The University of Kansas
Center of Biomedical Research Excellence
In Protein Structure and Function

Program Description (from the renewal application submitted July 2013)

Proteins comprise most of the functional and many of the structural components of living cells. Hence, they are vitally important to both human health and disease. For the past ten years COBRE-PSF has pursued basic health-related research in protein structure and function. While doing so we helped to recruit 25 new biomedical research faculty members to The University of Kansas and our three partner institutions (Kansas State University, Wichita State University and the KU School of Medicine). We also built three highly successful scientific Core Labs dedicated to a) protein production, b) protein X-ray crystallography, and c) biomolecular NMR spectroscopy.

As a result, COBRE-PSF has done much to strengthen both the human and the physical resources for biomedical research in the state of Kansas. This application requests five years of funding for Phase III of COBRE-PSF, during which time we will pursue the following aims: 1) we will continue growing a critical mass of new and continuing investigators focused on the very broad theme of protein structure and function; 2) we will continue a successful program of COBRE pilot project grants that utilize our Core Labs; 3) we will strengthen our existing Core Labs by expanding their capabilities and their user base and, by working with the KU Center for Research, position them for long-term sustainability based on a combination of fees generated plus a base of support from the University. The result of this will be a very strong cadre of successful mid-career biomedical research faculty and a self-sustaining group of Core Labs that support research in protein structure and function statewide.

Specific Aims (2014-2019)

1. To continue growing a critical mass of investigators focused on the theme of Protein Structure and Function by a) retaining current COBRE members, b) adding new members supported through COBRE Pilot Project grants leading to new external support, and c) expanding the client base of our Core Labs through both general and targeted outreach.
2. To support researchers on our four participating campuses by providing COBRE-funded Pilot Project grants and subsidized access to the services and facilities available through our Core Labs.
3. To sustain our existing Core Labs so they a) continue to grow by adding new clients and the technical staff needed to serve them, and b) continue to acquire new instruments and capabilities for the future.
4. To work with the KU administration to develop a viable plan, based on a combination of institutional support plus revenues generated from user fees, that will sustain for the long-term the Core Labs developed under COBRE-PSF.

Opportunities and Plans for the Future. COBRE-PSF plans to address three specific areas of future scientific opportunity:

A. Development of new, improved vaccines through protein stabilization. Vaccination has played a pivotal role in improving public health. According to the CDC, vaccination is one of the top public health achievements in the United States from 1900-1999. New vaccines to protect children continue to be developed. For example, vaccines against bacterial (meningococcal and pneumococcal) and viral (rotavirus and human papillomavirus) infections

were introduced in the 2000s. Nevertheless, vaccines are still lacking and urgently needed for many medical conditions such as infectious diseases (e.g., HIV, malaria) and cancer, as well as vaccines for emerging new infectious diseases and biodefense to protect the general public.

One key challenge is many new candidate vaccines fail to transfer from the laboratory to the patient due to insufficient potency and lack of stability. The formulation, stabilization and delivery of vaccines, especially in the presence of novel adjuvants to boost immunity, have emerged as key issues. In fact, a historical review of five key revolutions in the history of vaccine development predicts the sixth revolution in vaccinology will be novel vaccine formulations with novel delivery systems. At the Macromolecular and Vaccine Stabilization Center (MVSC) at KU, traditional trial and error approaches to vaccine formulation development are being replaced by more rational approaches that use high throughput biophysical stability analyses of vaccine antigens combined with new data visualization techniques to analyze and display large data sets. These methods have been successfully applied to stabilize a variety of new vaccine candidates, such as recombinant proteins and virus-like particles, along with various adjuvants. *The COBRE-PSF is well-positioned to collaborate with MVSC to expand ongoing efforts to better understand physicochemical stabilization and characterization of novel vaccine antigens and adjuvants for potential clinical use.* The MVSC is located in the Multidisciplinary Research Building (MRB), located next to the Structural Biology Center, the School of Pharmacy, and the Department of Pharmaceutical Chemistry on KU's west campus.

B. Fragment-Based Drug Discovery. In recent years, fragment based drug design (FBDD) has emerged as a primary method for identification of lead compound in drug discovery efforts. This method involves screening a protein target against a library of small molecules, generally less than 200 Da, that represent *substructures* (i.e. *fragments* of molecules) found in many drugs. The basic idea in fragment-based drug discovery (which is now well past the proof-of-concept stage and is being used increasingly in the pharmaceutical industry as a generic approach to "drug" new targets), is that small molecules that bind weakly to a target protein can be turned into strong-binding ligands by "growing" their structures outwardly and/or by linking them together covalently.

To engage in FBDD requires: a) a fragment library, b) an ability to detect moderately weak binding of small molecules to target proteins, c) a means for obtaining structural information about the location and orientation of the binding, and d) an ability to design and then synthesize optimally-linked fragments.

COBRE-PSF has all the appropriate capabilities for detection and structural characterization of fragment binding via Surface Plasmon Resonance, BNMR and X-ray crystallography, in an environment that is exceptionally strong in medicinal organic chemistry. We have already demonstrated the successful application of all three detection methods (each in a different one of our Core Labs) to screen a small fragment library (~200 compounds) for binding to bacterioferritin at a specific site. This led to the discovery of three fragments that bound moderately well; so well that even the fragments could inhibit *in vitro* a protein-protein interaction (PPI) known to be essential for growth of *Pseudomonas* bacteria. To advance this opportunity we will partner with a group of medicinal chemists at the NIH Specialized Chemistry Center at KU. This group has the experience and ability to turn fragments into new molecules with drug-like properties (i.e., lead compounds), and optimize them into potential therapeutics.

Through Phase III of COBRE-PSF we will extend this model to stimulate protein biochemists in Kansas to consider the possibilities of their protein as a drug target, particularly in the area of antimicrobial activity. We held a Regional Workshop on FBDD in June 2013 that drew 97

participants from three states. The strongly positive response to our workshop convinces us that in Phase III, opportunities for COBRE-PSF to pursue fragment-based drug discovery will be very great indeed. The use of COBRE and institutional matching funds to subsidize core lab users will be key to priming the pump in this area.

C. Development of New Antimicrobials Based on Protein Targets. The spread of antibiotic-resistant bacterial infections and a broken pipeline of new antibiotics worldwide have placed public health in a dire situation approaching that of the pre-antibiotic era of health care. Resistance to current antimicrobials not only affects the U.S. but also presents a serious problem in all parts of the world. Antibiotic resistant infections cause enormous suffering and disfigurement in adults and children, and millions of deaths worldwide. The Infectious Diseases Society of America (IDSA) reported there is “an urgent, immediate need for new agents” to fight antibiotic resistant bacterial infections. To address this enormous challenge, the University of Kansas is developing a strong multidisciplinary effort in the discovery and development of antimicrobials targeting bacterial, viral, and fungal infections.

COBRE-PSF is well-positioned to partner with and contribute to this effort, and we plan to do so. The identification and rational design of new antimicrobials mandates the seamless integration of fundamental research in chemical biology, microbiology, medicinal chemistry and pharmaceutical chemistry. Both individual proteins, as well as protein-protein and protein nucleic acid interactions, are viable targets for drug development. We have received many letters of intent indicating an interest in future pilot projects under a Phase III COBRE-PSF Center related directly to this broad area. This area also ties in strongly to FBDD as discussed above.

Plan for Sustaining COBRE-PSF Core Labs in the Future

As noted above, our Core Labs are transitioning to the same model of operation and institutional support used by other KU Core Labs of long standing. In this model, stability is assured by the University providing an annual base budget to each lab, such that revenues from billing clients for lab services balances costs with income. By the end of Phase III of COBRE-PSF, KUCR will cover approximately 80% of the salaries of our three core directors to support our Core Labs. This level of support is typical of what other core labs at KU have received in the past, some for as long as 30 years. With this stable base of funding in addition to reasonable user fees and a large list of repeat clients, we are confident we will be able to sustain our Core Labs into the future.

Other COBRE-PSF Programs

Pilot Project Program. A major purpose of a Phase III COBRE Center is to provide a program for identifying and supporting scientifically worthy pilot projects that will utilize existing COBRE Core Labs and generate preliminary results in support of new research grant proposals and applications. The COBRE-PSF Pilot Project Program will continue a successful program of supporting Pilot Projects by advertising competitions for pilot project awards broadly across the four participating institutions, obtaining external reviews of all applications, and consulting with our EAC to identify new projects to support. The Pilot Project Program will interact with other components of the Administrative Core to provide 1) mentoring and career development support for COBRE junior faculty by experienced senior faculty researchers, 2) a program for the overall enhancement of writing skills and especially for the writing of high-quality research publications and strongly competitive grant applications based on the results of pilot projects supported by COBRE, and 3) monitoring of scientific progress and career development of mentored COBRE

researchers. Individual COBRE Pilot Projects will interact strongly with one or more of our three COBRE Core Labs.

Whereas pilot projects for established investigators will generally be of one year in duration, pilot project awards for junior investigators in Phase III will generally be of two years duration. Two years should be enough time to accomplish the above goals or at least make major progress toward them.

Writing Program. We recognized an opportunity to help improve the overall writing skills of our researchers, whether pertaining to manuscripts, grants, or the communication of important scientific concepts to nonscientists. To address this need, we propose to provide advanced, professional training and coaching in writing for COBRE program participants. The program will provide *personalized* coaching in the art of written scientific communication by working on actual writing projects.

To accomplish our goal we will hire a coordinator for the Writing Program who is an accomplished instructor of technical writing and editing, with the technical and personal skills to improve all faculty writing. The Writing Program will be especially helpful for any pilot project PIs for whom English is not their native language. Participation in the writing program throughout the entire pilot project period will be required for all junior faculty PIs and available but optional for more senior faculty PIs. Interactions between the coordinator and pilot project PIs will be divided between individual coaching (~75%) and group workshops (~25%).

We expect this specialized form of mentoring will ultimately provide an edge in the communication of research (as evidenced in both numbers and quality of publications), and improved success rates with grant proposals.

Mentoring Program. The Mentoring Program incorporates numerous components known to be critical for helping junior scientists develop successful academic careers. Our overall goals for junior faculty development remain the same as in Phase I and Phase II. Each COBRE Pilot Project Leader will:

- Develop an excellent program of rigorous research related to the theme of Protein Structure and Function that will form the foundation for his or her academic career and eventual contributions to the biomedical sciences;
- Submit at least one major NIH R01 grant or the equivalent as an outgrowth of their pilot project and writing program participation.
- Meet all the career development criteria required for the successful attainment of academic promotion and tenure, including research, teaching, and service;
- Become part of an expanding critical mass of faculty in the State of Kansas who are developing individual and collaborative research programs on protein structure and function.

Long-term, high quality collaborative research involving both early career and senior investigators will be developed through interactions promoted by the COBRE-PSF and its enhanced infrastructure, leading to substantially enhanced competitiveness for NIH funding. The emphasis on recruiting, supporting and mentoring junior faculty that characterized COBRE Phases I and II is broadened in Phase III to focus on supporting both junior and senior researchers with shorter-term pilot projects rather than longer term research projects.