On the Same Page

Continued Success in Clinical and Translational Research Programs: Part 2—Claude Pepper Older Americans Independence Center

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Given the effort involved in the preparation of NIH grants, and the small percentage that can now be funded, it is heartening to acknowledge the scientific excellence of our faculty as recognized by their peers in the NIH review process. In the last issue of *On the Same Page*, I described a new NIH Program Project in the area of reproductive physiology that received a highly fundable score. This week, we are pleased to report that the renewal application for our "Pepper Center" (The Claude Pepper Older Americans Independence Center; Marco Pahor, M.D., Principal Investigator) also received an extremely favorable score. The funding decision of the National Institute on Aging is currently pending. If it is fully funded, UF will receive $5.8 million over the next five years to continue the work of this Center.

There was a time when renewal of an NIH Center grant provided an "inside track," and was easier to obtain than a new grant. Currently, however, no matter how successful a Center might be during the period of initial funding, nothing can be assumed except that the process will be extremely competitive. We must work hard on every grant renewal to ensure an innovative and rigorous application in which every detail has been addressed in a comprehensive and scientifically robust manner.

Dr. Pahor understands this process as well as anyone; he and his team, including Dr. Andresen, Dr. Carter, Dr. Daniels, Dr. Leeuwenburgh, Dr. Marsiske and Dr. Nayfield, engaged in careful advance planning, and were successful in balancing creative new ideas with careful attention to the many nooks and crannies of such a grant application. Their efforts were rewarded: It would be hard to imagine a more admiring response from the NIH reviewers. Many strengths were listed by each reviewer, but under "weaknesses," almost all the reviewers wrote "none" or simply left the space blank. What a pleasure to read this summary statement!

The goal of the Pepper Center program nationally is to increase scientific knowledge that will maintain or restore independence to older persons. The National Institute on Aging at NIH supports Pepper Centers at 15 leading research institutions nationally to develop and enhance critical areas of aging research by providing resources to address key scientific problems, technological limitations and the need for trained researchers.

History of the UF Pepper Center

Dr. Pahor was recruited to UF in 2005, having been highly successful in directing a Pepper Center at Wake Forest University. His task at UF was to direct a redesigned Institute on Aging, and a new Department of Aging and Geriatric Research in the College of Medicine, toward the major goal of establishing a Pepper Center at UF. There were major strengths at UF in the area of aging, particularly in basic and behavioral sciences. These were not coordinated into a cohesive program, however. Moreover, the clinical research program had to be built virtually *de novo*.

Initially, it was thought that it would take two to four years to submit a competitive application. With the help of newly recruited investigators, however, along with strong institutional support and the enthusiastic participation of existing UF researchers across several colleges, including

Dr. Beyth , Dr. Carter, Dr. Daniels, Dr. Duncan, Dr. Leeuwenburgh, Dr. Marsiske, Dr. Perri, Dr. Scarpace and Dr. Shenkman, Dr. Pahor and his team worked on an accelerated timeline to build the necessary infrastructure. The Pepper Center application was submitted in October 2005, just nine months after the start-up of the new restructured UF Institute on Aging. It was funded on the very first submission, a highly unusual accomplishment at NIH.

Human aging is associated with progressive decline in skeletal muscle mass, a downward spiral that often leads to decreased strength and functionality. In 1989, Irwin Rosenberg proposed the term “sarcopenia”’ (Greek “sarx” or flesh + “penia” or loss) to describe this age-related decrease of muscle mass (Rosenberg I, Am J Clin Nut 1989;50:1231-3). Sarcopenia has since been defined as the loss of skeletal muscle mass and strength that occurs with advancing age.

The UF Pepper Center has focused on the theme: “Sarcopenia: prevention and rehabilitation of disability.” This central theme is pursued using an interdisciplinary approach that traverses the entire spectrum of biomedical investigation, including molecular biology, animal studies, clinical research, behavioral sciences and epidemiology. The specific research objectives of the UF Pepper Center are to:

(1) assess, using translational research, multiple domains, including biological, co-morbid, psychosocial and behavioral factors, that contribute to sarcopenia, physical function decline and progression to disability; and
(2) develop and reliably test, in clinical and pre-clinical studies that target sarcopenia, interventions that prevent, delay or recover age-related declines in physical function and their progression to disability.

To address these objectives, the UF Pepper Center includes the following integrated cores, which support investigators, junior scholars, research infrastructure and services:

- Research Career Development
- Pilot Studies
- Clinical and Translational Research
- Metabolism and Biomarkers
- Biostatistics and Data Management
- Recruitment, Adherence and Retention Core
- Leadership and Administrative Services

A major strength of the UF Pepper Center is the concerted action of the interdisciplinary cores, projects and investigators to address a common research theme that is explored through the entire spectrum of biomedical investigation.

Successful Progress

The first submission of the Pepper Center grant represented a promise of success. The outstanding review in the competitive renewal application testifies that the initial promise was achieved, and that the future will be filled with additional success.

During the initial funding period, the UF Pepper Center supported three research development projects and 19 pilot and exploratory studies. More important, Center investigators were extremely productive in leveraging the pilot studies to submit larger independent grants during the initial funding period (four years to date). As a result of pilot studies, research development projects and their core support, 32 grants have been funded, seven grants are pending and six grants are in preparation.

Counting other grants in which the UF Pepper Center plays a supportive role, a total of 80 active grants are connected to the Center, with total funding of more than $177 million. Of the 80 active grants, 21 were awarded in the past 12 months. Moreover, a total of 38 grants linked to the Pepper Center have already been completed, with total funding of about $42 million. The total impact of Pepper Center on UF aging-related grants over a period of three and a half years has been 118 grants and about $219 million in funding.

The scientific productivity of Center scholars has translated into a prodigious list of peer-reviewed papers. Since inception, faculty in the UF Pepper Center contributed 502 papers that have been published or are in press in peer-reviewed journals. A total of 186 of these papers were produced in 2010.

Since inception, the Research Career Development Core has supported 11 Junior Scholars who have demonstrated outstanding productivity, and provided mentorship to a pool of 41 affiliate scholars. These affiliate scholars serve as a pool for recruiting the most talented and promising future Pepper Center Junior Scholars.

LIFE Study

The most important study that has been associated with the Pepper Center is the "LIFE" study, or *Lifestyle Interventions and Independence for Elders*. We all know that physical activity is good for our health, but in older individuals definitive evidence is lacking that exercise can promote independence, prevent disability, and improve cardiovascular and cognitive functioning. To fill this important gap in our knowledge, which has significant implications for clinical practice and public health, the LIFE study was awarded to UF (with Dr. Pahor as P.I.) by the National Institute on Aging (NIA). At $64 million over six years, plus a $9 million supplement from the NHLBI, this study represents among the largest awards issued in the history of the NIA, and is the largest NIH grant ever received by UF.

The LIFE Study is a multicenter randomized controlled trial designed to compare a moderate-intensity physical activity program with a successful aging health education program in 1,600 sedentary older persons who are followed for an average of 2.7 years at eight sites nationally. The primary outcome is major mobility disability, defined as inability to walk 400 meters. Additional outcomes include cognitive function, serious fall injuries, disability in activities of daily living, sleep-wake disturbances, dyspnea, ventilatory capacity, cardiopulmonary events, cardiovascular events and cost-effectiveness. The UF site is contributing 200 participants from the University of Florida (Gainesville) and Brooks Rehabilitation Research Center (Jacksonville) and is second in recruitment among the eight sites. Currently, the LIFE study has recruited more than 1,100 participants and is ahead of the recruitment schedule with excellent adherence and retention, all quite unusual for a large multicenter study.

The LIFE study is the result of over 10 years of planning, pilot projects and preliminary data. It takes advantage of all Pepper Center cores, collaborates with the other four Pepper Centers and is well-integrated into the UF CTSI, which supports the bio-specimens repository.

Institute on Aging and CTRB Building

Another important outgrowth of the Pepper Center is a C06 construction grant for the Institute of Aging Building, which then led to the Clinical and Translational Research Building, for which there will be a ribbon-cutting ceremony on May 26, and about which there will be more to tell in a newsletter at that time. Suffice it to say that the Pepper Center was integral to UF's successful application to NIH for a $15 million construction grant for the 40,000-square-foot Institute on Aging Building, and was also an important element in our successful CTSA award, which

prompted the plan to add an 80,000-square-foot wing, thus creating a 120,000-square-foot Clinical and Translational Research Building.

Plans for the Future

The decline in mobility and sarcopenia are virtually universal characteristics of aging, regardless of species. Common fundamental biological mechanisms that likely contribute to the age-related locomotor function decline and sarcopenia include decreased apoptosis or "programmed cell death" in skeletal muscle due to deficits in energy production by the mitochondria in these cells. A future direction of the Pepper Center, led by Dr. Leeuwenburgh, Professor of Biology of Aging, will be to assess deficits in mitochondrial energy production and consequent skeletal muscle apoptosis due to a variety of factors such as inflammation and oxidative stress. Moreover, the impact of fat cells on inflammation, oxidative stress, apoptosis and energy deficits, and the consequential impact on sarcopenia and functional limitations, will also be explored. These mechanisms have not been previously investigated in a comprehensive multidisciplinary approach that integrates epidemiology, behavioral, clinical and basic research. By identifying biological processes that can be favorably influenced by lifestyle modification, it is hoped that some of the effects of aging on sarcopenia, locomotor and other functional impairments can be mitigated.

In summary, the UF Pepper Center's ongoing and planned clinical studies, along with the future translational research described above, hold promise for fostering enhanced independence and an improved quality of life as we grow older. This program will yield positive results for citizens of Gainesville, and of Florida in general, and can only enhance the luster of the University of Florida.

Forward Together,

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