. The GSR also provides access to state-of-the-art informatics including bioinformatics software and tools, public/local data and databases and computing and machine-learning/artificial intelligence capabilities. Molecular biology computing personnel work closely with investigators early in the process to improve study design and assure generation of high-quality data that meets the needs of

the investigators. GSR also continues to evaluate and update services to remain cutting-edge and provide new services needed and serves HCCC investigators from each of the HCCC programs.

CRITIQUE: The Genomics Shared Resource (GSR) has been a long-standing shared resource in the HCCC. This SR provides a variety of standard as well as state-of-the-art services for HCCC members, including 1) DNA sequencing (targeted and WES), 2) custom oligos, 3) DNA microarrays using the Illumna BeadArray Station, 4) RT PCR, 5) molecular biology computing services, and 6) genome, mRNA and single-cell sequencing using NGS techniques.

Restructuring of the HCCC SRs has placed bioinformatics support within other SRs, and state-of-the-art bioinformatics analyses, access to high performance computing (HPC) and cloud computing, and artificial intelligence (AI) capabilities is indicated as an aim of the GSR. However, the effectiveness of this support and extent appears rather limited.

The GSR supports both HCCC and the Iowa Institute of Human Genetics (IIHG) and is jointly managed by these two entities. However, little detail is provided about how this is accomplished. HCCC members receive a discount for services although the overall amounts are modest, for example 15% discounts for DNA sequencing and 12.5% discounts for RT PCR. It does not seem that there is subsidy for bioinformatics services. It would be necessary to prospectively monitor and evaluate the needs and use of bioinformatics services in this transition.

In FY19, 83 HCCC members used the GSR which was 28% of overall users. The majority (52/83) of the users had peer-reviewed funding for their research. This SR is readily accessible to users; it is open from 8 am to 5 pm and trained users have the ability to access equipment after hours.

Future directions include optimization of workflows for single cell (ATAQ, mRNA, CNV) approaches, development of cfDNA approaches, and movement into spatial genomics. While some of these directions appear to be in response to HCCC member needs and/or an effort to remain current (e.g., scRNAseq, TCR profiling, scATAQ), others may be more niche. Given resource limitations, it is unclear how these various avenues will be prioritized to enhance member needs.

In summary, the GSR provides important and necessary services and equipment access to HCCC investigators, supporting impactful publications that are leading to novel insights into the molecular genetics of sarcomas, gynecologic malignancies and signatures of metastatic potential in panNETs. This SR with its strong leadership has adapted to the changing scientific landscape by embedding bioinformatics/biostats into the SR. However, further assessment of the new embedded biostatistical support model is needed to determine whether the current personnel will be able to meet the growing need of HCCC members. There are also some questions about HCCC's role in guiding/managing the GSR with the IIHG.

Personnel: The GSR is led by Dr. Kevin Knudtson since 1996. He has a long history of experience with molecular biology, sequencing and array technologies and relevant SR management experience. He devotes 100% of his time to the SR and oversees all GSR operations including the evaluation of personnel, data quality, instrumentation, and GSR services. He works closely with investigators to assist with experimental design and data analysis, especially for DNA microarray and next generation sequencing projects. Support staff and SR personnel seem appropriately qualified to carry out routine molecular biology sample and library preparation and sequencing.

Assessment: Excellent merit

Budget: The budget is appropriate as requested.

High Throughput Screening Core (HTS)

DESCRIPTION (provided by applicant): The High Throughput Screening Core (HTS) supports basic and translational biomedical research by designing, optimizing, and running high throughput assays that deliver potential therapeutics for cancer. This is done by integrating robotics, detection systems, chemical /biologics libraries and data management with expertise in optimizing technologies and outcomes along each step in the process. HTS provides Holden Comprehensive Cancer Center (HCCC) members with scalable early, pre-clinical development of therapeutics, including small molecule therapeutics, antibodies, siRNAs, antisense oligonucleotides and other biologics including patient-derived cell therapeutics. It also supports high throughput screening for studies exploring the biology of cancer. The HTS is equipped to perform high-throughput screening in 96-, 384- and 1536-well formats, with plate reader detection (Perkin-Elmer EnVision) using absorbance, fluorescence and luminescence, including advanced FRET and BRET techniques. HTS can also perform high content screening (HCS, Perkin-Elmer Operetta Confocal Imaging System) to detect and quantify phenotypic changes, i.e., cell differentiation, cell migration, neurite outgrowth, and target trafficking or by fluorescence intensities for target protein expression, transcription factor or signaling pathway analysis.

CRITIQUE: The HTS SR supports high-throughput screening by designing, optimizing and running high-throughput assays for development of cancer therapeutics. It provides state-of-the-art capabilities in both small molecule and genetic based screening that is important to current cancer research and contributes to development of improved therapeutics. The capabilities are flexible to use in different types of projects. Its aims are to assist investigators in the development and use of scalable screening approaches for discovery and development of therapeutics (Aim 1), high-throughput approaches for discovery of novel druggable targets, pathways and genes (Aim 2), and integration with other HCCC shared resources (Aim 3). This SR has a seed grant program. It is jointly managed by the HCCC and University of Iowa Vice President of Research (VPR) Office. An advisory committee, that includes active users and represents two programs (CGP and ET) and the executive HCCC leadership, meets every 3-6 months. There are 40 users, 27 of whom are HCCC members (68%) and 25 of the HCCC users have peer-reviewed support.

Future directions include expansion into arrayed CRISPR-gRNA collection and cell collections; absorption, distribution, metabolism, excretion, and toxicity testing; physiologically relevant in vitro approaches (ex vivo analysis of patient derived samples); and natural products and monoclonal antibody screening.

The HTS SR is well equipped with robotics and plate reading instruments that include confocal imaging of cells. The services are state of the science and include use of patient-derived specimens. The HTS has contributed to scientific accomplishments of member users including identification of new targets (RAD52) and compounds (monensin, progesterone receptor inducers); peer-reviewed publications; new grants, and clinical trials. There is a high percentage of usage by HCCC members with an obvious benefit to the HCCC in providing costly equipment and services that are too expensive for individual investigators. However, little information on the cost effectiveness or savings to HCCC members was

provided. While evidence of integration with bioinformatics and other SRs was not apparent in the application, but it was appropriately addressed during the site visit.

In summary, the HTS SR provides a valuable resource to HCCC members that is not easily obtainable for individual labs, adding benefit to the HCCC. Examples of scientific accomplishments of HCCC members, new peer-reviewed publications, grants, and a clinical trial supported by this SR are provided. The HTS provides seed grants, although accomplishments from these has not yet been reported. In the current funding period, the usage of this SR is appropriate based on the value of the accomplishments.

Personnel: Dr. Meng Wu has been the HTS Director since its inception. He has a high level of experience in HTS campaigns at the John Hopkins University and now at the University of Iowa. He has R50 funding from the NCI. Although the HTS SR description does not document support from other faculty or personnel with HTS expertise in running this SR, assistance by Dr. Maria Spies as a staff investigator to foster utilization of this SR is included and described in the Developmental Funds component.

Assessment: Outstanding merit

Budget: Of the $238,572 operating budget, 17.4% is provided by the HCCC, 37.9% by chargebacks and 44.7% by other. Support from the HCCC is proposed to be maintained at a similar level in the next funding period. The budget is appropriate as requested.

Population Research Core (PopRC)

DESCRIPTION (provided by applicant): The Population Research Core (PopRC) is a centralized resource dedicated to the needs of the Holden Comprehensive Cancer Center (HCCC) in the domain of population science. Quality epidemiology support promotes strong observational study designs and data collection and data curation methods. The primary resources of the PopRC are its scientific personnel and its curated and annotated population-based data. The PopRC provides HCCC members with guidance and assistance in accessing and using large databases of cancer patient data that include SEER-Medicare, SEER-Medicare Health Outcomes Study (MHOS), enhanced unlinked SEER research dataset, Iowa driver's license database, the Iowa Mortality database, the Greater Plains Collaborative, and others. A number of these resources are unique to the HCCC catchment area (the state of Iowa). In addition to database research activities, the PopRC supports personnel with a wide range of expertise including population study designs, field research methods and tools, and biospecimens linked to clinical registries. PopRC personnel collaborate closely with the Biostatistics Core on analytic plans and data analysis of population studies, and with the Biospecimen Procurement and Molecular Epidemiology Resource (BioMER) to ensure efficient and effective coordinated access for investigators to biospecimens. The PopRC collaborates with the BioMER by providing samples from the Iowa Residual Tissue Repository and Virtual Tissue Repository that are linked to SEER data. The PopRC supports HCCC members from all four research programs. Projects commonly involve collaborations of HCCC epidemiologists with clinician and basic scientists across the HCCC and from other academic institutions. The PopRC is a comprehensive, collaborative and integrated resource that is vital to the HCCC.

CRITIQUE: The Population Research Core (PopRC) provides high-quality epidemiology support that promotes strong observational study designs and data curation methods. The PopRC has four aims: (1) to work with HCCC investigators to develop and implement appropriate design and methodology to answer population-based questions, (2) to provide efficient use of large population-based datasets and other resources, (3) to support HCCC members in the conduct of population-based field research, and (4) to provide clinically annotated biospecimens from the Iowa Tissue Repository.

The PopRC continues to be an important resource for HCCC investigators. The PopRC Director, Dr. Bradley McDowell, interacts often with the HCCC leadership to discuss plans and obtain feedback and meets annually with the HCCC Research Executive Committee (which includes leaders from all four programs) to discuss the previous year's activities and plan for the future. He is a member of the CEPS Leadership Committee and represents the PopRC in its quarterly meetings.

Although data on the number of projects supported and total number of grants and publications were not provided, the application lists 17 users, of which 15 are HCCC members (88%) and nine (60% of member users) have peer-reviewed funding.

The application provides several examples of research supported by the PopRC. These include, for example, studies leveraging the SEER-Medicare database including important work on mental health and treatment adherence, and list a publication leveraging the Tissue Repository. Both the SEER and Residual Tissue Repositories (RTR) are extremely valuable resources; however, it is difficult to discern how impactful the usage has been. Importantly, the PopRC has been leveraged for several studies of patient-reported outcomes (PROs) by HCCC members and external users.

With regard to oversight, it is noted that the PopRC Director meets often with HCCC leadership, meets monthly with the Research Executive Committee, and meets weekly with a group of CEPS leaders and members, including the AD for Population Science. Changes made in response to oversight mechanisms are not mentioned. However, the Shared Resource Management section indicates that in response to comments from the Core Survey of members, Dr. McDowell's R50 award will be leveraged to enhance PopRC resources. This is also mentioned in the PopRC's future plans with the goal of enhancing data to follow patients prospectively.

The future goals are to enhance cancer data resources to provide researchers with a complete picture of cancer patients' experiences prior to diagnosis, during treatment, and through long-term survival by integrating existing hospital data with state cancer registry data, insurance claims, and other cancer-related datasets to create a multi-purpose data resource that will support collaborations within UI as well as multi-site studies.

In summary, the PopRC is an important SR for population scientists and potentially for clinical researchers. However, data provided to evaluate its impact are not complete. Both the SEER and RTR are extremely valuable resources; however, it is difficult to discern how impactful the usage has been due to the issues noted above. Overall, it appears that this resource is meeting its objectives and requirements for serving investigators across the HCCC. While linkage with and support of investigators in the CEPS program is most logical, there are also areas of potential collaboration with other research programs as well as the Biostats for study design and data analysis, or opportunities for collaboration with the BioMER with the use of the Iowa Tissue Repository.

Personnel: Dr. Bradley McDowell directs the activities of the PopRC. His skills and experience were recently recognized through an NCI R50 grant awarded in 2019 entitled “Building a patient-centered cancer data mart in a rural state”.

Assessment: Outstanding to Excellent merit

Budget: Found in the SR Management Component, the total operating budget is $180,706 of which 27% is from the CCSG and the remainder is institutionally supported. The budget is appropriate as requested.

Radiation and Free Radical Research Core (RFRRC)

DESCRIPTION (provided by applicant): The Radiation Free Radical Research Core (RFRRC) facilitates Holden Comprehensive Cancer Center (HCCC) researcher investigations that require radiation services or quantitative methods for analyzing and manipulating redox status and redox based biological changes. It serves both HCCC members and cancer researchers at other institutions. The RFRRC has been in operation since 1947, and is directed by Douglas **Spitz**, PhD; Frederick **Domann**, Jr, PhD; Garry **Buettner**, PhD; and Prabhat **Goswami**, PhD all of whom have extensive experience and international reputations in free radical-focused cancer research. The RFRRC provides three basic services. Ionizing radiation services are supplemented by phosphorimaging and cell-cycle analytical tools critical to understanding basic cellular behavior and responses to radiation and chemotherapy. Electron paramagnetic resonance spectroscopy and other analytical chemistry detection methodologies are available for measuring free radicals, singlet oxygen, small molecule antioxidants, nitric oxide and the array of related oxidants and oxidative damage products. Antioxidant enzyme services provide easy access to technologies for modifying and measuring molecules responsible for pro-oxidant formation and oxidative damage. Major equipment available in the RFRRC includes several radiation sources, a Seahorse analyzer, various types of spectrophotometers, hypoxia chambers, and equipment for HPLC separation and analyte detection. The RFRRC provides HCCC members with easy access to specialized knowledge, reagents, equipment and resources in a highly collaborative and helpful environment.

CRITIQUE: The Radiation Free Radical Research Core (RFRRC) facilitates HCCC researcher investigations that require radiation services or quantitative methods for analyzing and manipulating redox status and redox-based biological changes. It serves both HCCC members and cancer researchers at other institutions.

The RFRRC is one of two United States shared research resources with the knowledge and reagents to provide the needed services. Over the current funding period, the RFRRC services have been utilized by over 60 HCCC members from all programs as well as 11 external cancer researchers. While the overall usage is relatively low, the percentage of HCCC members using the RFRRC is 60% making this SR an important SR within the HCCC, especially for FRMI members. The RFRRC has state-of-the-art facilities including several radiation sources, a Seahorse analyzer, various types of spectrophotometers, hypoxia chambers, and equipment for HPLC separation and analyte detection. This SR uses a highly collaborative framework to help provide innovative resources to HCCC members.

Tumor cells living in a hostile niche are generally considered to be more pro-oxidant. With the clear connection to mitochondria, bioenergetics and metabolisms, the RFRRC fulfills an important role at the HCCC and provides outstanding expertise and analytics to follow oxidant injury in cells.

The strengths of the RFRRC include both targeted and whole-body radiation platforms as well as phosphorimaging/gamma counting services for radionuclide and theragnostics, EPR for measuring free radicals and related pro-oxidants, and wide range of enzymology and biochemistry services and reagents.

The nicely described future goals would enhance research at the HCCC and the addition of a stereotactic irradiation platform for treating tumors in mice is state-of-the-art.

Personnel: The RFRRC is directed by Drs. Douglas Spitz, Frederick Domann, Garry Buettner, and Prabhat Goswami. They have appropriate roles and expertise.

Assessment: Outstanding merit

Budget: The budget is appropriate as requested.

Viral Vector Core (VVC)

DESCRIPTION (provided by applicant): The Viral Vector Core (VVC) serves as a research facility that supports gene transfer studies. Its overall objective is to support investigators in the use of gene transfer technologies, including consultation with investigators, development of novel vectors, collaborative testing of vectors generated for function and purity, and preparation including quality control. The facility serves both HCCC members and a significant number of investigators from other NCI-designated cancer centers. VVC staff are active participants in the development of gene transfer technologies in the cancer field. The interaction with multiple investigators from various disciplines and institutions allows for cross-fertilization of ideas, technical advancements, and innovations in vector designs. The VVC provides purified and concentrated preparations of recombinant adenovirus, adeno-associated virus, vaccinia, baculovirus and retrovirus (including lentivirus). It also provides access to standard cell lines, expression plasmids and a stock of recombinant reporter viral vectors. The main responsibilities of the VVC are to: prepare recombinant vectors; perform relevant quality control; disseminate vectors; maintain a database of vector stocks available for use; maintain a database of expression vectors; develop new expression vectors as needed; develop novel methods for vector production; and assist in the design and development of novel vectors.

CRITIQUE: The Viral Vector Core (VVC) is a long-standing shared resource. The primary goal of the VVC is to provide research support for gene transfer studies. This SR has been supporting investigators in using gene transfer technologies by providing consultation with investigators, development of new vectors, collaborative testing of functionality, and quality control. In addition to supporting the HCCC members, it also provides services to investigators from other NCI-designated cancer centers.

The VVC provides purified and concentrated preparations of recombinant adenovirus, adeno-associated virus, vaccinia virus, baculovirus and retrovirus (including lentivirus). It also provides access to standard cell lines, expression plasmids, and a stock of recombinant reporter viral vectors. The main

responsibilities of the VVC are to prepare recombinant vectors, perform relevant quality control, distribute vectors, keep a database of vector stocks available for use, maintain a database of expression vectors, develop new expression vectors as needed, develop novel methods for vector production, and assist in the design and development of novel vectors. In FY19, the VVC had 146 users, of which 39 (27%) were HCCC members. An advisory committee is in place.

The staff members in this SR have expertise in viral vector development and application. They have a strong track record of providing service to investigators at HCCC and investigators across the country. The operational procedures are well established. The turn-around time is excellent.

In summary, the VVC has a strong track record of supporting both internal and external investigators. The overall goals are well defined and its operation is highly efficient. The management of the VVC is outstanding.

Personnel: The VVC is led by Dr. Patrick Sinn. Dr. Sinn has directed the VVC since 2014. He has 20 years of experience in designing and implementing vector delivery. He is highly qualified to lead this SR.

Assessment: Outstanding merit

Budget: The budget is appropriate as requested.

CANCER RESEARCH TRAINING AND EDUCATION COORDINATION

DESCRIPTION (provided by applicant): The most critical resource of any cancer center are the diverse and talented researchers, clinicians, trainees, and staff that drive the mission of the organization. The Holden Comprehensive Cancer Center (HCCC) has established and supported a robust Office of Cancer Career Enhancement and Training (OCCET) to facilitate the education and training of researchers, clinicians, trainees, staff, and community providers. The overall goal of the HCCC OCCET is to establish and foster infrastructure that coordinates and facilitates educational opportunities to enhance the careers of cancer researchers, clinicians, and community providers. OCCET initiatives include summer research programs, graduate programs, an annual research retreat, HCCC-supported seminar series, and support for staff participation in national conferences. These programs are targeted towards multiple levels of training, from “from teens to tenure” and beyond. The OCCET is committed to enhancing the inclusion of underrepresented minorities and trainees from lower socioeconomic households and rural populations who represent a significant untapped pool of talent from our catchment area. As a matrix cancer center, the HCCC’s educational initiatives are integrated with other educational programs at the University of Iowa (UI) and are designed to leverage, but not duplicate, institutional career enhancement efforts. The OCCET also provides the framework for intra- and interprogrammatic interactions and collaborations between researchers in the HCCC’s four research programs. The OCCET is led by the Associate Director for Career Enhancement, Jon Houtman, PhD, and supported by the Assistant Director for Career Enhancement, Gregory Thomas, PhD, and staff at the HCCC. The staff in the OCCET are advised by several committees, including the Career Enhancement Advisory Committee, composed of leaders of training grants and graduate programs and representatives of various trainee groups. The efforts of the OCCET are 1) to establish and maintain a robust cancer career enhancement and training infrastructure at the HCCC by fostering the career enhancement infrastructure responsible for the training of HCCC trainees, faculty, staff, and

community providers and integrating these efforts into wider programs at both UI and within the HCCC catchment area, 2) to assure quality training and mentoring of diverse trainees at all stages of training by supporting the development of a cancer workforce through training initiatives at every career stage, and 3) to facilitate educational and career enhancement opportunities for trainees, faculty, clinicians, and staff of the HCCC and across Iowa by facilitating existing, and generating new, opportunities for learning and scientific discussion at all levels including trainees, faculty, clinicians, and staff at the HCCC, as well as at other stakeholders both within and outside the HCCC catchment area.

CRITIQUE: The HCCC has established and supported a robust Office of Cancer Career Enhancement and Training (OCCET) to facilitate the education and training of researchers, clinicians, trainees, staff, and community providers. The overall goal of the HCCC OCCET is to establish and foster infrastructure that facilitates educational opportunities to enhance the careers of cancer researchers, clinicians, and community providers. The OCCET has the following aims: (1) to establish and maintain a robust cancer career enhancement and training infrastructure at the HCCC; (2) to assure quality training and mentoring of diverse trainees at all stages of training; and (3) to facilitate educational and career enhancement opportunities for trainees, faculty, clinicians, and staff of the HCCC and across Iowa.

Dr. Jon Houtman chairs the Cancer Career Enhancement Advisory Committee with assistance of Dr. Gregory Thomas. This committee meets at least twice yearly to provide advice to the OCCET and to identify gaps in education and training programs at UI. The committee includes directors of fellowship programs, T32 programs, director of the cancer biology graduate program, a graduate student, a post-doc, a clinical fellow, and an assistant professor. Dr. Houtman attends meetings of the HCCC COE Community Advisory Board, which provides advice on catchment area needs including educational and training needs of cancer care givers, researchers, and community organizations.

The OCCET is currently instituting a program to identify and track the career outcomes of all trainees. Trainees will be identified through an annual survey of HCCC members and tracked through email communication and indirectly through scientific social media resources including LinkedIn and ORCID to obtain educational and employment outcomes. The program described during the site visit was strong and very comprehensive. However, a weakness is that, given the educational nature of the institution, there is a lack of past tracking data beyond the past year and new systems have not yet been implemented.

Aim 2 focuses on the existing career development and educational activities. Several cancer career enhancement and training programs have been implemented that span high school through faculty as well as community providers. Aim 3 focuses on integrating programmatic and shared resource research efforts. The HCCC holds an annual research retreat that facilitates interactions with researchers from other colleges and university in the state and averages over 250 attendees over the past five years. In addition, OCCET supports HCCC Grand Rounds, which has brought in 59 external speakers since 2016; coordinates dual retreats for the research programs where two programs identify areas of research overlap, averaging 45 attendees; and supports education of cancer nurses via travel awards supporting 99 oncology nurses who have traveled to national nursing conferences.

Future directions are focused on 1) establishing a robust R25 YES program to enhance high school and undergraduate summer research experiences, 2) partnering with the CCOM and Graduate College to increase the size and scope of the Cancer Biology Graduate Program, 3) enhancing mentoring of postdoctoral fellows, 4) creating robust mechanisms to increase external fellowship applications and

awards, 5) identifying best practices for the tracking of trainee outcomes, and 6) developing a centralized mechanism for training community providers and clinicians.

Personnel: Drs. Jon Houtman and Gregory Thomas are strong and appropriate leaders of the CRTEC component. Dr. Houtman was appointed as the HCCC Associate Director for Career Enhancement in 2018, after serving as the HCCC Assistant Director of Cancer Education since 2015. Gregory Thomas, PhD, was hired as a full-time Assistant Director for Career Enhancement in 2019. Dr. Thomas completed his graduate and postdoctoral training at UI. Dr. Thomas serves full time in the HCCC OCCET, where he develops and coordinates educational efforts, leads efforts for enhancing postdoctoral mentoring, coordinates HCCC Grand Rounds, and manages the tracking of current and former trainees.

Assessment: Outstanding to Exceptional merit

Budget: The budget is appropriate as requested.

COMMUNITY OUTREACH AND ENGAGEMENT

DESCRIPTION (provided by applicant): Holden Comprehensive Cancer Center (HCCC) Community Outreach and Engagement (COE) is dedicated to assuring that the efforts of the HCCC are relevant to the State of Iowa, and that the HCCC and the people of Iowa, including minority and underserved populations, are engaged in HCCC cancer research. The overarching goal of HCCC COE is to alleviate Iowans' cancer burden by activating researchers and the population in assessing and addressing community-aligned priorities. Priorities include cancers in which Iowa is a top 5 state in incidence, mortality, or is increasing over time (colorectal, kidney, leukemia, lymphoma, melanoma, pancreatic); rural access to cancer screening and care; obesity-related cancers; environmental exposures to radon and agricultural chemicals; HPV-related cancers; and racial/ethnic disparities in cancer mortality.

HCCC COE includes three interrelated specific aims and associated activities: (1) to assess the catchment area needs and understand health disparities; (2) to address these needs through strategic research across the HCCC; and (3) to engage the community and disseminate and evaluate evidence-based interventions. At the center of these aims is the HCCC Community Advisory Board whose advice guides priority-setting, inclusion of under-represented populations in research, and assuring cancer control activities are aligned with priorities. HCCC COE activities include providing data and geospatial visualizations to monitor goals and support community health needs assessment; communicating with researchers about community-driven priorities; pilot grants and technical assistance for researchers from any program for community-engaged research; expansion of efforts to enhance inclusion of under-represented populations; expansion of a rural cancer research network; and linking research to policy and disseminating information about cancer prevention and control guidelines and policies.

HCCC Director George Weiner, MD and Associate Director of Population Science and Community Engagement, Elizabeth Chrischilles**,** PhD conduct strategic planning in consultation with the 20-member HCCC Community Advisory Board and three HCCC COE co-leaders Mary Charlton, PhD (Aim 1); Natoshia Askelson**,** PhD (Aim 2); and Kelly Sittig (Aim 3). The Co-leaders implement the HCCC COE logic model which includes a continuous cycle of interactions with the Community Advisory Board and associated activities, outcomes, and evaluation metrics.

CRITIQUE: HCCC's catchment area is the state of Iowa which includes a population of over 3 million with 36% living in rural areas. Data indicate that 92% of Iowans are White, 3.8% are African American, 2.7% are Asian, 0.5% are American Indian/Native American and ~2% are more than one race. Hispanics or Latinos represent 6.2% of the population. The catchment area burdens are defined based on annual reports from the Iowa Cancer Registry. Iowa ranks third in the nation for obesity. Breast, lung, prostate and colorectal cancers are the highest incident cancers, consistent with the nation overall. Mortality rates for pancreatic cancer are increasing in Iowa and leukemia is now the third leading cause of mortality. African Americans in Iowa have higher mortality rates than Whites for lung, prostate, colorectal, and pancreatic cancer.

The overarching goal of HCCC COE is to alleviate Iowans' cancer burden by activating researchers and the population in assessing and addressing community-aligned priorities. The COE has four specific aims: (1) to assess catchment area needs by understanding cancer burden and risk factors and characterizing sociodemographic and health disparities; (2) to address cancer burden in Iowa through research across the HCCC addressing underserved populations; and (3) to engage the community and promote dissemination and implementation of evidence-based interventions for cancer prevention and screening, cancer control and therapy, and care delivery in the catchment area.

Notable is the fact that HCCC COE evolved out of the Iowa Consortium for Comprehensive Cancer Control (ICC), a 501c3 non-profit organization led by Dr. Weiner since 2008 and presented as the "fulcrum" for HCCC COE activities. The ICC includes an ICC Board that represents over 400 members across Iowa and is charged to implement the Iowa Cancer Plan. An advantage of this relationship is the state-appropriated and federal funds ($476,219 in FY2019). Formed in 2019, the HCCC now has its own Community Advisory Board (CAB) meeting quarterly, although it is still in the early stages of development. Prior to 2019, the ICC Board provided community input to the HCCC. Now that these boards are distinct, there is some lack of clarity regarding how the CAB and ICC work together to identify priorities in the catchment area. The CAB appears to be highly engaged, but examples of specific research initiatives in response to CAB feedback were not clearly described.

The HCCC COE has several strengths. One example is the creation of the Iowa Cancer Maps Initiative to identify geographic patterns in cancer incidence, with updating to include behavioral, environmental, demographic, socioeconomic and clinical care data. Also, there are many examples of cancer prevention and control activities fostered by COE, including childhood nutrition initiatives, physical activity promotion, and telehealth initiatives to address barriers to access to care in rural populations. Also focused on rural cancer control, there is a robust research agenda to understand and address barriers to HPV vaccination, supported in part by a CCSG supplement. Also notable is the colorectal cancer research within community health systems that bridges epidemiology to community engagement in research to increase rates of colorectal cancer screening. A web-based quality of life intervention for ovarian cancer survivors has generated some promising clinical results. COE has also contributed to guidelines and/or policies, including those for HPV and radon, which are impactful for the community. HCCC members also serve on national and international committees to influence cancer policy, such as the US Preventive Services Task Force, and they engage with the EPA and WHO on environmental exposure policies.

There are a number of weaknesses, however. COE activities to increase accrual of under-represented minorities in HCCC clinical trials remain in the planning stages and there are limited details on how clinical trial enrollment will be monitored and improved to address this. Although the catchment area includes counties with sizable African-American populations and those with significant Hispanic/Latino

populations, it is not clear how outreach and access to clinical services are promoted in these groups. Disparities in cancer mortality by race/ethnicity are considered priorities for HCCC COE, yet descriptions of research conducted during this grant period are not aligned. LGBTQ disparities are also described based on a statewide assessment through an implementation grant, although more data are needed to identify unique barriers and to develop appropriate interventions.

An important limitation of COE concerns the engagement of basic science investigators. There was limited attention to catchment area-relevant research in HCCC programs other than CEPS. When questioned at the site visit, the processes for engagement and promotion of catchment area-relevant research among investigators in these programs was not adequately described. Also, at the site visit, it appeared that Dr. Chrischilles delegates significant oversight responsibilities to the leaders of the three aims, and evidence for her deep knowledge of key activities and outcomes was not apparent. While she is a very prominent scientist and leader, she may be overcommitted and COE would benefit from having a senior leader who is dedicated to this effort.

The evaluation plan of the COE is well-thought through and detailed with process and outcome metrics described for each aim. Actual data on these metrics were not provided in the application, although information on numbers of individuals reached was presented at the site visit. There is a need for a tracking system to capture these metrics and staffing to monitor progress.

Future plans for COE are likely to heighten COE's impact. These include an update of the Community Needs Assessment based on CAB recommendations, which will include the impact of COVID-19 on cancer care, enhanced depth of data, focus on changing cancer needs in rapidly growing ethnic minority populations and how to address these needs, prevention focus, increased statewide research, and improved access to clinical trials for rural underserved communities.

Leaders: COE at the HCCC is directed by Dr. Elizabeth Chrischilles, who is also AD for Population Science and an expert on patient-centered cancer outcomes research and comparative effectiveness research. In addition to providing operational oversight of COE, she works with Dr. Henry and the other ADs to ensure that catchment area needs are communicated with all HCCC research programs. She is assisted by co-investigators Dr. Mary Charlton, Dr. Natoshia Askelson, and Ms. Sittig who oversee Aims 1, 2, and 3, respectively. Specific Aim 1 is led by Dr. Mary Charlton who leverages the Iowa Cancer Registry and her epidemiologic expertise to design and share assessments of the catchment area. Dr. Natoshia Askelson leads Aim 2 activities. With her expertise in community-engaged research, evidence-based interventions, and implementation science research, she oversees the seed grant program and implementation science training for rural teams. Ms. Sittig is a certified communicator in public health. She oversees outreach and community partnerships in Aim 3. COE is also supported by a community health educator, two outreach specialists, and an administrative coordinator.

Assessment: Excellent merit

Budget: The budget is appropriate as requested.

CLINICAL PROTOCOL & DATA MANAGEMENT, DSM, and INCLUSION

DESCRIPTION (provided by applicant): The Clinical Protocol and Data Management (CPDM) efforts of the Holden Comprehensive Cancer Center (HCCC) are managed through two related components –

Clinical Research Services (CRS) and Data and Safety Monitoring (DSM). These components have grown and strengthened significantly over the prior funding period. They are critical to the mission of the HCCC and support HCCC clinical cancer research including treatment, non-treatment interventional and non-interventional studies. They encompass clinical research, regulatory, and data and safety monitoring. This includes investigator-initiated trials (IITs), National Clinical Trials Network (NCTN) trials, consortium trials, and industry sponsored trials. Services provided by the CRS related to protocol management include protocol selection, development, routing, modification and adverse event monitoring. The CRS also provides trial specific support through staff that assist in assignment of trials to teams, protocol listing and promotion, accrual tracking, assistance with screening and consenting subjects, data management, quality assurance, and education for early career clinical investigators. The CRS works closely with other shared research resources to support translational cancer research, particularly Biostatistics (Biostats) and the Biospecimens Procurement and Molecular Epidemiology Resource (BioMER). A new component of the CRS is the Radiology Core Lab (RCL) that provides quantitative imaging services for clinical trials. DSM is coordinated through HCCC's DSM Committee. The DSM has a distinct function from the Protocol Review and Monitoring Committee and IRB. DSM focuses on IITs and ensures the development of an acceptable data and safety monitoring plan, assesses subject safety, monitors clinical trial data veracity and protocol adherence, and provides education to investigators. CPDM also solicits feedback and responds to that feedback by providing innovative infrastructure that meets the needs of clinical investigators.

CRITIQUE: The Clinical Protocol and Data Management (CPDM) efforts of the HCCC are managed through two components: Clinical Research Services (CRS) and Data and Safety Monitoring (DSM). During the current project period, the lack of a centralized database noted in the prior review has been addressed by fully incorporating the OnCore clinical trials management system. Since the last CCSG review five years ago, HCCC leadership engaged with state-wide leaders to understand the needs of the community. The state of Iowa has two NCI Community Oncology Research Programs (NCORPs) and therefore it was deemed that patients have reasonable access to NCTN trials. HCCC leadership decided that their focus should be on strengthening their phase 1 clinical trials portfolio as well as investing in innovative studies involving new technologies such as CAR-T cells. They also elected to grow their clinical trials for less common malignancies. In 2019, roughly half of the clinical trial accrual at HCCC was supported by industry. Slightly over a third of the studies were IIT's and the remainder of the trial accrual was attributed to NCTN studies. Of note, there also has been a significant increase in observational studies largely as a result of a HCCC's engagement with ORIEN.

The Clinical Trials Support Office (CTSO) is housed in ~3,600 ft^2 of dedicated space on the first floor of the ambulatory cancer center facility adjacent to the outpatient clinic and one floor below the infusion center. Since the last renewal, an additional 3,800 ft^2 of CTSO space for personnel, who do not require direct patient contact (e.g., regulatory, finance, IT), was added at a second location within walking distance. An additional 30 FTEs were added to CRS during the current funding period, doubling the size of the unit. Thirty nine of these work in clinical research coordination while 16 are assigned to regulatory affairs and finance. Two specialists are assigned to the clinical trials management system, OnCore.

The CRS currently has three aims focused on protocol development and regulatory affairs, trials and data management, and quality improvement. Data and Safety Monitoring is a separate aim. The number of new interventional clinical trials opened to accrual has increased by ~25% during the current funding period of 2016-2019, with most of that increase in the 2019 calendar year. In 2019, there were 631 accruals to interventional trials, representing a 26% increase over 2016 (502). Of these, 147 (23%)

were to institutional trials, 98 (16%) to phase I trials, and 395 (63%) to treatment trials. The number of open interventional trials was fairly flat at around 170 until 2019, when it increased by ~20% to 2015. Trials where the HCCC holds the IND increased from 10 to 18 over the current funding period. HCCC participates in the ORIEN program and accrued over 3,000 patients to observational trials in 2019. While the growth in the clinical research activity during the current period is commendable, it seems that overall level of activity as measured by number of open trials and interventional and treatment trial accrual is low relative to the number of new analytic cases seen annually by HCCC (>5,000) and HCCC's role as the only NCI cancer center in Iowa.

A CRS Leadership Committee consisting of Drs. Furqan, Laux and Milhem and other ad hoc attendees meets weekly to oversee HCCC clinical research, with an expanded meeting that includes the HCCC Director and PRMC and DSMC chairs occurring every 6 months. Management of trials is organized by six trial support teams, including neuroendocrine, cellular immunotherapy, melanoma/sarcoma/head and neck cancer, NCTN, pediatrics, and phase I teams. The workload of clinical research coordinators is measured by scoring system that includes trial complexity and subject load.

A central feature of HCCC clinical research is the Multidisciplinary Oncology Groups (MOGs), working groups of basic, population and clinical investigators with interest in different anatomical tumor types. There are currently 12 disease-based MOGs─breast, GI, GU, GynOnc, head and neck, leukemia, lymphoma, myeloma, lung, brain, melanoma, and sarcoma, plus a separate Phase I group─all led by clinician investigators, most of whom are in the ET program. MOGs are responsible for review of clinical trial protocols and the development of IITs. About 35% of clinical protocols considered by the MOGs did not move forward during the last two years because of lack of interest or presence of competing trials. It is not clear how clinical research questions relevant to the catchment area are encouraged, developed, and fostered by the MOGs.

Once approved by a MOG, a protocol moves to the Trial Resource Evaluation Committee (TREC), which assesses whether the CRS and HCCC have the resources to support the trial. During the current funding period, about 8-12% of all protocols were returned to the MOG for revision (presumably relevant to IITs). There was little information in the CPDM section about time to trial activation. In the PRMS section, it was stated that the median number of days from PRMC submission to trial opening has varied from 108 to 122 over the past three years, but this does not include the part of the process involving MOGs and TREC. It would be valuable to know the average (mean) time to trial activation from initial MOG approval vote to trial activation, as the median time might be biased by rapid activation of some trials (e.g., NCTN trials).

Once activated, a trial is promoted internally through a mobile application and a desktop link to the HCCC clinical trials list, and through an e-newsletter in collaboration with the UI Clinical and Translational Science group. In terms of the assessment of accrual progress, there was little mention in the application of whether the current level of accruals is judged to be satisfactory or whether there is a specific plan to identify barriers to increasing accrual and provide remedies. At the site visit, it was clarified that >30% of the targeted accrual was considered acceptable. This same parameter was criticized at the time of the last review as being too lax. The management of an active trial following activation is typical, with involvement of research coordinators, development of Beacon order sets in Epic, and data collection and entry into OnCore. Cancer trials in Radiation Oncology and Radiology are managed by those departments and not by the CRS but are stated to go through the same approval process. Dashboards are provided to MOGs and CPDM leadership to track accrual progress.

New junior clinical investigators are provided formal mentoring by a senior primary clinician mentor and a three-member committee. The mentor assists the mentee with development of IITs and monitors the mentee's initial performance as a clinical investigator with respect to data collection (RECIST measurements, AE attribution, etc.).

Quality improvement efforts in the CRS takes place through several mechanisms, including a MOG Steering Committee that is really a CRS user's group, and through HCCC-wide planning and evaluation activities. There are mechanisms to provide feedback at individual and group levels as well as through center-wide planning and evaluation processes. There is also a strong commitment to developing new capabilities. This includes the development of theranostics as well as studies of the microbiome. There is also a plan to develop the capabilities to conduct multicenter IITs. There is little mention in the CPDM section of quality assurance activities with respect to the CRS IIT portfolio, whether there is a regular process for auditing these trials for compliance and data quality, functions not usually carried out by the PRMC or DSMB. However, in the Data and Safety Monitoring Plan, there is a description of an auditing program within the CRS with an emphasis on IITs and new PIs. It would be important to provide documentation of this quality assurance program including number of studies audited and outcomes.

Personnel: The CRS is co-led by Drs. Muhammad Furqan and Douglas Laux, reporting to the HCCC Associate Director of Clinical Research, Dr. Mohammed Milhem. Dr. Laux has served as Director of CRS at HCCC since 2017. He serves as Chair of the HCCC Trials Resource and Evaluation Committee (TREC) and physician leader of the HCCC Information Technology Committee. As CPDM co-leader, he focuses on organizational development and policymaking, operational management of Phase II and III clinical teams, and leads the training, education and mentorship of junior clinical research faculty. Dr. Furqan chairs the thoracic MOG and serves on the ALLIANCE-NCTN and Big Ten Cancer Research Consortium thoracic committees. As co-leader, he is responsible for the day-to-day activities of CRS with a particular focus on early phase clinical trials, including the HCCC Phase I program.

Assessment: Very Good to Excellent merit

Budget: The overall budget for CRS and DSM has grown from $3.3 million in 2015 to $5.8 million in 2019, with $2.8 million (48%) coming from institutional (UI Health Care) support. A total of $181,688 in annual direct costs is requested in year one. Of this, $171,688 is for salaries and benefits, including 1.2 calendar months (10%) effort for Drs. Laux, Furqan, and Berg, with the remainder supporting two clinical trial managers (45% effort), two clinical trial specialists (25% effort), one research support administrator (10% effort) and one financial analyst (5% effort). This modest budget is appropriate as requested.

Protections for Human Subjects

Data and Safety Monitoring (DSM)

CRITIQUE: The DSM functions of the HCCC are centralized in the Data and Safety Monitoring Committee (DSMC) and the Data and Safety Monitoring Plan (DSMP; version 5.5, dated December 2018). The DSMC is chaired by Dr. Berg, who has extensive experience in the conduct of early phase clinical trials and is very well qualified to serve in this role. DSMC consists of 10 members at the associate professor level or above, including two clinical pharmacists and two biostatisticians. The DSMP states that the DSMC will include a basic research member of the HCCC but this is not apparent

in the membership table on p. 723. The DSMC reviews only IITs, both for adequacy of the trial design for data and safety prior to PRMC approval, and subsequently during trial management according to the parameters of the DSMP. Since 2016, 26 interventional IITs have been opened to accrual following DSMC approval. The DSMC meets every 6 weeks (definition of a quorum is not presented). OnCore is currently used to enhance the efficiency of remote monitoring and auditing of trials.

Frequency of review is dictated by assignment of risk level (1-4), with the highest level (4) being studies supporting IND applications. Risk levels are defined in the DSMP and are assigned by the study PI in consultation with the DMSC during protocol development. (The DSMP lists “Physical, non-interventional studies” including those with music therapy, healing touch studies, gait assessments in Risk Level 1, but such studies are in fact interventional). Risk Level 2 includes interventional trials with risk of death (100-day treatment-related mortality) <1%. Level 1 and 2 studies are reviewed by the DSMC annually. Risk Level 3 includes interventional treatment and non-treatment IITs with risk of death or grade 4/5 serious adverse event (SAE) 1-5%, which would likely include the majority of phase II/III IITs; these are monitored at least annually or more frequently “depending on the protocol, risks to subjects, reported AE/SAE, patient population and accrual rate.” Level 4 are studies with risk of death >5%, including all investigator-initiated INDs and “most” phase I trials, including any with first-in-human drug or agent use. These studies are reviewed at a minimum twice yearly, subject to the previous qualifications. The PI is ultimately responsible for attribution of AEs, and it was clarified at the site visit that these attributions are reviewed for consistency by the DSMC. Dr. Vaena, a visiting professor and medical oncologist (former HCCC faculty member), is responsible for overseeing the Quality Assurance (QA) audit programs, which is well described.

In the application, it was stated that the DSMC, following its regular review of monitoring reports, AEs/SAEs, and accruals, makes “recommendations to the PRMC when suspending or terminating a study as (sic) deemed appropriate”. The DSMC should have full authority to halt or close a trial for data and safety reasons without requiring PRMC action, while accruals (scientific progress) is the purview of the PRMC and not the DSMC. At the site visit, it was clarified by the HCCC Director that the DSMC has full authority to suspend or close a trial, independent of the PRMC.

Assessment: Acceptable

Budget: Support is requested for 1.2 calendar months (10%) effort for Dr. Daniel Berg, the chair of the DSMC. This is appropriate and recommended as requested.

Inclusion of Women in Clinical Research: The state of Iowa has a population that is 50.2% women and the percentage of women seen at the HCCC for evaluation and/or treatment is 49.9%. Despite these statistics, the percentage of women in interventional treatment, interventional, and non-interventional trials is 40.5%, 45% and 44.5%, respectively. It is of concern that these percentages have been consistently below 50% with the exception of 2017. These declines are attributed to the closure of high-accruing breast and gyn-onc trials with concordant increased enrollment in prostate cancer trials, and analyses/monitoring and strategies are provided to address this problem.

Assessment: Acceptable

Inclusion of Minorities in Clinical Research: Racial and ethnic minorities are relatively scarce in Iowa, and it is noted that trial enrollment reflects the minority make-up of cancer diagnosis in the state. However, African American Iowans have higher mortality rates for several cancers, and immigrants experience more barriers to care including reduced access. Enrollment of African American and Latinx subjects is below the census and the HCCC patients. The same is true for the Asian population, though the numbers more closely reflect the percentage of HCCC patients. Plans are in the works to address the issues of minority inequities in cancer incidence and mortality, as well as projected increases in Latinx residents. In addition, LGBTQ disparities are reported using a statewide health assessment that shows high levels of depression, anxiety, binge drinking, and perceptions that healthcare providers have limited knowledge of LGBTQ health issues. It is hoped that an on-campus LGBTQ Clinic will be instrumental in addressing these concerns.

There is not enough information to determine the degree to which minority disparities are addressed. It is noted that the COE and CPDM work together to ease access to trials for rural Iowans, through providing information and supportive services that provide housing (Hope Lodge) and a transportation program.

Assessment: Acceptable

Inclusion of Individuals Across the Lifespan in Clinical Research: The HCCC conducts pediatric clinical research and has accrued an average of 19 subjects under the age of 18 and 78 adolescent young adult (AYA) subjects annually to interventional trials. There has been a marked decline in accrual of those under age 18 to interventional trials from 29 in 2016 to 15 in 2019 (24 in 2016 to 15 in 2019 for interventional treatment trials), but an increase in non-interventional trials from 124 in 2016 to 148 in 2019. For the AYA population, accruals have remained fairly steady for interventional accruals (82 in 2016 to 99 in 2019), declined for interventional treatment trials (67 in 2016 to 48 in 2019), and saw a dramatic decrease in non-interventional trials (390 in 2016 to 38 in 2019). The declines are attributed in part to decreased COG clinical trial availability, especially for leukemia and CNS tumor patients. HCCC is stated to be in the top half of COG main member institutions for this category. However, according to Withycombe et al. (J. Pediatr. Oncol. Nurs. 2019;36:24), only 9% of COG member institutions had a 3-year rolling average of accruals <20/year, although it is unclear whether this includes non-interventional trials. Regardless, it is clear that this accrual activity is less than optimal and the HCCC has instituted several changes to address this area, including discussion of pediatric oncology in HCCC leadership meetings, recruitment of additional leaders in pediatric oncology, increased funding through philanthropy, strengthened AYA oncology efforts, and a strengthened pediatric adult CAR-T program through combined efforts of the HCCC and Pediatric Hematology and Oncology.

In contrast, accruals of adults 65 years and older have grown in all areas of research, from 142 in 2016 to 234 in 2019 for interventional accruals; from 96 in 2016 to 176 in 2019 for interventional treatment accruals, and from 792 in 2016 to 1758 in 2019 for non-interventional trials. There is no statement about whether age limits are not recommended for investigator-initiated trials unless specific reasons are provided. However, for 5 out of 7 IITs reviewed for the PRMC, the age eligibility was ≥ 18 years; one protocol specified age < 90, while another did not specify age limits.

Assessment: Acceptable

PROTOCOL REVIEW AND MONITORING SYSTEM

DESCRIPTION (provided by applicant): The goal of the Protocol Review and Monitoring System (PRMS) at the Holden Comprehensive Cancer Center (HCCC) is to ensure the highest scientific quality of clinical oncology research is conducted at the HCCC. A two-step review process is used. Trial concepts are first reviewed by the disease-specific Multidisciplinary Oncology Groups (MOGs) to determine enthusiasm for the proposed science, potential impact of the results and whether the resources and patient population are adequate to complete the proposed studies. The Trial Resource Evaluation Committee (TREC) provides input into whether the institutional resources are available to support the trial. Once a protocol is approved by the MOG and has TREC endorsement, it is fully developed and reviewed by the Protocol Review and Monitoring Committee (PRMC). The PRMC approves, rejects or defers the protocol for further development. Studies which have already undergone rigorous peer review including NCI-approved NCTN studies and studies approved by other NCI-designated cancer centers with an acceptable PRMS, are reviewed administratively by the PRMC Chair. PRMC approval is required before IRB review. The PRMC also monitors accrual to ongoing clinical trials. The PRMC closes protocols that do not demonstrate scientific progress or that are no longer addressing a scientifically valid question.

CRITIQUE: The HCCC PRMS has four aims: to carry out the requisite two-step assessment of scientific quality of proposed clinical studies (Aims 1 and 2), to monitor scientific progress and accruals (Aim 3), and to continuously improve the protocol review and monitoring system at HCCC (Aim 4).

The Protocol Review and Monitoring Committee (PRMC) is chaired by Dr. Michael Goodheart, an associate professor in Ob/Gyn and gynecologic oncology who is responsible for the supervision and coordination of all aspects of the PRMC's mission. He specifically oversees the following:

1) Conduct structure and process analyses of the committee to improve overall functionality and efficiency
2) Supervise work done relevant to the PRMC by the Protocol Manager
3) Conduct an administrative review of all cooperative group protocols, and other CTEP-approved protocols, submitted to the committee
4) Facilitate a fair, appropriate and comprehensive discussion of each protocol in committee
5) Contact investigators of studies that are not accruing appropriately, and close studies that are not going to meet their scientific goals because of poor accrual
6) Collaborate with the DSMC Chair on studies that need to be closed for safety reasons and execute closure proceedings
7) Receive and review all DSMC reports on currently active HCCC clinical trials

Dr. Goodheart dedicates 10% effort to the PRMC and has served in this role since 2013. The rest of the PRMC includes co-chair Dr. Michael Knudson (Pathology) and 40 additional members, with representation from breast oncology (2), neuro-oncology (2), heme malignancies (2), GU oncology, GI oncology (2), melanoma (2), gynecologic oncology, radiation oncology (2), surgical oncology (2), thoracic oncology, immuno-oncology, oncology pharmacy (9), biostatistics (2), and patient advocates (3). Two members (Zamba and Smith, biostatistics) also serve on the DMSC; however, it is not clear if there is a plan for managing potential conflicts of interest in these dual roles. The PRMC meets twice a month. A meeting quorum of four voting members must be present for a protocol to be reviewed. This quorum, a very low expectation for such a large committee, is of persisting concern of potentially jeopardizing the discussion process through a lack of broad representation of PRMC members. Indeed, it is difficult to see how a quorum of the PRMC chair, two protocol reviewers, and a biostatistician for

example could be sufficient to allow a reasoned assessment to be conducted. Further, the voting rules are not described. Is a simple majority sufficient to approve a protocol? How would a tie be adjudicated?

In the two-step review process, the initial step is taken by the MOGs with consideration of accrual projections and feasibility and competing studies. Approved studies are then forwarded to the TREC for resource assessment and, if approved, then go to the PRMC for the second step. The PRMC meets twice monthly. The IRB will not schedule a full committee review until PRMC approval is obtained, possibly creating delays in trial activation. NCTN and CTEP-approved protocols and those approved by the PRMC of another NCI CC are subject to rapid administrative review. For other protocols, the "oncologic science" is evaluated by a primary and secondary reviewer from PRMC membership. For some cancers, depending on particular attendance, it might be difficult to identify two PRMC member with such expertise, although assignment of ad hoc reviewers is permitted. "Pharmacy and therapeutic science" is reviewed by PRMC members with pharmacy and therapeutics expertise, which may be clinical pharmacists. Statistical aspects are reviewed by a biostatistician member of the PRMC. Potential patient concerns are vetted by the patient advocates. It is noted that industry trials were nearly half of the PRMC workload during the current funding period, but these trials, which are usually multi-institutional and extensively vetted, can almost never be modified and hence the decision to activate such a trial at the HCCC should perhaps depend just on scientific interest and ability to accrue. The median number of days from PRMC submission to trial opening has varied from 108 to 122 over the past three years.

Protocols are discussed and scored by the PRMC, with a range of action decisions—full approval, approved pending response to comments or for minor or major modifications, and disapproval. The PRMC reviewed a total of 97 protocols in 2019 (table on p. 738); in that year, 140 protocols were approved by the MOGs and only three did not move forward (table on p. 721), suggesting 137 protocols should have been forwarded to the PRMC. In the table on p. 766, between 2016 and 2019, the PRMC reviewed 298 trials, of which 293 were ultimately approved either outright or after provision of comments or modifications. A total of 26 protocols did not move forward to activation but 24 of these were abandoned after approval. This does not include trials that were halted at the first (MOG) step (for example, 45 protocols returned to MOGs by the TREC) but an overall accounting of the workflow through steps 1 and 2 is lacking in the application.

Scientific progress and accruals are based on the projected accrual provided by the PI and vetted by the MOGs. Accrual on all trials is assessed initially at the 6-month time point following trial activation. Guidelines are not provided as to what constitutes adequate accrual. At the site visit, it was clarified that >30% of the targeted accrual was still considered acceptable. Trials judged not to have made adequate progress trigger a letter from the PRMC to the PI requesting an explanation and corrective action plan. Special consideration is given to "rare cancers" including uncommon subtypes of common cancers but which cancers qualify for this exemption (NCI, ESMO, EORTC rare cancer lists?) and what defines rare (incidence of <5-6 cases/100,000 population?) was not detailed. There may be HCCC-based exceptions granted for phase I studies, high priority NCTN or IIT studies, or recent protocol revisions. If a trial does not exhibit adequate accrual following PI notification and response, it can be closed by a 2/3 vote of the PRMC. A second reason for closure would be if a study has become outdated or obsolete. It is not clear how the portfolio of trials is monitored by the PRMC for obsolescence, as this function would probably best be done by the MOGs. It is also not clear how the potential for accruing minority and underrepresented patients from the catchment area is considered during both initial scientific review and continued monitoring of open protocols.

Seven institutional protocols were reviewed for compliance with PRMS policies and procedures. The PRMC documentation was bookmarked but was not provided in temporal order, making it difficult to navigate the documents. There was evidence of adequate monitoring of accrual progress. Biostatistics review was judged to be adequate as well. In one protocol (Monga, NCT02959164) the response of the PI to the initial PRMC query was not found.

The PRMS and corresponding committee of the HCCC is well structured and functions appropriately together with the MOGs to assess scientific quality of proposed clinical trial protocols, and to monitor accrual progress and trial scientific relevance. Some areas for improvement include increasing the size of a PRMC quorum, and tightening criteria for judging accrual progress.

Assessment: Satisfactory

Budget: Funds are requested for 1.2 calendar months (10%) effort for Dr. Michael Goodheart (PRMC chair), and for 4.8 calendar months (40%) effort for two clinical trials managers. This is deemed appropriate as requested.

DEVELOPMENTAL FUNDS

DESCRIPTION (provided by applicant): The Holden Comprehensive Cancer Center (HCCC) uses developmental funds to advance the research mission of the HCCC based on the HCCC strategic plan and to address the needs of the HCCC catchment area. This includes supporting promising research through seed grants, new faculty recruitments in areas of high priority for HCCC research and support for a staff investigator. Developmental fund support for the P30 is combined with institutional and philanthropic resources to achieve these goals.

Two classes of seed grants are awarded to support new cancer research ideas. These grants are named in memory of prior HCCC investigators. Oberley Award recipients are selected by program leaders based on the most promising, high risk research taking place within their programs. In some cases, program leaders have chosen to work across programs to select Oberley Awards to support interprogrammatic collaborations that address issues of high priority for the catchment area. Mezhir Awards are provided to support transdisciplinary team science with a focus on new teams that have promise for larger P-award level funding.

Developmental funds are used to support recruitment of both senior and junior faculty. These recruitments focus on areas where there is a particular need as outlined in the HCCC strategic plan, including for scientific leadership within the HCCC.

Finally, developmental funds are used to support staff investigators who fill a unique role in the cancer center. In the upcoming funding period, such funding is requested for Maria Spies, PhD who leads the HCCC DNA repair group.

CRITIQUE: Developmental funds have been used to advance the research mission of the center, with use of funds to support new faculty recruitment, support staff investigators, and encourage new research that is innovative, cross-disciplinary and focused on the needs of the catchment area.

Developmental funds are used for recruitment of both senior and junior faculty and have been appropriately prioritized to attract individuals with expertise in areas lacking within the HCCC strategic plans and scientific leadership. The institution also supplements the recruitment.

Seed funding is directed to mechanisms to encourage collaboration and develop program project team science. Seed grants are named in memory of prior HCCC investigators. Oberley Awards are used to support new high-risk/high payoff research concepts, and sometimes have been given to support inter-programmatic efforts. Mezhir Awards support transdisciplinary team science prioritized on new teams that have potential for achieving program project grants. An amount of $150,000 is used to support the Oberley ($100,000/year) and Mezhir ($50,000/year instituted in 2019) awards, which are matched by institutional funds.

Return on investment (calculated at more than 13-fold) is evident in the current funding period with funds appropriately distributed across basic, clinical and population studies. Priority for research area to support going forward are appropriate, particularly around new faculty recruitment targeting obesity and cancer, early phase clinical trials with a focus on breast cancer, translational immunology, and a translational investigator in redox metabolism. Strategic use of Developmental Funds will continue to build on strengths of the institution and aid with major strategic directions in the center.

Assessment: Outstanding to Excellent merit

Staff Investigators:

CRITIQUE: Questions were raised about the use of developmental funds to support Dr. Maria Spies as a staff investigator as part of an effort to build more strength around DNA repair basic science area, and facilitate translation of those basic findings into the clinic though interactions with the HTS core. Dr. Spies is a well-funded senior investigator who helps anchor a strong basic science program in DNA repair, with funding as a staff scientist proposed for her to expand capabilities of the HTS core. This use of developmental funds was unusual given the existing strength in DNA repair, and whether Dr. Spies' activities to enhance HTS activities would benefit from support over the entire coming cycle. While use of funds for this position was deemed acceptable, there was dissention on whether this was an appropriate use of developmental resources.

Assessment: Acceptable

Budget: The budget is appropriate as requested.

LEADERSHIP, PLANNING AND EVALUATION

DESCRIPTION (provided by applicant): Holden Comprehensive Cancer Center (HCCC) Director, George Weiner, MD is responsible for overseeing all aspects of the HCCC including appointment of other senior leaders, setting the overarching vision for the cancer center and implementing that vision. He is assisted by Michael Henry, PhD who serves as Deputy Director and five Associate Directors (ADs). Gail Bishop, PhD is AD for Basic Research and also oversees the basic research cores. Mohammed Milhem, MBBS is AD for Clinical Research. Elizabeth Chrischilles, PhD is AD for Population Science and Community Engagement. Jon Houtman, PhD is AD for Career Enhancement. Tina Devery is AD for Administration. Invaluable advice is provided to the HCCC leadership team

during annual meetings of the HCCC External Advisory Board that has been expanded since the last review. Community perspective is provided by quarterly meetings with the Community Advisory Board. Dr. Weiner chairs the University of Iowa (UI) Health Care Cancer Strategic Investment Committee that serves a role similar to an internal advisory board and provides input on use of recently designated institutional resources targeted towards support of new strategic cancer research initiatives. Planning and Evaluation efforts of the HCCC over the prior funding period include development of a comprehensive strategic plan that is reviewed on an annual basis to identify top priorities which then serve as the foundation for strengthening current, and advancing new, initiatives. Over the prior funding period, the HCCC used P30 funds, institutional resources, philanthropy and cancer strategic investment funding to pursue the goals outlined in its strategic plan. The HCCC is continuing to implement these concepts while engaging in ongoing planning and evaluation efforts with its members to identify and pursue future opportunities with a particular focus on the needs of the people of Iowa.

CRITIQUE: As the HCCC Director, Dr. George Weiner provides the overall vision for the HCCC, with oversight and accountability for all HCCC activities including HCCC membership, program structure, shared resources, and institutional and private funds designated for the HCCC. He also serves as the Director of the cancer service line for UI Health Care. He is responsible for short- and long-term strategic planning activities of the HCCC and for the cancer programs of UI as a whole. As the longstanding director of the HCCC since 1998, he brings an important set of skills to this position as a leader in the field of cancer immunotherapy and seasoned leader.

The goals for leadership, planning, and evaluation are 1) to identify and empower the HCCC leadership team, 2) to obtain advice from the HCCC's internal and external constituencies, 3) to develop a comprehensive strategic plan, and 4) to implement the strategic plan of the HCCC. To achieve these goals, Dr. Weiner leads a team of highly engaged senior leaders. They include Dr. Michael Henry, the Deputy Director for Research Programs. Meeting weekly with Dr. Weiner, Dr. Henry has broad responsibilities including oversight of new research initiatives, faculty recruitment, and mentorship. His pharmaceutical industry background provides particular strength to the HCCC's efforts in anti-cancer drug discovery and development. Dr. Gail Bishop serves as AD for Basic Research. A highly respected immunologist appointed to this role in 2004, she advises the Director and Deputy Director on basic science recruitments, oversees the seven cores used by basic scientists, and ensures that early stage basic cancer researchers have appropriate mentorship. Appointed in 2018, the AD for Clinical Research, Dr. Mohammed Milhem previously served as the co-leader of the Experimental Therapeutics Program at the HCCC. He played a central role in the development of investigator-initiated trials of novel therapeutics with a focus on melanoma and sarcoma. Dr. Elizabeth Chrischilles is AD of Population Science and AD for Community Outreach and Engagement. She is also head of the Department of Epidemiology in the College of Public Health specializing in cancer health outcomes and comparative effectiveness research. Appointed in 2004, the AD for Administration, Ms. Tina Devery, provides administrative leadership, facilitating interactions with the NCI and the IU, and managing all HCCC fiscal activities. Lastly, the AD for Career Enhancement, Dr. Jon Houtman, is responsible for developing educational opportunities at all levels including secondary students, undergraduates, graduate and medical students, postdoctoral fellows, medical residents, and junior faculty.

This highly qualified leadership team works together to achieve HCCC's strategic priorities. They meet biweekly for the HCCC Leadership Council and monthly for the Research Executive Committee which also includes HCCC's program leaders. Community perspective is provided by quarterly meetings with the Community Advisory Board and the Cancer Strategic Investment Committee meets quarterly to

identify and recommend best uses of cancer strategic investment resources. The nine members of the External Advisory Board meet annually, providing important input on HCCC's strategic direction.

Dr. Bishop advises the Director and Deputy Director on faculty recruitment and new program activities and supports basic cancer research in general; however, it is notable that specific research initiatives and accomplishments arising from this role are not well described in the application. In addition, while the process on decision-making regarding the cancer relevance of certain grants and publications listed in the application and SOPs for cancer relatedness provided and discussed at the site visit appear appropriate, there remains a lack of clarity regarding the involvement of program leaders in this process. Further, questions were raised at the site visit about the assignment of a 100% cancer relatedness level for certain grants in the CEPS program.

Over the current funding period, HCCC developed a comprehensive strategic plan with broad engagement of the membership and key stakeholders. Examples of key priorities include 1) to develop a metric-driven and predictable financial incentive for clinical research, leading to an agreement with the Department of Internal Medicine and UI Health Care to support the recruitment of 17 clinical cancer investigators, each with a package that includes a $1 million investment to support protected time and start-up support; 2) to strengthen mentorship and career enhancement for trainees and junior cancer center members, resulting in the hiring of Dr. Gregory Thomas as Assistant Director for Career Development and Mentorship activities; and 3) to create a new Human Immunology Core, to support theranostics research, and to enhance research on obesity and cancer, all resulting in allocation of resources.

These successes attest to a robust planning and evaluation process that gathers input from a broad range of internal and external constituencies to drive new initiatives and investments; however, opportunities to enhance these processes and outcomes remain. For example, concerns about the dual role of Dr. Chrischilles as AD for Population Science and AD for COE were reinforced by the COE discussion at the site visit. While she is an impressive scientist and leader, she did not appear to have a sufficiently deep knowledge of COE activities and outcomes when questioned. Further, the sharp focus of COE on population-based research and the lack of a well-articulated process for engaging basic researchers to foster catchment-relevant research suggests that HCCC may be better served by appointing an independent AD for COE. Other issues include the limited discussion of the planning process or evaluation metrics for decisions made regarding bioinformatics. The application overall and the strategic plan specifically was light on tangible metrics of success.

On the whole, this is a very strong and experienced leadership team with a history of working well together. The rigorous strategic planning process sought input from a wide range of stakeholders and there is evidence for key accomplishments aligned with the strategic plan. Opportunities include separation of the role of AD for Population Science from the AD for COE and tighter data-driven evaluation processes with tangible metrics of success.

Assessment: Outstanding merit

Budget: The budget is appropriate as requested.

ADMINISTRATION

DESCRIPTION (provided by applicant): The Holden Comprehensive Cancer Center (HCCC) functions administratively as a matrix cancer center, with administrative staff providing support to 170 HCCC members who have over $23.4 million in direct annual cancer-related, peer-reviewed, external research support, including $11.0 million from the NCI. The administrative office of HCCC excels in providing strategic and operational support across the full complement of services that advance the clinical, research and education missions of HCCC. The outstanding growth and development that has occurred during this past funding cycle is a direct reflection of the advanced capabilities of the administrative team to strategically plan, advocate for, grow and refine operations to meet current and future demands.

CRITIQUE: The Holden Comprehensive Cancer Center (HCCC) Administration seeks to provide 1) administrative leadership for planning and evaluation; 2) operational infrastructure for finance, human resources, space, grants administration, and shared resources; 3) facilitated transdisciplinary interactions and community engagement; and 4) enhanced internal and external communications.

Administrative staff are well qualified for their roles, as exemplified by their individual experience (e.g., Associate Director [25 years], Senior Accountant [24 years], Administrative Coordinator [31 years]) and the team collaboration reflected in this HCCC progress report. Oversight was readily apparent in the application, for which the Research Administrator had the lead role, as well as in supplemental applications and annual progress reports.

Accuracy and completeness in the current application conveyed improvements made on data-reporting during the current project period. While relying on institutional tools for financial and member activity reporting, center-initiated tools include tracking of publication use of shared resources in Redcap and special attention to improved determination of cancer relevance and monthly grant funding updates. The pending transition from reliance on the UC Davis-developed Café tracking system has led to center's dependence on institutional information systems which, while permitting customized reporting of inter-departmental faculty and CCSG-specified reporting period, needs to be assessed by the HCCC Administration to reconfirm that center-specific data fields are captured with ability to fulfill HCCC reporting that requires linking information that may arise from different institutional systems.

While reliant on institutional assessment of space assignments, the Associate Director participates in that process, and the HCCC administration assigns and tracks space under the control of the HCCC Director. Given the HCCC programmatic need to place new and current collaborating members in clusters that promote desired scientific interactions, it would be important to have scientific as well as administrative HCCC participation in those institutional assessments.

HCCC Administration has led responsibility for the new BioMER, Biostats, and PopRC, with the other SRs under the purview of the College of Medicine Vice President for Research (or the Department of Radiation Oncology for the Radiation Free Radical Research Core). The Administration provides a lead role in reviewing the usage by HCCC members, participation in advisory committees, and annual review by the HCCC Research Executive Committee.

Finances managed by the HCCC totals $18.3 million annually, spanning the CCSG award, eight CCSG supplements, three R50 Research Specialist awards, philanthropic funds, UI Health Care discretionary funds, and Strategic Investment funds. Beyond preparation of budgets and tracking of these

expenditures, the Administration provides input into departmental management of member start-up funds and institutional management of shared resource support.

Administrative contribution to promotion and tenure was highlighted in new career enhancement infrastructure, as exemplified by the PhD-granting Cancer Biology Graduate Program. Input is provided into department-led faculty recruitment and retention, with HCCC Administration-led initiatives in administration of trainee Wenger travel awards and tracking of trainee investments and progress in general.

Arrangement and documentation of meetings was evident in standing Leadership committees, bi-weekly HCCC Grand Rounds, the annual HCCC and inter-programmatic retreats, and center-wide symposia. HCCC Administration provides administrative support to the Deputy Director for pilot project processes, including review of institutional sole application responses, management of pilot award accounts, and calculation of outcomes and return on investment. New pilot calls were issued for High Throughput Screening and Near Miss seed grants.

HCCC Administration administers on-line member applications at three levels (full, associate, affiliate), through Membership Committee recommendations to the Director and annual review of current members.

In addition to representation of HCCC by the Associate Director on major institution decision-making forums, the HCCC Administration has oversight of the Iowa Cancer Consortium and close interface with institutional offices of sponsored research, grant accounting, and the UI Research Information system.

Ongoing support for planning and evaluation is apparent in the convening of over 100 HCCC leadership meetings annually and annual visits by the External Advisory Board. Past contributions to growth of the Phase I clinical research program and accrual to clinical trials is cited, and future planned contributions include new seed grant programs and fostering community outreach exchanges. A proactive role in providing ongoing Administration infrastructure support to new programmatic center initiatives, such as obesity/cancer, would benefit further the strategic advance of center plans. While follow-up on the strategic plan is a recurring item on Center Leadership meeting agendas, evidence of leadership evaluation of recent initiatives, in general, was not readily apparent, and the Administration could advance this effort through a clearer definition of the metrics to be collected to inform those considerations. Communication has been fostered by a biweekly internal newsletter and relaunch of a new website. Examples of facilitating multi-center collaborations include participation in Big Ten Cancer Research Consortium Clinical/Translational Research teams and HCCC participation in the ORIEN multi-center network.

Personnel: The Administrative team has clearly defined lead roles. The Associate Director for Administration, Ms. Tina Devery, throughout the current five-year reporting period has had the lead responsibility for cross-departmental initiatives, large budgets, and strategic planning, resolving prior concerns for leadership stability in the Administration. The Senior Accountant, Ms. Debra Wrede, has lead responsibility for monitoring HCCC expenditures and preparing financial information. The Administrative Coordinator, Ms. Tami Thompson, is key to supporting the Director and Deputy Director leadership roles, as well as coordinating the membership process. The Research Administrator, Ms. Ann Sieren, leads CCSG and its supplement submissions while coordinating the cancer relevance assessment of the broader portfolio and the deliberations of the Research Review Committee. Ms.

Kelly Wells Sittig is Executive Director of the Iowa Cancer Consortium, a highly effective state-wide cancer control partnership.

Assessment: Outstanding merit

Budget: The total CCSG Administration budget represents an appropriate portion of the total HCCC Administration Budget (21%) and the total CCSG award (12%). The five positions requesting CCSG support address CCSG-related responsibilities at appropriate levels of effort (i.e., 1.90 total FTE). The budget is appropriate as requested.

ESSENTIAL CHARACTERISTICS

Physical Space is rated excellent to outstanding.
The HCCC has a distinct physical identity on the UI Iowa City campus in the space assigned by the Dean of the School of Medicine and institutionally reassessed annually. Space components span research (including clinical research), clinical care, shared resources, administration, and statewide registry and cancer consortium initiatives.

The adequacy of HCCC physical space is exemplified by a more than doubling of reported HCCC member-occupied research space since 2015 (132,086 ft^2 from 52,788 ft^2). However, the proportion of research space under the director's authority (32,000 ft^2 in the Holden Cancer Research Laboratories) is relatively small compared to campus-wide space currently used by HCCC members. Significant HCCC clinic space in the Pomerantz Family Pavilion (64,000 ft^2) remains at the level reported in 2015. HCCC Administration (3,000 ft^2) in the John Pappajohn Pavilion (JPP) appropriately is sited between HCCC clinical and research facilities. A new 25-bed unit opened in 2018 for adult and pediatric stem cell transplant and cellular therapy. Special facilities on which the Center capitalizes include Iowa's only certified CAR-T Cell Therapy center and an ACS Hope Lodge.

Physical facility plans have aligned with emerging program initiatives. Clinical research space, although modest (7,400 ft^2), has doubled, with 3,800 ft^2 now available for clinical research support personnel. An opportunity exists to establish a dedicated research study infusion area. Ability to align/realign space assignments as the HCCC needs are identified is somewhat constrained by all space reassignments being subject to annual determinations by the UI Health Care Space Committee, with new assignments requiring the Dean's approval. As noted above, while the Director controls only Holden laboratory space, HCCC is represented in the institutional allocation considerations by its Associate Director for Administration, and outcomes to date have been favorable for Center plans. Importantly, no involuntary reassignments occur without HCCC approval. In the short term, it would be important to assure that HCCC scientific leadership has input into institutional decisions on programmatic priorities for space assignments to new faculty recruits and the inter-departmental clustering of current faculty. For the long term, it would be important that the role of the Cancer Center in these institutional considerations are codified so that the current collaboration is sustained beyond the inevitable future time of leadership transitions.

Member access to Shared Resources is facilitated by HCCC operation on a single (Iowa City) campus. Shared Resources and 90% of member laboratories are in a cluster of three adjacent buildings (Holden Cancer Research Laboratories, Bowen Science Building, and Medical Laboratories). Several major instrumentation cores (i.e., Radiation Free Radical, Flow Cytometry, Viral Vector, Genomics, and

Central Microscopy) are clustered within the Eckstein Medical Research Building. Clustering of population science-related space appears limited to the resources of the statewide Oncology Registry and Iowa Cancer Consortium (on the UI Oakdale Research Campus) rather than attained for members, who remain departmentally based.

Organizational Capabilities is rated outstanding to excellent.
The HCCC is a matrix center of the University of Iowa, spanning seven colleges and UI Health Multidisciplinary Oncology Groups. The Center has organized members around four inter-departmental research programs and supports nine shared resources to advance the strategic priorities outlined in the new HCCC Strategic Plan. The HCCC's oversight bodies continue to include the HCCC Leadership Committee which includes the Director, Deputy Director, ADs, the Director of Pediatric Hematology and Oncology, and the Chair of Obstetrics and Gynecology. This group meets twice a month to discuss key initiatives and challenges faced by HCCC. The HCCC Research Executive was expanded to include program leaders. Meeting monthly, this group identifies ways to foster collaboration, oversees the HCCC's research operations, and nominates areas for investment in new initiatives. Additional committees include the Community Advisory Board, Cancer Strategic Investment Committee, Shared Resource Advisory Committees and MOG Steering Committees.

In this grant period, the MOGs continue with greater clarity in responsibility for oversight. A strong example of the Center fostering scientific interactions to support translational research is the strategic organization of the BioMER SR, which includes a new global consent process. Enhancement in transdisciplinary collaboration is evidenced by two NCI SPORE and a new NCI P01 grants as well as high levels of intra- (23%) and inter- (21%) programmatic publications. Additional developments include the leveraging of the Graduate Program in Cancer Biology and securing of three NCI R50 Research Award-funded HCCC SR directors. Examples of community collaboration via the Iowa Cancer Consortium and inter-center collaboration through the Big Ten Cancer Research Consortium collaborations are also evident.

Lines of authority are clear, with the Director reporting to the VP of Medical Affairs/Dean of the Carver College of Medicine. The Deputy Director has significant authority, supervising the research programs, the Research Executive Committee, the Research Review Committee, and the Associate Directors for Population Science, Basic Research, and Clinical Research. Associate Directors have distinct individual responsibilities, with the exception of the Community Outreach and Engagement, a position that is held by the Associate Director for Population Sciences, Dr. Chrischilles. While Dr. Chrischilles is highly qualified, this decision seems to understate the importance of COE activities to engage members across the cancer center, including basic, translational, and clinical scientists. This was reflected in responses to questions at the site visit as well as COE performance related to basic investigators' engagement in research relevant to the catchment area. Where clear lines of authority are less apparent is in the oversight of newly launched or emerging center initiatives, such as obesity/cancer and theranostics clinical trials, where the investment to date is not accompanied by clear leadership oversight nor assignment of administrative infrastructure.

Noteworthy is the elimination of the Bioinformatics Core. These services have been decentralized and embedded in other shared resources to facilitate technology-specific expertise. While this is sensible, it is unclear to whom bioinformatics activities report and the processes to foster synergies to accelerate cancer research are not well described. While this was discussed at the site visit, there are lingering concerns regarding the lack of clarity in the process leading to this decision as well as the processes to evaluate the success of this reorganization. Limited attention to ongoing metric-driven evaluation

processes is also reflected in the performance of the Shared Resource Management and CPDM components.

Transdisciplinary Collaboration and Coordination is rated exceptional.
The HCCC is doing very well in promoting transdisciplinary collaboration and translation of basic science discovery into clinical trials. A number of mechanisms are in place to improve collaboration between basic, clinical, and population scientists, and efforts have been made over the current funding cycle to strengthen the multidisciplinary oncology groups and various research programs. Carver College of Medicine has transitioned from a traditional model of departmental owned space to a model in which space is assigned by a university committee based on current science, collaborative teams, and available space across the medical center. In the current project period, there were no involuntary reassignments of HCCC member research space.

The center has developed Multidisciplinary Oncology Groups (MOGs) based on cancer type that include various clinical modalities as well as basic and population scientists. Most MOGs have members in all four research programs and hold symposiums and retreats. A Cancer Center annual retreat, joint program retreats, weekly grand rounds, and inter-institutional conferences are also held to foster transdisciplinary research. Some MOGs have philanthropic resources and award pilot grants, and there are several multi-investigator grants across the center with clear efforts to promote collaborative transdisciplinary research. In the current funding cycle, Pipeline Acceleration for Cancer Therapeutics (PACT) grants were established to support preclinical studies of drugs needed for FDA IND applications. Nine PACT grants were awarded and resulted in four clinical trials and two clinically focused grants. PACT leaders also help to identify additional resources for preclinical studies. The success of these efforts is documented by multiple P01, SPORE and multi-PI R01s and 21% inter-programmatic publications. Overall, no major weaknesses were noted in this essential characteristic.

Cancer Focus is rated outstanding.
The HCCC maintains a clear cancer focus in its program emphases and initiatives. Over the current funding cycle, careful review of the membership, publication and funding policies and revision of program aims has served to tighten the focus on the most cancer-relevant research activities. HCCC members currently hold $22 million in peer-reviewed cancer-relevant funding, of which $11 million (~50%) is from the NCI, an increase of 18%. Transdisciplinary cancer activities across the center are solid (23% intra- and 21% inter-programmatic publications) and there is a solid portfolio of cancer-focused translational program grants, including two NCI SPORE and two NCI P01 grants. There has been a steady increase in accruals to cancer clinical trials across the spectrum of early phase, therapeutic and non-therapeutic interventional and observational. Notably, investigator-initiated treatment trials have doubled since 2015 and now make up 44% of therapeutic accruals. HCCC investigators have held 31 INDs for IITs over the last cycle. New cancer education programs have been developed, including a new PhD program in Cancer Biology, supported by a newly funded NCI T32 grant. Through leadership of the Iowa Cancer Consortium and partnership with several funded NCORP sites, the HCCC extends its reach throughout Iowa to serve as the nexus for cancer research and education. Overall, cancer focus is strong with some residual issues regarding the robustness of the processes used and the questionable cancer relevance of certain grants.

Institutional Commitment is rated outstanding to excellent.
In 2018, the HCCC led a strategic planning activity with HCCC membership and the EAB. Aligned with this plan, two new committees were formed, the Cancer Strategic Investment Committee (which serves as the HCCC IAB) and the Cancer Service Line Executive Committee, both chaired by the HCCC

Director. Along with full authority over philanthropic funds and oversight of a senior-level HCCC development officer, specific additional commitments included $3.2 million annual discretionary support for implementation of the HCCC strategic plan, $8.6 million for recruitment of clinical and translational investigators, and $1 million in Shared Resource support. Strategic institutional investments increased support for clinical research with >$1 million/year for a Phase I clinical trials group that formed in 2016. The director has authority over HCCC budgets, membership/personnel, cancer-related philanthropy, and HCCC programs. In 2019, $10 million ($2 million per year for five years) was committed from UI Health Care to cancer research initiatives through the Cancer Strategic Investment Committee, which identified in alignment with the 2018 strategic plan five funding priorities for year one of this investment (Human Immunology Core, Phase I trials, obesity and cancer research, theranostics, and near miss grant funding). Year two funding is paused pending evaluation of the impact of the COVID-19 pandemic on institutional resources. HCCC, UI and CCOM invested $0.5 million in Shared Resources over the past year to contribute to the purchase of a Cytec flow cytometer and a new irradiator. UI supports CPDM ($1.5 million/year), Chair for AD of Clinical Research ($70,000/year), support for clinical cancer research ($145,000/year), and PACT funding for early trials ($150,000/year). A policy exists for a change in HCCC Director with a recommendation from the HCCC Leadership Committee to the VP Medical Affairs/Dean CCOM for an interim Director, followed by a national search for a permanent Director.

It appears that the institution substantially met specific prior commitments, with $4.7 million annual discretionary support, $14.6 million invested by UI Health Care in the past five years in cancer-focused recruitments, $0.5 million for Shared Resources in the most recent year, and HCCC management of all unrestricted donor gifts and four development officers focused on patients and community leaders. Resource commitments for the next project period are significant, including $17 million for 17 clinical investigator recruitments, $4.1 million annually in discretionary funds from UI Health Care, and the potential for year two through five $2 million funds annually from the Strategic Investment Initiative.

The Director’s appointment as Chair of the UI Health Care Cancer Strategic Investment Committee and the Cancer Service Line Executive Committee is superior to that of an academic department chair. The Director holds positions on key institutional decision-making committees, such as the UI Health Care Enterprise Committee, the College of Medicine Medical Council, the Clinical Services Committee, the Basic Science Chairs Committee, and the UI Research Foundation Board of Directors. Although a matrix center for faculty appointments, the Director has clear authority over appointment and discontinuation of Center membership. The ability to influence joint appointments is evident in the span of recent joint recruitments across UI colleges and departments, totaling $14.6 million invested. The Director continues to have authority over 64,000 ft^2 dedicated to inpatient and outpatient facilities, including a modest amount (7,000 ft^2) of clinical research space, with a significant increase in clinical research support facilities. Authority over research space in the Holden Cancer Research Laboratories (32,000 ft^2) is small compared to the current campus-wide footprint of Cancer Center Members (132,000 ft^2). The Cancer Center has fared well through participation in the determination of recent institutional space commitments to new faculty recruitments and the clustering of interdepartmental teams, but the Center’s role should be codified so that it can be sustained beyond the working relationships of current leadership.

Impressive philanthropic support includes $38 million in cancer-relevant endowment and $70 million in bequests, deferred gifts, and commitments. Clinical revenues underwrite a $4.1 million discretionary funding commitment from UI Health Care. The paused commitment of $2 million of the institutional Strategic Investment Initiative to cancer appears relatively modest given the estimated representation

of cancer services (i.e., 10% Medical Oncology, 40% cancer-relevant service line) in the overall Medical Center revenue and margin streams.

A clear plan for changes in leadership, with interim leadership by a designated deputy director and a commitment to a subsequent national search, is explicit in the application.

Team science in promotion and tenure decisions is pursued through Letters of Support from the Cancer Center Director. Institutional expectations for clinician participation in clinical trials now are being advanced through sharing of clinical trial financial support with enrolling physicians. New clinician scientist researchers are receiving 30% five-year protected time to establish their clinical research revenue stream.

Center Director is rated exceptional.
Dr. George Weiner, MD, is the Founding Director of the IU HCCC. He is leading his fifth CCSG submission overall and fourth competing renewal. Dr. Weiner received an undergraduate degree from the Johns Hopkins University and an MD from the Ohio State University. He was fellowship trained in Hematology/Oncology and in laboratory tumor immunology at the University of Michigan. He joined UI in 1989 as an Assistant Professor of Internal Medicine, was promoted to Associate Professor with tenure in 1994, and to Professor in 2017.

The Cancer Center at UI was established as a matrix cancer center in 1980. Dr. Weiner became the Cancer Center Director in 1998. CCSG funding and NCI designation, including comprehensive status, was awarded in 2000 under his directorship. In 2001, the Center was renamed the Holden Comprehensive Cancer Center (HCCC) in recognition of major support provided by the Holden family of Williamsburg, Iowa.

Dr. Weiner is an accomplished, board-certified medical oncologist with research activities in cancer immunotherapy, particularly for lymphoma, using mAb and, more recently, nanoparticle approaches. He has been continuously funded by NCI since 1990, has a publication h-index of 61 with over 100 manuscripts, and holds eight patents.

Dr. Weiner has served in multiple key leadership positions for UI, where he led the cancer center to NCI comprehensive designation in 2000. He is PI and Director of the P50 Lymphoma SPORE since 2002 and was Director of the Heme/Onc Fellowship Program from 1996 to 1999, Cancer Center AD for Research Education from 1993 to 1997, and Center Deputy Director from 1997 to 1998.

Dr. Weiner has a strong leadership role for the state of Iowa as the inaugural Chair and President of the Iowa Cancer Consortium (ICC) from 2002 to present, leading the ICC to become a 501c3 organization, and in 2016 he received the State of Iowa Board of Regents Award for Faculty Excellence.

Nationally, Dr. Weiner was Chair of NCI subcommittee A from 2007 to 2009 and President of AACI from 2014 to 2016. He serves as Chair for the EAB of six cancer centers and is an EAB member at an additional four cancer centers, many of which are NCI designated as comprehensive. He also has extensive leadership in national advocacy/policy. He is Chair of Policy Committee for the Society for the Immunotherapy of Cancer, was Chair ASH Governmental Affairs Committee from 2008 to 2012, was Vice Chair AACR Science Policy and Governmental Affairs Committee from 2012 to 2015, and is a current member of the National Cancer Policy Forum. He has numerous peer-review contributions for NIH, NCI, NSF, LLS, and additional funding agencies.

Dr. Weiner commits 50% of his time to HCCC administration and 50% to research, teaching, and management of clinical cancer activities at UI Health Care. As HCCC Director, he leads all cancer-related efforts at UI and oversees all HCCC activities.

He leads the UI Health Care cancer service line. Dr. Weiner chairs the Cancer Strategic Investment Committee, reports to the VP Medical Affairs/Dean of CCOM, and serves on the Enterprise Committee, Medical Council for CCOM, UI Research Foundation Board, Clinical Services Committee, and Basic Science Chairs Committee. His institutional-level leadership provides a broad and deep role superior to that of a Department Chair.

Dr. Weiner has budgetary, recruitment and hiring authority over the HCCC, with faculty hiring done in collaboration with departments/divisions, where UI faculty hold their primary appointments in a matrix organization. However, CCOM space is no longer assigned to Departments or Centers and it is the UI Health Care Space Committee that assigns available space across the medical center. Space undergoes annual review in this new institutional structure. Dr. Weiner has direct authority over 32,000 ft^2 of HCCC research space.

A policy exists for a change in HCCC Director with a recommendation from the HCCC Leadership Committee to the VP Medical Affairs/Dean CCOM for an interim director, followed by a national search for a permanent director.

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 $1,603,949 (from Data Table 5); requested budget is $1,764,344 (from Data Table 5 and/or Face Page); and the recommended budget is $1,764,344. 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 $1,764,344. This recommendation does not reflect an evaluation of the institution's indirect cost rate.

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 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 $
Program Leadership (including other budget categories, where appropriate)	94,650	94,650
Cancer Research Career Enhancement and Related Activities	38,166	38,166
Leadership, Planning and Evaluation	279,444	279,444
Developmental Funds (including staff investigators, where appropriate)	267,931	267,931
Administration	210,652	210,652
Shared Resource Management	50,000	50,000
Biospecimen Procurement and Molecular Epidemiology Resource	54,789	54,789
Biostatistics Core	77,089	77,089
Central Microscopy Research Facility	46,453	46,453
Flow Cytometry Core	54,571	54,571
Genomics Shared Resource	40,309	40,309
High Throughput Screening Core	42,458	42,458
Population Research Core	51,219	51,219
Radiation and Free Radical Research Core	41,482	41,482
Viral Vector Core	35,435	35,435
Community Outreach and Engagement	135,825	135,825
Clinical Protocol & Data Management (CPDM) Data & Safety Monitoring	181,668	181,668
Protocol Review and Monitoring System	62,196	62,196

SUMMARY OF RECOMMENDED BUDGETS/SITE VISIT TEAM'S RECOMMENDATIONS

Budget Categories	YEAR 21 $	YEAR 22 $	YEAR 23 $	YEAR 24 $	YEAR 25 $
Salary, Wages and Fringe Benefits	1,241,288	1,241,288	1,241,288	1,241,288	1,241,288
Equipment					
Travel	29,408	29,408	29,408	29,408	29,408
Participant/Trainee Support Costs					
Other Direct Costs (excluding Consortium)	493,645	493,645	493,645	493,645	493,645
Consortium Costs					
Direct Costs	1,764,344	1,764,344	1,764,344	1,764,344	1,764,344
Indirect Costs	961,570	961,570	961,570	961,570	961,570
Total Costs	2,725,914	2,725,914	2,725,914	2,725,914	2,725,914

RECOMMENDED BUDGET/NCI SUBCOMMITTEE A *

Budget Categories	YEAR 21 $	YEAR 22 $	YEAR 23 $	YEAR 24 $	YEAR 25 $
Total Direct Costs	1,764,344	1,764,344	1,764,344	1,764,344	1,764,344
Total Costs	2,725,914	2,725,914	2,725,914	2,725,914	2,725,914

* 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 CA086862-21; PI Name: WEINER, GEORGE J.

NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.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. George Weiner (2 P30 CA086862-21)
NCI-A RTRB-G (E1) Work Group# 1
09/16/2020 - 09/18/2020

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

MEETING ROSTER

Subcommittee A - Cancer Centers
National Cancer Institute Initial Review Group
NATIONAL CANCER INSTITUTE
NCI-A
12/03/2020

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