REPORT OF THE NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES (NIAMS) SPECIALIZED CENTERS OF RESEARCH (SCOR) PROGRAM REVIEW COMMITTEE: RECOMMENDATIONS FOR THE FUTURE

EXECUTIVE SUMMARY

Committee Process and Conclusions

In the summer of 2003, Dr. Stephen Katz, Director of the NIAMS, invited eight people to serve on the NIAMS SCOR Program Review Committee (henceforth referred to as the Committee). Dr. Sue K. Donaldson was Chair of the Committee. The Committee Roster and Biographical Summaries of the Members are in Appendices A and B, respectively.

Dr. Katz charged the Committee to make recommendations on the appropriateness of the NIAMS SCOR Program as a mechanism for the advancement of translational research for NIAMS. He noted that the review by the Committee was to be of the SCOR Program, not individual SCORs, and of the anticipated usefulness of the SCOR Program for meeting the future goals of NIAMS. Dr. Katz requested that the Committee recommend changes to SCOR to make it a means of advancing translational research or, alternatively, to recommend a new research approach as a funding opportunity through NIAMS. The Committee met on the NIH campus three times to conduct its deliberations and to gather information as a group. The meeting dates were: August 6-7; September 30-October 1; and November 18-19, 2003. The Committee also reviewed written materials and communicated via email between meetings. Agendas for these meetings are in Appendix C. All Committee members participated in the writing of the Report and reviewed its content prior to submission.

The Committee considered the options in the context of NIAMS priorities and the NIH Roadmap. Also factored in were the dramatic changes in the expectations of the NIH as to research that contributes to improved health of the public, defined in part by persons affected by disease, and the participation of lay and advocacy group representatives in the research enterprise. These expectations must be addressed in any successful mechanism for translation in addition to the expectation of the generation of new research knowledge for prevention or treatment of disease. The re-directing of the NIAMS research enterprise towards translation is ultimately intended to facilitate and accelerate the benefits to society, in terms of improved quality of life as well as improved health status. The Committee used a very broad view of health of the public that encompasses all types of translation, products, and outcomes as the basis for developing a Model of Research Translation (Figure 1, Chapter 5). This Model of research delineates the scope of research translation for NIAMS within the larger context of translation from basic science to improved health of the public. The adequacy of SCOR was considered in the context of this Model and a new Center mechanism was developed based on this model.

In its consideration of SCOR as a part of the future direction of NIAMS, the Committee evaluated the history and current status of NIAMS SCOR as well as abstracts of funded SCOR and responses to a Survey sent by the Committee to current and former SCOR Directors. The Committee also reviewed information about other center mechanisms funded within the NIH and NIAMS that include clinical research and research translation as priorities.

The Committee determined that the NIAMS SCOR Program has set the stage for future research translation in that SCOR developed new mechanisms for synergistic and productive interactions between basic and clinical researchers. SCOR brought together scientists who would not have otherwise interacted, breaking down silos; SCOR attracted scientists beyond the PIs of the projects it funded; and SCOR was able to make positive and long-lasting changes in the research culture of the home institution. The SCOR Administrative Core and Scientific Cores were absolutely essential to the establishment and maintenance of these desirable changes in scientific interactions, research teams, and institutional culture. Another important lesson learned from SCOR is that the disease focus is critical to unifying the goals of basic and clinical researchers. These elements of the SCOR Program need to be incorporated into future center mechanisms directed towards research translation.

Despite these positive attributes of SCOR, the Committee felt that retaining or changing the SCOR Program is not the best approach to establishing a funding mechanism for research translation within NIAMS. The Committee noted that, although some transformation of basic to clinical knowledge and research did occur in SCOR, translation was not the predominant contribution of SCOR. While the Committee concurs that a single five year round of funding may not be long enough for translation, translation did not emerge as a significant theme even for SCOR that were funded for more than one cycle. This is understandable in that SCOR did not have translation as its stated aim. But the experience with SCOR demonstrates that having the critical elements in place for the translation process is not sufficient for translation to emerge as the major theme. The Committee agreed that specific and overriding goals for translation are essential to the realization of basic to clinical research translation as the dominant outcome. SCOR has a distinct and well known identity that has been established and honed over many years; the Committee decided that it would be very difficult to transform this identity into one that reflects research translation as the priority. Also, since SCOR has lost some of its appeal for many reasons, including low funding caps, it was determined that it would be difficult to use SCOR as the mechanism to attract scientists to a new goal of translation. Thus the Committee considered options that are alternatives to SCOR to meet the future needs of NIAMS.

In considering the future direction of NIAMS in translational research and the process of research translation, the Committee determined that a mechanism of centers of excellence was the best approach. The Committee recommends that the proposals

for this type of center be solicited through Requests for Applications in targeted areas and developed using the new model for these Centers.

The Committee developed the framework for a new translation-focused center mechanism: the Center of Research Translation (CORT, see Figure 2, Chapter 7). The proposed CORT is grounded in the Committee's conceptual Model of Research Translation (Figure1, Chapter 5) and re-creates elements from SCOR that are relevant to the translation process, such as the combination of basic and clinical researchers and projects focused on a common disease theme, scientific cores, and the coordinating functions of an administrative core. Two major features distinguish CORT from SCOR: 1) the overarching aim of disease-specific research translation from basic to clinical, and 2) the inclusion of resources and a new administrative structure to facilitate research translation. CORT is designed to create a center of research excellence that brings together resources and individuals in an administrative structure that facilitates disease-specific research translation. The resources are research (i.e., scientific projects and scientific cores), as well as administrative. In addition to a central Administrative Unit, CORT includes in its administrative structure both a Scientific Advisory Group (SAG) and a Translation Advisory Group (TAG), each charged with oversight, coordination, and communication. SAG's role is related to rigor, conduct of the research, and scientific interactions and TAG's role is related to translational progress, innovative approaches, lay/advocacy group participation, and new outside partnerships. Thus the role of TAG is completely new, and TAG members should include lay persons and representatives from advocacy organizations as the primary members along with health care professionals, scientists, and industry representatives who share an interest in the specific disease and translation related to it.

Recommendations of the Committee

1. Discontinue NIAMS SCOR at the end of its Current Funding Cycle.

The Committee recommends funding through the full award period of currently funded SCOR.

2. Create a new research center mechanism specifically for translation and consistent with CORT.

The organizational structure and functional components of CORT are proposed as the means for moving forward with research translation within the scope of funding opportunities of NIAMS. The CORT concept is dual, embracing both the translation of new scientific information to clinical application and of clinical findings and methodology to community practice. Thus, CORT offers the opportunity of engaging not only scientists and clinicians, but also lay and advocacy group representatives, in the translation process.

2a. Institute 5 year award periods for CORT with competitive review criteria that take into account progress in the direction of translation.

The Committee agreed that the time period needed for significant translation manifested as improved health is likely to be longer than 5 years. Thus interim goals indicating directional progress (i.e., basic knowledge into clinical) in research translation should be used as the basis for renewals of CORT awards for additional funding cycles.

2b. Create a mechanism for sharing translational progress across funded CORTs and adaptation of CORT over time.

Since a directed effort towards research translation is new, CORT should be viewed as a pioneering effort that will need revision over time to achieve the desired outcomes. Sharing among CORT PIs will allow the most effective approaches and mechanisms to be incorporated over time. The Committee also viewed the gathering of CORT PIs at least annually as a means of creating translational synergy that parallels the basic-clinical synergy of the scientific interactions.

2c. Create flexibility in the implementation of the CORT Translational Advisory Group (TAG).

In its discussions the Committee considered how TAG might be created and came to the conclusion that it might not be wise to fully engage outside partners until a CORT is actually funded. It is recommended that CORT applications be reviewed with a plan for constituting TAG with letters of agreement to be obtained after the CORT is funded. However, the plan for TAG in the proposal should be fully formulated including its general member composition and goals as well as the methods for achieving short and long-term measurable outcomes. It is expected that TAG members will be put in place quickly since the CORT cannot fund any Pilot Projects until this advisory group is in place (see 2d).

2d. Provide adequate funding for CORT.

The funding level for SCOR would be inadequate for CORT, especially in view of the expanded structure, functions, and translational aims of CORT. The Committee recommends a minimum of $1.0 million for each CORT to cover all aspects of CORT except funding of the Pilot Projects. Each CORT should be eligible for an additional $200,000 per grant year to internally fund Pilot Projects at a level of $50K each per year for up to two years per pilot. These Pilot Projects are screened for scientific merit by SAG and selected for funding by TAG. TAG must be fully implemented before the CORT becomes eligible to fund Pilot Projects.

2e. Create a special review process for CORT that weights the quality of the overall translational plan as the highest priority, recognizing that research projects must be scientifically sound.

The Committee recommends that the group constituted to review CORT, or any other type of application for research translation funding, be given careful instructions as to their determination of scientific merit of the CORT Projects. Traditionally, reviewers factor in contribution to a particular field of science as a part of their merit score. While this is appropriate for R01 type applications, it needs to be adjusted for CORT. The scientific review for CORT should focus on the feasibility and rigor of each CORT Project. The value of the contribution of each proposed project to the overall aim of research translation should be for the major criterion for review of the Center, rather than its specific contribution to a field of science. CORT applications need to be evaluated as to the combination of research projects, scientific cores, advisory groups, and administration as the means for achieving specific aims for research translation. Each CORT proposal should include translational aims and methods for achieving them in addition to the specific aims for each component research project and the scientific cores.

2f. Foster partnerships between CORT and lay/advocacy groups and foundations invested in the disease-specific translation.

The Committee encourages NIAMS to assist funded CORTS to engage in partnerships with interested lay/advocacy groups for the purposes of broadening the perspective of CORT to improved health of persons affected by the disease and generating additional resources for translation.

CHAPTER 1: Convening and Charging of the SCOR Program Review Committee

In the summer of 2003, Dr. Stephen Katz, Director of the NIAMS, invited eight people to serve on the NIAMS SCOR Program Review Committee. Dr. Sue K. Donaldson agreed to serve as the Chair of the Committee. The Committee Roster and Biographical Summaries of the Members are in Appendices A and B, respectively.

The SCOR Program Review Committee (henceforth referred to as the Committee) held its first meeting August 6-7, 2003. After introductions, Dr. Katz charged the Committee to make recommendations on the appropriateness of the NIAMS SCOR Program as a mechanism for the advancement of translational research. He noted that the review by the Committee was to be of the SCOR Program, not individual SCOR, and of the anticipated usefulness of the SCOR Program for meeting the future goals of NIAMS. Dr. Katz presented his model of a continuum of advances in scientific knowledge that lead to the translation of basic science into clinical forms (i.e., new therapies and treatments for disease and for prevention of disease) directly relevant to the people that NIAMS serves. Translational research was discussed in the usual patient-based framework of “bench to bedside,” but was expanded to include translation of knowledge from basic science to clinical research to knowledge

useful to persons (individuals, families, populations) affected by or at risk for specific diseases.

Dr. Katz noted that there were two major factors leading him to seek a review of the SCOR Program at this time. The first factor relates to excellence, in that any funding mechanism requires periodic evaluation and revision to remain excellent over time. The most recent review of the NIAMS Centers Programs in 1997 did include the SCOR, but the SCOR Program was not a major focus of the review. There is a need to focus on the SCOR Program, which began in 1987, especially in terms of its relevance for the future of NIAMS. The second factor relates to changes in the goals and direction of the NIAMS and the NIH in the areas of clinical research and translational research. Dr. Katz specifically asked the Committee to consider the new directions that the NIH is taking in the Roadmap Initiative as well as new paradigms to respond to the Roadmap Initiatives in the area of translational research. Dr. Katz requested that the Committee evaluate the SCOR Program specifically in terms of its appropriateness for emerging translational paradigms and also to make recommendations as to new translational models and funding mechanisms, if applicable.

CHAPTER 2: Meetings and Methods of the Committee in the Conduct of the Program Review and Preparation of the Report

A. Overview

The Committee met on the NIH campus three times to conduct its deliberations and to gather information as a group. The meeting dates were: August 6-7; September 30-October 1; and November 18-19, 2003. The Committee also reviewed written materials and communicated via email between meetings. Agendas for these meetings are in Appendix C.

In advance of the first meeting, the Committee members were mailed a number of items as background information, including: an overview of the requested review; a brief history of the NIAMS SCOR Program; graphs showing the history of SCOR Applications and Funded SCOR by disease areas; a historical list of SCOR with projects and cores; abstracts of NIAMS SCOR projects in FY 2002; and the NIAMS Guidelines for SCOR applications. Additional background materials, that were provided to the Committee members for the second meeting, include a summary of SCOR translational themes, a table of U54s (Specialized Center Cooperative Agreements) funded in FY 2002 by various other NIH components, a brief synopsis of four of the U54 Programs supported by other (i.e., not NIAMS) NIH components, and abstracts from the NIAMS Multidisciplinary Clinical Research Centers (P60s).

The development of the Report was the work of the entire Committee. Each member of the Committee undertook the writing of one or more sections of the Report, and all recommendations in the Report were fully vetted by all of the members. There was

provision for responses from all members of the Committee (whether or not they were able to attend all of the meetings), and every member of the Committee was invited to respond to and ultimately approve all aspects of the Report. The Committee members were actively engaged in a participatory process.

B. Brief Summary of the First Meeting

Following Dr. Katz's charge to the Committee, Dr. Donaldson started the first session by outlining the process that she intended to use for this review, noting that the work of the Committee would culminate in a Report that would be sent to Dr. Katz and then presented by Dr. Donaldson at the January 2004 meeting of the NIAMS Advisory Council.

Dr. Julia Freeman, NIAMS Centers Program Director, provided a historical perspective on the SCOR Program as well as information on other large grant mechanisms and an overview of how other NIH Institutes use the Centers mechanism. Dr. Joan McGowan, Bone Diseases Program Director, and Dr. Susana Serrate-Sztein, Genetics and Clinical Studies Program Director, provided their perspectives on the SCOR Program from their experiences as Directors of Programs within the Extramural Program. Dr. Gail Pearson from the National Heart, Lung, and Blood Institute (NHLBI) shared the experiences of her Institute with the review of their SCOR program in a talk entitled, "Methods, Tools, and Data from the NHLBI SCOR Review – An Example."

Following the presentations, the Committee focused on the following five key areas: (1) major aspects of SCOR to be reviewed; (2) sections of the Committee's Report to Dr. Katz; (3) scope/nature of recommendations in the Committee's Report; (4) information and data needed to evaluate the SCOR Program and to make recommendations as to future NIAMS funding opportunities; and (5) review of existing NIAMS outcome data for funded SCOR and formulation of methods and additional data gathering tools that will be used by the Committee.

At the first meeting it was decided to create a tool and method for soliciting information from SCOR Program Directors, present and past. The Committee developed a letter and Survey tool that were sent to all SCOR Program Directors after the first meeting. The next section addresses the Survey.

C. Information Requested from Present and Past NIAMS SCOR Directors

A key source of information that the Committee considered was the responses from current and former SCOR Directors to the Survey that was sent to them. The Committee sent out requests for information to 20 individuals and received responses from 12. A second, targeted solicitation was sent to the 8 who had not yet responded, and two more response was received. Thus the respondents to the survey were 70% of those solicited. The current and former Directors were asked to respond to the following request for information that was sent to them by email:

INFORMATION REQUESTED FROM CURRENT AND FORMER NIAMS SCOR DIRECTORS BY THE COMMITTEE REVIEWING THE SCOR PROGRAM

The NIAMS has undertaken a review of the SCOR Program. This is not a review of any individual projects, but of the Program as a whole. The Committee has been asked by Dr. Stephen Katz to evaluate the current criteria for the SCOR Program and to provide recommendations to him, and ultimately to the NIAMS Advisory Council, for ways in which the SCOR mechanism can be most effective in advancing the scientific enterprise and improving public health. We know that the whole landscape of research has changed over the last several years, and we want to assess all of the available options for pursuing the translation of research from bench to bedside and from bedside to bench in the most effective and efficient ways. The Committee is seeking advice from all of the investigators who are current or former directors of a SCOR program because you are the front line experts who can tell us the strengths and weaknesses of the current model, as well as your thoughts for the future design of the SCOR mechanism.

We are asking that you take a few minutes and answer in all candor the questions that we posed below.

Describe the most important scientific accomplishments of your SCOR.

We are always seeking information on the results of SCORs, what progress they led to (such as new grants that were derived, new clinical tests, new therapies, new areas of research that might not have happened without the SCOR). To help us get at this kind of information:

Please provide examples of how your SCOR has stimulated and maintained collaboration and coordination among investigators, particularly basic and clinical scientists.

- Please provide examples of how your SCOR has resulted in scientific progress that was transferred to clinical applications.

- Distinguish the SCOR mechanism from other funding mechanisms (such as Program Projects and R01 grants), noting the advantages and disadvantages of the SCOR mechanism.

- The Committee is considering ways in which future SCORs can include features like flexibility, an enhanced clinical component, and a strong translational research bridge. We would like your perspective on the most important aspects of the current SCOR program that you think should be preserved? What aspects would you recommend be changed or eliminated?

- Do you think that the disease focus of SCORs has been useful? Would you recommend keeping the current disease focus, opening SCOR applications up to other diseases, or changing the focus to be broad areas such as autoimmunity or vasculitis (by way of illustration of the scope of what could be considered)?

We extend our thanks to you for taking the time to provide our Committee with information on the vitally important perspective that you have from your involvement with the SCOR Program. We want to assure you that your thoughts will be considered in the aggregate with responses from all the other current and former SCOR Directors, and we will not report our findings with any identification of the sources of particular responses.

In order for our Committee to have time to analyze these responses, we are requesting that you send your responses to Helen Simon, Chief of Program Planning at the NIAMS, at simonh@mail.nih.gov, by September 12, 2003.

Thank you.

Members of the Committee to Review the NIAMS Specialized Centers of Research:

Sue Donaldson, Ph.D., Chair
Peggy Crow, M.D.
Howard Dickler, M.D.
Thomas Einhorn, M.D.
Brian Kotzin, M.D.
Lawrence Raisz, M.D.
John Stanley, M.D.
Sharon Terry, M.A.

D. Brief Summary of the Second Meeting

The second meeting was held on September 30 and November 1. On the first day, following a welcome and brief overview of the work of the Committee to date by Dr. Donaldson, Dr. Freeman provided a review of the U54 mechanism across NIH Institutes. Dr. Richard Lymn then described the NIH's recent experience with the new U54 Muscular Dystrophy Centers and how NIAMS is involved. Following the presentations, the Committee members discussed the materials that had been sent in advance as well as any issues that members had. In addition, they discussed the responses from current and former SCOR Directors that the Committee had received in the Survey that the Committee sent seeking the perspectives of these SCOR Directors (see below for a fuller description of the survey and responses). The Committee spent the rest of the time on the first day formulating preliminary recommendations and identifying issues that should be included in the Report. The Committee devoted the second meeting day to discussing suggested major recommendations and delineating the key points to be included in the prose discussion that would be developed for each major recommendation in the Report. The Committee discussed additional information that would be useful as well as individuals that the Committee might like to invite to the November meeting.

E. Brief Summary of the Third Meeting

The third meeting of the Committee was held on November 18-19. Following a review of the status of the work of the Committee to date, the Committee focused on the draft recommendations in the Report and the rationale for each. Members of the Committee developed a schematic view of what a translation research center would include and discussed the various cores that would be needed to support such a center. They also analyzed the draft Report in detail to ensure that there was consensus on all major points included in the Report. The Committee members discussed outstanding issues, identification of additional materials that would be

useful for them to have, and Report writing and review that would be needed to finalize the Report. The Committee agreed that the rest of the work would be done by e mail, and that all members of the Committee would be invited to review and approve the final Report before Dr. Donaldson presented it to the Advisory Council. Members of the Committee were also invited to participate in the Advisory Council discussion on January 29th, either by attending the meeting or by conference call. Dr. Donaldson concluded the meeting by expressing her gratitude to members of the group for all the work they had done in such a short time and how pleased she was with the development of the Report.

CHAPTER 3: Historical Perspective of the NIAMS SCOR Program

In 1985, the National Arthritis Advisory Board recommended initiation of a Specialized Centers of Research (SCOR) program for arthritis. The scope was soon expanded to arthritis and musculoskeletal diseases. The rationale behind this recommendation was that a greater emphasis on specific diseases was needed than could be brought to bear by the Multipurpose Arthritis Centers alone. The initial competition for the new SCOR was begun in 1986.

A. SCOR Competitions

See the Budget History of the SCOR Program, Table I and Charts 1 – 7 in the Appendix for summaries of the SCOR history.

1. *Initial Competition: 1986*

The first SCOR guidelines and Requests for Applications were issued shortly after the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) became a separate institute in 1986. This was in response to an appropriation of $7.7 million from the Congress to establish the NIAMS SCOR program. NIAMS targeted the program for three diseases: rheumatoid arthritis, osteoarthritis, and osteoporosis.

Thirty-three SCOR applications were received; 7 for rheumatoid arthritis, 11 for osteoarthritis, and 15 for osteoporosis. It was decided that each disease should be represented by three SCOR in order to provide a critical mass for research.

2. *First Recompetition: 1991-1993*

When the program was reissued in 1991, only 13 applications were received, 5 for rheumatoid arthritis, 4 for osteoarthritis, and 4 for osteoporosis. Four applications were funded for rheumatoid arthritis, 1 for osteoarthritis and 2 for osteoporosis. The decision was made to expand the program to lupus. Fourteen applications were received and two were funded in 1993.

3. *Second Recompetition: 1996-1998*

For the next announcement of the SCOR program in 1996, the guidelines were revised to include (1) the expectation of a strong clinical research project, (2) a significant percent effort required of component PIs, (3) that the Core Director must be a project PI and (4) a $750,000 cap in direct costs. Scleroderma was added to the disease list, so that the Requests for Applications issued included SCOR in (1) rheumatoid arthritis, (2) osteoarthritis, (3) osteoporosis. (4) lupus, and (5) scleroderma. Because there was an ongoing review of the centers program, funding was limited to 4 years.

Although there were 29 applications for SCOR in rheumatoid arthritis, osteoporosis and scleroderma in 1997, peer review of these applications did not reflect much enthusiasm. Only 1 application for each disease was funded. The Request for Applications was reissued for these three diseases, and from the 14 applications received, one additional SCOR in rheumatoid arthritis and one in osteoporosis were funded.

Applications for SCOR in lupus and osteoarthritis were also solicited. Five applications were received for osteoarthritis; one application was funded. Eleven applications were received for lupus; two were funded.

4. *Third Recompetition: 2001-2003*

The SCOR program recently completed a third major renewal cycle, now spread over three years. The number of applications has been down. Two solicitations for SCOR in rheumatoid arthritis brought 6 applications; one has been funded. Two solicitations for SCOR in osteoporosis brought 3 applications; one has been funded. In contrast, the one solicitation for SCOR in osteoarthritis brought 4 applications; two were funded. For SCOR in scleroderma, the numbers were the same: four applications with two being funded. The solicitation of SCOR in lupus brought 8 applications; two were funded.

B. SCOR Guidelines

The objective of the SCOR program has been to expedite development and application of new knowledge of specific importance to a disease. Each SCOR provided a multidisciplinary approach utilizing both laboratory and clinical research to focus on aspects of research in a disease for a mutually supportive interaction between basic scientists and clinical investigators. Emphasis in proposed projects was to be on the development of innovative approaches, elaboration of new and significant hypotheses, and generation of improved strategies for approaching current issues relating to the disease. A SCOR program was neither for the support of large clinical trials nor for research programs that were either exclusively clinical or exclusively basic in focus.

The guidelines for the SCOR program have elaborated the expectations for the program. Each SCOR was envisioned as a national resource associated with a major medical complex and dedicated to working with the NIAMS in furthering the research effort related to a given arthritis and musculoskeletal disease area. The SCOR program complemented other programs in research and training supported by the Institute. SCOR fostered research efforts that strongly involved significant interaction between basic research and clinical investigations in specific diseases.

Guidelines have evolved for the SCOR program throughout, from 1986 – 2003. From the beginning, the model has been the inclusion of at least three individual but interrelated basic and clinical research projects, an administrative core, and supporting research cores as needed. The SCOR also had an overall research theme uniting the proposed research projects.

Revisions were added in the guidelines to emphasize new policies. In 1991 a section was added on the inclusion of women and minorities in clinical research study populations and direct costs were limited to $1 million per year. In 1996 additional programmatic adjustments were made. These adjustments were: (1) the expectation of a strong clinical research project, (2) a significant percent effort required of component PIs, (3) that the Core Director must be a project PI and (4) a $750,000 cap in direct costs. The newly established NIH definition of clinical research was included as a guide for determining a clinical research project.

The review factors listed for a SCOR application included:

1. How the proposed SCOR combines basic and clinical research into the scientific goals;
2. Scientific merit of each proposed project, including originality and feasibility of the project and adequacy of the experimental design;
3. Scientific merit of combining the component parts into a SCOR;
4. Technical merit and justification of each core unit;
5. Competence of the investigators to accomplish the proposed research goals, their commitment, and the time they will devote to the research program;
6. Adequacy of facilities to perform the proposed research, including laboratory and clinical facilities, instrumentation, and data management systems, when needed;
7. Adequacy of plans for interaction among investigators, and integration of the various projects and core units;
8. Qualifications, experience and commitment of the SCOR Director and his/her ability to devote time and effort to provide effective leadership;
9. Scientific and administrative structure, including internal and external procedures for monitoring and evaluating the proposed research and for providing ongoing quality control and scientific review;

10. Institutional commitment to the program, and the appropriateness of resources and policies for the administration of a SCOR; and
11. Appropriateness of the budget for the proposed program and its individual components.

C. Disease Foci for SCOR Programs

The research themes of NIAMS Specialized Centers of Research (from abstracts and summary statements) are as follows:

1. *Specialized Centers of Research in Lupus*

Hospital for Special Surgery: 1993 -1998
The research involved defining the role of molecular defects or gene polymorphisms in the pathogenesis of SLE, and the use of the information obtained to develop new therapeutic approaches. Areas of research: mouse model for defect in fas gene; control of T helper cells and cytokine-mediated autoantibody production in SLE; and cellular and molecular mechanisms by which antiphospholipd antibodies provoke thrombosis, focusing on interactions with endothelial cells.

University of North Carolina, Chapel Hill: 1993 – 1998
The four projects were concerned with immunoregulatory mechanisms of autoantibody production in lupus. Areas of research: murine models of lupus, exploring events influencing B cell development and selection that produce autoantibodies and studies of apoptosis; and studies of positive feedback regulation of ANA production in mice and patients.

University of Virginia: 1998 – Present
The research theme and rationale for the proposed program were directly focused on discovering the immunological and genetic basis of autoimmunity primarily involving T cell responses to autoantigens in lupus. The major hypothesis tested was that multiple molecular mimics of auto-epitopes can initiate an immunological response leading to autoimmunity and disease manifestation in genetically susceptible hosts by an epitope spreading mechanisms involving intra- and inter-molecular determinants. The four projects included both basic and clinical research. Areas of research: mapping T and B cell epitopes on ribonucleoproteins in transgenic mice expressing HLA-DR and DQ antigens and in lupus patients to correlate the findings in humans with those in mice; murine T cell response to Ro60; role of non-MHC genes in the development of lupus in to murine models; and autoantibody responses in lupus patients with serial serum samples over a number of years.

University of Alabama, Birmingham: 1998 – 2002 (Renewed as a P01)
This SCOR was a multidisciplinary, multicenter effort to address the genetics of human lupus employing genome-wide searches as sell as studies of specific candidate genes lying within associate chromosomal regions. Areas of research: two

projects that exchanged lupus cohort samples and performed genetic find mapping; an assessment of polymorphic and functional characteristics of certain candidate genes on chromosome 1, and a study of genetic risks in longitudinal lupus cohorts.

2. Specialized Centers of Research in Osteoarthritis

Rush Presbyterian-St. Luke's Medical Center: 1987 – Present
This SCOR focused throughout on examining osteoarthritis in a continuum from basic chondrocyte biology through clinical application of new therapies. Areas of research: mechanism involved in the formation of cartilage tissue by OA cells, cellular basis of the heterogeneity of chondrocytes in knee and ankle cartilage; use of orthotics to modify biomechanics in OA; and regulation of superficial zone protein expression in articular chondrocytes as a therapeutic target.

University of Iowa: 2002 – Present
The SCOR coordinates a multidisciplinary effort to advance understanding of the pathogenesis of post-traumatic OA. Post-traumatic OA at the ankle is the focus because of the low risk of primary OA and the relatively high risk of post-traumatic OA at this site. Areas of research: prospective study to define the role of acute energy absorption and chronic articular surface contact stress as risk factors for post-traumatic ankle OA; prospective randomized trial of the effects of decreased articular surface contact stress; and a laboratory investigation of the effects of age and mechanically induced oxidative stress on chondrocyte senescence on the effects of anti-oxidant defenses on chondrocyte senescence.

Indiana University: 1987 – 1992
This SCOR was developed from the perspective that osteoarthritis does not represent failure merely of joint cartilage, but of an entire organ, the diarthroidal joint, comprising subchondral bone, synovium, ligaments, cartilage and the neuromuscular apparatus. Areas of research: a specific glycoprotein to serve as a marker for OA; characterization of the pericellular matrix of the chondrocyte; joint breakdown in OA; importance of inflammation in the repair of cartilage in OA, and drug therapy for pain in OA.

University of Minnesota: 1987 – 1992
The hypotheses of this SCOR were that the osteoarthritic process is characterized by disturbance in the equilibrium between mechanical demands on the joint and the ability of joint tissues to support or adapt to those demands. OA was seen as an organ failure and the changes in the articular cartilage, calcified cartilage, subchondral plate and trabecular bone were all interrelated. Secondary to the initiating damage, all of the joint tissue elements remodel or repair and that whether this process leads to OA or new function state depends upon joint loads, the nature of initial damage, the healing potential, and the strength and healing of the remaining tissues. Areas of research: two animal models studied for the result of a quantified mechanical disturbance to a normal joint; the spine facet OA joint model; effect of

joint denervation on neuromuscular control mechanisms in a dog knee; and role of functional joint laxity in humans with ACL injury.

3. *Specialized Centers of Research in Osteoporosis*

Helen Hayes Hospital: 1987 –2003
This SCOR has focused on understanding the mechanisms of parathyroid hormone (PTH) on bone with the goal of using it to restore bone mass in osteoporosis. The most recent funding period supported four projects. Areas of research: isolation of human osteoblasts and assessment of mechanisms underlying differentiation and death; interactions between PTH and estrogen in rodent models; clinical trial of PTH and alendronate in postmenopausal women; and the effect of primary hyperparathyroidism on the bones of postmenopausal women.

Creighton University: 1987 – 1997
This SCOR focused on the etiology, prevention and treatment of osteoporosis. Basic and clinical studies of the pivotal role of calcium in the pathogenesis and management of osteoporosis were carried out. The clinical studies focused on the role of calcium in health and disease. Areas of research: bone histomorphometry before and after menopause; continuous low dose estrogen/progesterone in elderly women; factors affecting calcium availability; calcium absorption physiology; control of bone mass in the aged, osteoporotic skeleton; and components of exercise intensity to define training principles for bone.

University of Pennsylvania: 1987 – 1992
This SCOR investigated the interrelationships of hormones, such as calcitonin and estrogen and environmental stress, both mechanical and electrical, in the loss, inhibition and restoration of bone mass. Areas of research: effect of an applied electric field on osteoporosis; skeletal effects of calcitonin and estrogen; effect of strain generated electrical potentials in bone; and whether levels of bone mineral are genetically determined.

Massachusetts General Hospital: 1997 – 2005
This SCOR focuses on the effects and mechanisms of action in the use of exogenous parathyroid hormone (PTH) in humans and animals. Areas of research: clinical trial of PTH/alendronate in treating osteoporotic men and women; mechanisms by which PTH can induce bone resorption; and evaluation of how the PTH/PTHrP receptor regulates osteoblast and osteoclast differentiation.

4. *Specialized Centers of Research in Rheumatoid Arthritis*

Duke University: 1987 – 2001
This SCOR focused on identifying mechanisms of activation and recruitment of immune cells in the joint, particularly as they relate to molecules governing interaction of immunocytes with endothelial cells and matrix elements, and the role of cytokines and chemokines in these processes. Areas of research: Role of CD44 isoforms and

adhesion molecules in models of synovitis, nitric oxide as an inflammatory mediator, and the role of chemokines in synovitis.

University of Tennessee: Memphis 1987 – Present
The theme of this SCOR is that immune responses to type II collagen are central to the pathogenesis of rheumatoid arthritis. In large part this hypothesis has been driven forward by the investigation of the collagen induced arthritis model in rodents, developed and extensively studied at this institution. Area of research: collagen autoimmunity and collagen induced arthritis in animal models and humans.

University of Texas, Southwest Medical Center at Dallas: 1987 – 1997
The overall theme of this SCOR was the genetic and immunological basis of rheumatoid arthritis. Areas of research: development of a transgenic animal model for RA, migration of lymphocytes across endothelial barriers, and characterization of T cell receptors.

University of Michigan, Ann Arbor: 1992 – 1997
The central hypotheses of this SCOR were that rheumatoid arthritis is a multiphasic disease with distinct early and late stages and that triggering events in the early disease stage involve a specific immune response followed by a separate antigen nonspecific self-perpetuating phase. Several different mechanisms of inflammation contribute to various phases of the disease. Areas of research: role of specific lymphocytes in various phases of the disease, adhesion mechanisms, and activation pathways for various lymphocytes.

University of California, San Diego: 1998 – 2003
This SCOR focused on the molecular basis of immune dysfunction and pannus formation in rheumatoid arthritis. Areas of research: role of immunostimulatory DNA in the pathogenesis of rheumatoid arthritis, the synovium at an immune underprivileged site, the use of vaccination strategies to create immune deviation, and functional properties of isolated T cells recognizing the shared epitope.

5. *Specialized Centers of Research in Scleroderma*

University of Texas – Houston: 1997 – Present
This SCOR focuses on the use of molecular approaches to understanding pathogenetic mechanisms, especially genetic factors, and the predictors of outcomes in scleroderma. Areas of research: candidate genes for scleroderma in a population with high prevalence of scleroderma; animal model for the genetics of scleroderma; gene expression profiles of effected tissue; and prospective study of patients with scleroderma for demographic, clinical, autoantibody and genetic predictors.

University of Tennessee, Memphis: 2001 – Present
This SCOR focuses on the biology of fibrosis in scleroderma. Areas of research: role of collagen in inducting fibroblast growth and in inducing platelet aggregation, refractoriness of fibroblasts from scleroderma patients to regulation by cytokines.

CHAPTER 4: Recurring Themes and Issues Identified by the Committee from the Survey Responses and SCOR Abstract Records

A. Overview

The content of Chapter 4 is derived from the Committee's analysis of information derived primarily from the SCOR Director responses to the Survey. Abstracts previously submitted by the SCOR Directors in reports to NIAMS were used for clarification of specific points but were not systematically analyzed. The intent of this analysis by the Committee was not to review the scientific quality of SCOR or the total contribution of SCOR. Rather, the Committee focused on identifying the overall thrust and selected examples of the contributions of SCOR, including the major research themes, that relate to the relevance of SCOR for a future direction in translational research. The Committee recognizes that SCOR was a combination of basic and clinical projects and scientists that were organized around the goal of generating knowledge related to a specific disease focus, and not around a specified goal of translation of knowledge from basic to clinical. Thus the Committee's analysis is not of the SCOR progress towards original goals, but rather of the relevance of the SCOR contributions, research themes, and center mechanisms and experience for future goals in translational research.

1. *Selected Examples of SCOR Contributions and Research Themes in Rheumatoid Arthritis*

Five SCOR in rheumatoid arthritis (RA) have been supported since initiation of the NIAMS SCOR program. The role of altered immune responses in the pathogenesis of RA was the major scientific theme emphasized by the RA SCOR. All of the centers identified the role of autoantigen-specific T lymphocytes as an important mechanism for study in RA, and B lymphocytes and their autoantibody products were the focus of projects in two of the SCOR. Mechanisms of recruitment of inflammatory cells to the synovial membrane, including the role of chemokines and adhesion molecules, were emphasized by one of the centers. Therapeutic approaches that were investigated included induction of T cell tolerance to collagen and immune deviation induced by gene vaccination. Human tissue material, particularly synovial tissue, was used by most of the SCOR, and one of the centers developed a "research resources" core facility that stored valuable tissue specimens from patients. Those specimens were made generally available to the scientific community. Animal models of inflammatory arthritis were heavily used by several of the groups.

Positive outcomes of all RA SCOR included the development of infrastructure supportive of RA research and the generation of preliminary data helpful in gaining additional research grant funding. Although it is difficult to identify any one of the RA SCOR as having made a "breakthrough" in understanding or management of RA, the centers made important contributions to the body of knowledge regarding immune

system activation in RA. The concept of early RA was developed by one of the SCOR, and several of the centers extended their work in animal models to develop potential therapeutic interventions. The identification of collagen peptides that are relevant to inflammatory arthritis in both mice and humans has prompted interesting clinical trials of those peptides, or soluble T cell receptors specific for those peptides, as potential tolerizing agents in humans. Through the study of nitric oxide in RA, the role of that inflammatory mediator in additional clinical conditions was recognized. All of the RA SCOR directors valued the SCOR mechanism for its contribution to building collaborations among basic and clinical investigators as well as recruiting investigators who were new to RA research into interactive projects. It was felt that a higher budget allocation would be useful to assure that highly competitive projects would be among those proposed in SCOR applications.

2. *Selected Examples of SCOR Contributions and Research Themes in* Osteoarthritis

Four SCOR in osteoarthritis (OA) have been supported since initiation of the NIAMS SCOR Program. There was unanimous agreement that the greatest strengths of a SCOR are the ability to focus multiple disciplines on a single problem, develop a central hypothesis, pursue the testing of that hypothesis with common goals in mind, and directly link basic investigation to the advancement of clinical outcomes. The ability to bring together scientists from disparate disciplines such as bioengineering, cellular and molecular biology, and clinical science resulted in synergistic interactions that led to new knowledge and new research directions. Collaboration and coordination among basic and clinical scientists, the ability to demonstrate very striking and potentially important direct clinical applications of scientific progress, and the learning which took place among the participants of the projects led to an improved understanding of osteoarthritis and the ability to formulate new questions and hence new research proposals. All four investigators were very positive in their comments regarding this program.

The major accomplishments achieved by the Osteoarthritis SCOR were an enhanced understanding of the optimal treatments for transarticular fractures and an enhanced understanding of the role of repetitive impact loading in articular cartilage and the pathogenesis of osteoarthritis.

3. *Selected Examples of SCOR Contributions and Research Themes in Scleroderma*

Translational advances from reports of two SCOR grants on scleroderma were reviewed.

In vitro studies showed that CD14+ monocytes from scleroderma patients, but not normal people, differentiate into fibroblasts when exposed to mediators produced by normal peripheral blood mononuclear cells. Potentially significant from the point of view of therapy is their observation that pamidronate inhibits this "transdifferentiation." These observations have led to further insights into other

human diseases because similar transdifferentiation takes place in idiopathic pulmonary fibrosis and pulmonary sarcoidosis. Similar mechanisms may also be important in cardiac fibrosis in congestive heart failure. Not only monocytes, but also lung epithelial cells can be induced to transdifferentiate into fibroblasts, in this case with IL-1.

Further insights into the pathophysiology of scleroderma were provided by correlating the degree and type of involvement in scleroderma patients with IL-10 vs. IFNg production of peripheral blood mononuclear cells stimulated by collagen. A reduction in matrix metalloproteinase-1 (MMP-1) expression in scleroderma fibroblasts was correlated with increased intracellular IL-1 receptor antagonist which decreases c-fos and c-jun signal transduction, and may increase smad 3. Such regulation of these transcription factor pathways tend to decrease MMP-1. Finally, receptors on platelets that may lead to aggregation on collagen contact have been characterized.

The most direct applications of the above findings to patient care in scleroderma are the potential of pamidronate for therapy and T cell responses to collagen to predict clinical outcomes.

Other studies focused on the genetics of this disease. Basic scientists and clinical geneticists have further characterized and mapped disease susceptibility genes, and have collaborated on microarray analysis to define gene transcription changes specific for scleroderma fibroblasts. These projects have the potential for increasing our diagnostic abilities and our understanding of the pathophysiology of this disease.

4. Selected Examples of SCOR Contributions and Research Themes in Osteoporosis

Four SCOR in Osteoporosis have been supported since the initiation of the NIAMs SCOR program. The duration of support ranged from 5-16 years. The research emphasis of these scores focused on critical areas in the field of osteoporosis, emphasizing those in which translational studies from the laboratory to the clinic seemed particularly likely to be developed. A major area of emphasis has been studies on the effect of parathyroid hormone (PTH) on bone, with the goal of using this hormone to restore bone mass in osteoporosis. The interactions between PTH, which stimulates bone formation, and antiresorptives such as estrogen and bisphosphonates, which inhibit bone resorption, have been examined both in animal models and in patients. These studies set the stage for the development of intermittent low dose PTH therapy in osteoporosis, which has now been approved by the FDA, and for an analysis of the use of PTH in the various clinical contexts encountered in osteoporosis.

Other critical areas in bone biology that were studied extensively in the SCOR program included an analysis of the role of calcium, in terms of its availability, absorption and efficacy in preventing bone loss. The importance of mechanical

forces in maintaining the skeleton was examined both in vitro using applied electric fields and in clinical studies of exercise effects on bone.

The Directors of the SCOR programs emphasized that this support not only enhanced their overall research programs but also led to the development of interactive faculty groups who could then attack new and exciting problems. The SCOR Directors cited not only new interactions between basic and clinical investigators, but also interactions within the clinical and basic groups themselves as a major benefit of the SCOR program. For example the discovery of a new gene which regulated bone mass came out of the interaction among clinicians, molecular biologist and geneticists which was made possible by having a SCOR program. The program helped both in bringing established investigators into this research area and recruiting and training young investigators new to the field of osteoporosis, who could bring their specific laboratory and/or clinical skills to bear on the problem. However, it was also pointed out that the budget limits of the SCOR program sometimes made it difficult to bring in established investigators or even new investigators because the funding was not sufficient for the programs that they wished to conduct. A clear benefit of the SCOR was the potential for building infrastructure in research that could be used by both the SCOR investigators and others at the institution. One limitation of this approach was the need to develop sustainable infrastructure in the setting of relatively short-term grant support.

5. Selected Examples of SCOR Contributions and Research Themes in Lupus

Five SCOR in systemic lupus erythematosus (lupus) have been supported by NIAMS since initiation of the SCOR program. Overall, the SCOR included a strong mix of studies in both human lupus and mouse models of the disease, although projects within individual SCOR were frequently devoted to mouse or human disease rather than a mix of both. Many different aspects of mechanisms of disease were investigated by the lupus SCOR. Two of the SCOR focused almost entirely on studies of the genetic basis of disease, one in human lupus and the other in mouse models. In addition, studies of genetic contributions were included in most of the SCOR. Other major themes included the events involved in the induction and evolution of autoantibody production, the role of particular autoantibody specificities in different disease manifestations, the role of defective apoptosis in the pathogenesis of disease, and studies of B cell dysfunction and tolerance.

Overall, the SCOR in lupus were involved in the initiation of a number of important studies, and they frequently led to additional major research funding. The SCOR directors also pointed out that a number of meaningful interactions between basic scientists, researchers from other fields, and lupus-oriented scientists were initiated as part of their SCOR and may not have occurred without support of the SCOR. It was emphasized that the SCOR provided a mechanism to attract researchers from other disease fields into lupus research. One example included an investigator focusing on thrombosis related to anti-phospholipid antibodies and collaboration with an investigator studying the pathogenesis of atherosclerotic vascular disease. The

involvement of inflammation in these processes was a common mechanism and has led to new funded programs investigating the increased frequency of atherosclerotic vascular disease in lupus patients as well as mechanisms of anti-phospholipid antibody induced thrombosis and pregnancy loss. The involvement of complement activation in anti-phospholipid antibody disease has led to complement inhibition as a possible new therapeutic strategy. Among the SCOR, new interactions occurred with experts in mouse genetic manipulation, estrogen-receptor biology, and researchers previously only studying the genetic basis of type 1 diabetes and other autoimmune endocrine diseases. The SCOR mechanism was instrumental in initiating studies in unique mouse models of lupus and genetic analyses to understand the progression of lupus nephritis from acute inflammatory disease to more chronic scarring forms. In addition, the SCOR helped initiate long-term studies of the evolution of autoantibody production, including the period before the onset of clinical disease. Overall, all of the responding SCOR directors valued the disease-specific SCOR funding mechanism. They emphasized that the SCOR broadened the expertise of investigators interested in lupus and promoted collaborations between lupus investigators and investigators in other fields. They also noted that long-term funding was one of the keys to continued development of programs and the likelihood of translation to the clinical situation. It was also felt that higher budget amounts would be key for SCOR to attract the best scientists and most important projects.

B. Survey Respondents' Support for the Disease Focus of SCOR

The majority of the Survey respondents were in favor of keeping the disease focus of SCOR. Only one respondent thought that the disease focus, although "useful," was not necessary. Respondents in general thought the disease focus very important, even "essential," as the common ground for uniting the basic scientists and the clinical researchers as to the goal for their collaborative research and regularly scheduled interactions. One respondent related that although his SCOR had primarily studies of processes, including some that were generalizable across diseases, it was still important that all of the studies were linked to at least one specific disease. One Respondent pointed out that the disease focus is necessary to a goal of translational research where the goal is new clinical knowledge of the disease not the disease processes *per se*.

C. Survey Respondents' Views of Distinguishing Features of SCOR as a Funding Mechanism

The Respondents clearly identified the SCOR mechanism as unique because of its overall requirement of inclusion of basic science and clinical research projects. They pointed out that R01's are isolated projects and that the other Program Project mechanisms are entirely basic science. They were overwhelming in support of this basic/clinical project requirement and cited numerous benefits resulting from the interactions of the scientists from disparate backgrounds in the development of

designs and view of knowledge developed; they indicated the positive impact of the mutual learning experiences for all scientists involved in the SCOR. One Respondent indicated that the clinical studies informed the basic ones as well as the reverse direction.

Respondents noted that the combination of the structure of the SCOR Program and the disease focus created a sense of unity of purpose that transcended the usual research divisions at their institution as well as the existing informal linkages of basic to basic scientist and clinical to clinical scientist. They elaborated that the SCOR created new linkages of basic, applied, and clinical researchers that would not have happened otherwise, since the researchers were already present at the recipient institution and yet they had not sought each out for collaboration on a common topic before the introduction of the SCOR Program.

In general, Respondents liked the SCOR Cores. The Methodological/Service cores were cited as a major means of resource distribution and sharing across the separate research projects as well as a source of quality control and standardization of data. The Respondents noted that this would not occur with separate R01's and that the other Program Project mechanisms would not provide for sharing of techniques and methods across basic and clinical research projects.

The Respondents identified the Administrative Core as very important to maintaining the interactions of the various SCOR scientists and the unity of goals for the research. They cited SCOR as responsible for continued and productive collaborations and coordination among the basic and clinical scientists and felt that without the SCOR Program these would not have occurred at their institution.

D. Survey Respondent's Views of the Impact of SCOR on the Function and Organizational Structure of the Home Institution

In addition to the contributions of the SCOR grants to scientific knowledge, many of the directors of current or former SCOR grants noted a variety of positive effects on the institutional research culture. Of the 14 directors (out of 20) who responded to the committee's request for information, 10 reported marked increases in collaborative research between basic scientists and clinical researchers. Such collaborations brought state of the art methodologies to both sides, and also increased awareness of the problems, issues, and difficulties that each group of scientists faced. The directors noted that important factors in generating this increased collaboration were the regular weekly meetings involving all of the SCOR investigators, as well as the focus on the pathogenesis of a single disease entity. In many cases the increased collaborations were across departmental lines and involved true multidisciplinary collaborations. Thus, the SCOR grants could definitely be said to have broken down at least some institutional silos. Additionally, 4 directors mentioned that the SCOR led to collaborations with investigators at other institutions, broadening the reach of this grant mechanism.

Interestingly, of the 10 directors reporting increased collaborations between basic and clinical scientists, 9 reported the generation or enhancement of translational research. Those that did not observe basic/clinical collaborations did not report enhanced translational research. The translational research reported included identification of promising new interventions, promising new diagnostic tools, and early stage clinical trials to evaluate the new interventions and diagnostics.

Another positive institutional effect reported by 8 directors was that SCOR research produced novel discoveries, observations and leads that generated new "spin-off" research funding for SCOR investigators. The majority of such funding was for individual investigator initiated grants (e.g., NIH R01 funding), but there were several examples of newly funded program grants, training grants, and even a subsequent SCOR grant in another disease. These latter types of grants emphasize the value of the multidisciplinary basic/clinical collaborative research fostered by the SCOR.

Four directors indicated that the SCOR grant and its resultant multidisciplinary group of interactive and collaborative investigators contributed to their ability to recruit additional outstanding scientists. Two directors noted that diseases registries were established as a result of SCOR funding and the interests and needs of a group of investigators targeting that disease.

One particularly interesting institutional outcome was the recognition by the host institution of the value of a large group of talented, successful and interactive investigators. The institution provided support to coalesce the SCOR investigators and related scientists into an Institute to both enhance the intellectual environment to promote discovery and to serve as a vehicle for new philanthropy. The latter resulted in the purchase of expensive state of the art technology and in the establishment of endowed professorships specifically for research in the area of the SCOR. Thus the SCOR investigators were able to dramatically leverage their SCOR support to the benefit of both science and the institution.

Although difficult to quantify from the information provided, it is the Committee's impression that the greater the duration of SCOR funding, the more profound are the effects on the institutional culture. For example, in the case where the SCOR investigators were able to dramatically leverage their support from the host institution, the SCOR is in its 4th funding cycle.

It is important to note that the effects of a SCOR grant on an institution persist even after the grant ends. Several directors of SCOR that had ended noted that the collaborations that were established during the funding period continued, multidisciplinary interactions continued, translational research continued, and new funding was obtained to carry on the work begun during the SCOR funding period.

E. Survey Respondents' Recommended Changes to SCOR

The Respondents were very thoughtful in their evaluation of and recommendations for SCOR. The majority thought that the SCOR combination of basic and clinical research should be preserved but had mixed views as to its appropriateness for translational research as an outcome. The SCOR Program did not have translation as its primary goal, but rather the combination of basic and clinical research on a common disease focus. The Respondents cited the period of 5 years of funding as a possible problem in that the time required for translation of basic to clinical may vary between disease foci, depending on the state of readiness in each disease field, and will probably be longer than the current period of one SCOR grant cycle. They emphasized that time is needed for translation and that any mechanism for translational research needs to plan for sustained funding for periods longer than 5 years.

The Respondents also cited the low funding cap ($750,000) as a major limitation to both attracting the best scientists and for adequately funding the projects. They felt that the individual projects were under-funded compared to R01's. The Respondents' cited the funding cap as a major factor contributing to the decline in the number of SCOR applications over time and in the failure to attract additional talented scientists as applicants to the Program.

Some of the Respondents suggested that more flexibility be added to the SCOR mechanism, particularly in the form of internal SCOR Program funding of pilot projects and high-risk spin-off projects. It was suggested that this might be a means of stimulating the translational aspects of the research. A few Respondents suggested making the individual SCOR projects portable should an investigator leave; but this was countered by the common view that the on-site interactions and use of the Cores were essential to the accomplishments of the SCOR Program. The Committee felt that the loss of either the basic science or the clinical project from the site would undo what the majority of the Respondents considers the most essential characteristic of the SCOR Program.

The Respondents were adamant that the review process/mechanism for the SCOR applications needed to be improved. They felt that the individual projects were all, including the clinical projects, evaluated as basic science R01's with too little credit given to the overall resources, track record, and synergistic mechanisms. Some went on to say that the review was harsher than that for an R01 in that some of the projects from unfunded SCOR were subsequently deemed highly meritorious and funded as individual R01's. They suggested a new approach be developed for evaluating the programmatic strengths of each SCOR beyond the evaluation of the component science projects. Another suggestion was to require that the SCOR component projects already be funded by an R01 as a requirement for application.

CHAPTER 5: Translation of Knowledge and Translational Research

A. Overview

The charge to the Committee was to evaluate the SCOR Program in terms of its relevance and applicability to emerging translational paradigms and to make recommendations for funding translational research relevant to the goals of NIAMS. It was quickly determined that there are no generally agreed upon definitions of the terms translation and translational research. In addition there were very few models of translation available in the literature (Sung et al. 2003) and papers published varied on the topic as to the types of activities included and as to the end products of the translation (Sung et al. 2003; Nathan& Wilson 2003; Rosenberg 2003). The Committee did find general consistency in the meanings and use of the following terms: basic research (pure, without constraint of practical application), applied research (addressing a practical aim), clinical research (applied, directly involving living human subjects), and scientific research (employing scientific methodology).

B. Definition of Terms

The Committee used the following definitions:

1.*Translation*

Translation is the process of transforming scientific knowledge from its form in the context of basic science to a form relevant to human health and disease.
The product of translation is new knowledge that can be used by clinicians, policy makers, practitioners and the lay public. The definition of translation presented by Sung et al.(2003) also includes products beyond knowledge, such as implementation in health care practice and policy. The mechanisms for implementation of translation are sociopolitical and not necessarily those of research. The Committee adhered to translation defined solely as knowledge generation and knowledge transformation, because only this definition requires research as the mechanism for translation. In order to distinguish its definition of translation as a research process with knowledge as the product from other definitions in the literature, the Committee adopted the term *research translation*. The Committee did agree with Sung et al. (2003) that the ultimate and orienting, or directional, goal for translation is improved human health.

2. *Research Translation*

Research Translation is the process of transforming knowledge through research toward the goal of generating knowledge that can serve as the basis for improved human health. The Committee viewed human health very broadly including diagnosis, treatment, and cure of disease and disability; management of manifestations of disease and disability; prevention of disease and disability; and human quality of life. The Committee delineated the broadest possible scope of human health, in terms of individual and societal health, rather than use the more limited view of “bench to bedside” and clinical care in order to allow for the greatest breadth of research translation. From this perspective of human health, the lay

public and advocacy groups are stakeholders in research translation along with health care practitioners and policy makers.

3. *Translational Research*

Translational research is applied and clinical scientific research that is directed towards testing the validity and limits of applicability of knowledge derived from basic science and engineering to the understanding of human disease and health. It could be research involving living human subjects (i.e., clinical) but it might also be nonclinical involving the study of human genes, tissues, specimens, or cells. Thus, although it is directed towards generation of knowledge about humans, it could be nonclinical or clinical research. Others (Sung 2003; Nathan & Wilson 2003) have defined translational research only as a subset of clinical research, thus requiring the study of living human subjects. The Committee could identify many nonclinical, applied research projects that would serve as a translational bridge from basic to clinical research and thus chose not to restrict translational research to the definition of clinical research. Translational research is a type of research necessary for research translation.

4. *Directed Basic Research*

Directed basic research is an extension of basic research that develops or adapts methods and knowledge for use in translational research. This type of research derives directly from ongoing basic science, but is not intended to develop the basic science; rather, the basic scientist is asked to participate in readying the knowledge and techniques for translational research. Although this is technically a type of applied research, the Committee created the term *directed basic research* to clearly identify that this type of research is conducted by a basic scientist, in collaboration with applied and clinical researchers, and that this research is directly relevant to the clinical research. The purpose of directed basic research is to inform the clinical research. Thus, the goal of this research is preparing the basic science knowledge into a form that can be used in applied human and clinical research. An example of a directed basic science project in a muscle disease-focused program would be basic studies of imaging that might ultimately result in techniques that are adapted to diagnosing muscle disease at the molecular level in the living human.

C. Proposed Model of Research Translation

The Committee discussed research translation as a continuum of research directed towards generating clinical knowledge to be used as the basis for diagnosis, prevention, and treatment of disease and ultimately improved human health. NIAMS does not fund large clinical trials and so the translation is from basic science into clinical science and clinical methods. The Committee identified a disease focus as essential for effective research translation. If disease is not the organizing theme, then the translation is unlikely to be into disease-relevant knowledge.

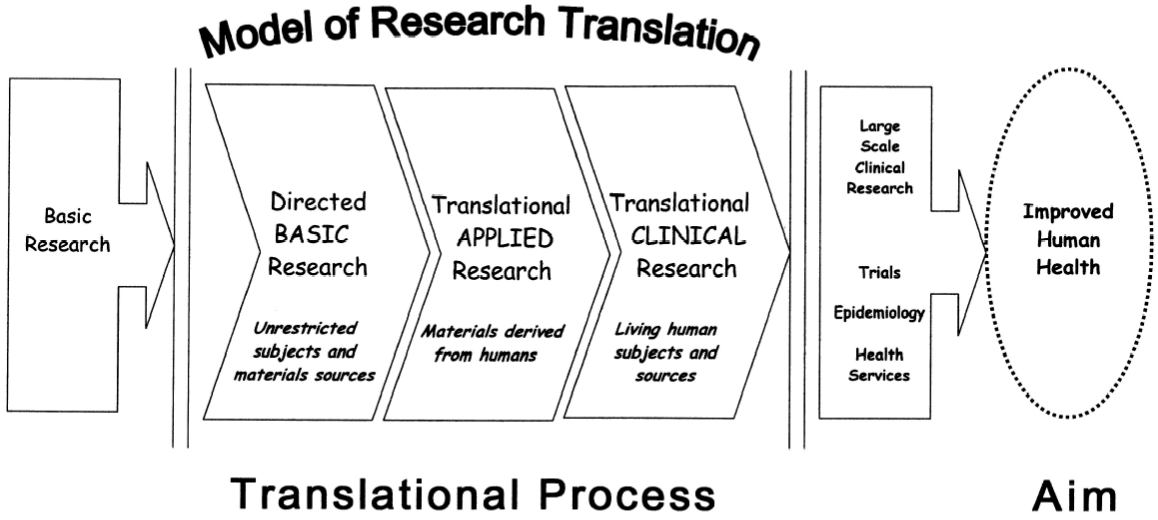


Figure 1

The Committee developed a model (Figure 1) for research translation, derived in part from the model of Sung et al. (2003); this model was developed to reflect the nature and scope of research supported by NIAMS. The model in Figure 1 is the basis for many of the Recommendations in Chapter 7. Figure 1 illustrates both the types of the research and the direction of knowledge translation. Basic research is included in a box to the left because it is the origin of directed basic research; however, a double line separates it from the translational process. The Committee acknowledges the importance of basic research as a source of new knowledge and new paradigms, but does not see the advancement of basic research as a goal of research translation. Similarly, on the far right side of Figure 1 a box for large scale clinical research is the directional recipient of the translated knowledge and logically might be included in a translational process; however, because the model is tailored to NIAMS, which does not fund large scale clinical research, this box is placed outside of the core of research translation in the model. The core of the translational process is shown as a progression of separate research projects, conducted by basic and clinical researchers coordinated though collaborations toward a common goal of human health. The Committee decided that the types of research representing the translational process are directed basic, applied human, and clinical research; it included applied research as separate from clinical research to emphasize that there is likely to be a translational step between directed basic and clinical research involving living human subjects. At a minimum the model of research translation requires a directed basic science project and a clinical research project. The progression of research and knowledge from left to right is a key feature of the model. The Committee recognizes that knowledge sharing in collaborative research

is bi-directional but asserts that the goal of translation is uni-directional from basic to clinical. The societal goal of the translational process is shown to the far right as improved human health.

The Committee considered several models for research translation, including one in which the core of the translational process included only applied human and clinical research. However, this model was based upon the assumption that the basic knowledge already exists and that the clinical researchers are able to access this knowledge independent of collaborating basic scientists. One identified limitation of this model is that basic science knowledge might not exist in an equally translatable form across diseases; this might limit translation for some diseases. A second identified limitation is the documented barrier that clinical researchers encounter in attempting to independently access and use basic science knowledge. Basic scientists experience equivalent difficulty in attempting to access and understand clinical knowledge. The form and organization of knowledge in the basic sciences is distinct from those of the clinical sciences. The basic sciences and the clinical sciences have distinct research paradigms, conceptualizations, methods, and terminology that imprint their respective research studies and the knowledge generated by them. Unless researchers are fluent in both the basic and clinical sciences, they will need collaborators for successful translation of knowledge. The SCOR Committee agreed that translational research was likely to be most successful in the context of a team of researchers that includes basic and clinical researchers.

D. References

Nathan, DG, & Wilson, JD. 2003. "Clinical Research and the NIH—A Report Card," *N Eng J Med.* 39 (19): 1860-1864.

Rosenberg, RN. 2003. "Translating Biomedical Research to the Bedside," *JAMA*. 289 (10): 1305-1306.

Sung, NS, et al. 2003. "Central Challenges Facing the National Clinical Research Enterprise," *JAMA.* 289 (10): 1278-1287.

CHAPTER 6: Leadership Role for NIAMS in Research Translation

The Committee discussed a future role for NIAMS in the context of the NIH Roadmap. The Road Map includes, as a major theme, the re-engineering of the clinical research enterprise to facilitate the translation of basic research knowledge and discoveries into clinical advances in the diagnosis, treatment, and prevention of disease. The Committee agrees that NIAMS is well poised for continuing its leadership role in the development of research translation. *The SCOR Committee recommends that NIAMS continue to directly fund its diverse portfolio of basic, applied, and clinical research, while adding funding mechanisms for translation.* NIAMS is encouraged to participate in creating NIH resources for the centralized

support and coordination of clinical research, and also to continue to develop its own research portfolio in clinical research. The rationale for maintaining a diverse and strong research portfolio within the Institute is that the diseases addressed by NIAMS are likely to be of high priority particularly within NIAMS. NIAMS is also encouraged by the SCOR Committee to continue funding critical research that will not be supported by industry or other agencies.

NIAMS has already created new funding mechanisms and partnerships/teams for translational research, such as the U54 Muscular Dystrophy Centers. The SCOR Committee discussed the leadership role of NIAMS in research translation in the context of NIAMS' historical support of basic and clinical research focused on specific diseases. When viewed in this context, the NIAMS SCOR Program represents a significant initial model in the development of research translation, because the SCOR Program established a mechanism for bringing together new teams of basic and clinical scientists who focused their research on a common disease theme.

The SCOR basic-clinical researcher teams used their separate but related research studies to translate knowledge between the two science realms and to teach each other how to access and use their separate bodies of knowledge. The clinical and basic scientist partnership and pairing of basic and clinical research projects of SCOR should be preserved in at least one funding mechanism because this partnership created a synergy that must be present for research translation.

In addition, the Committee felt that NIAMS should develop a portfolio of research translation funding mechanisms that represent different approaches. The planned NIH initiative for re-engineering the clinical research enterprise to enhance translation is in itself a discovery process. The Committee's recommendation of a centers of research translation mechanism, that is based upon pairing of basic and clinical research projects in a program of investigator- initiated and directed research, is only one form of research translation that NIAMS might add to its portfolio. Different diseases might require different translation mechanisms.

The Committee also felt that continuing lay and advocacy group partnerships would benefit the translational process and provide new resources for and insights about the diseases of interest. These partnerships would facilitate the communication of advances and new knowledge to the lay constituents of NIAMS and clarify the long term health goals that are of highest priority to the recipients of health care. The Committee agreed that NIAMS could offer exceptional leadership in pioneering this type of lay and advocacy partnership as an integral part of a translational funding mechanism.

CHAPTER 7: Conclusions and Recommendations of the Committee

A. Overview

The recommendations all relate to Dr. Steve Katz's charge to the Committee to review the SCOR Program as a mechanism for future advancement of translational research and to propose a new mechanism if appropriate. The Committee considered the options in the context of NIAMS priorities and the NIH Roadmap. Also factored in were the dramatic changes in the expectations of the NIH as to research that contributes to improved health of the public, defined in part by persons affected by disease, and the participation of lay and advocacy group representatives in the research enterprise. These expectations must be addressed in any successful mechanism for translation in addition to the expectation of the generation of new research knowledge for prevention or treatment of disease. The re-directing of the NIAMS research enterprise towards translation is ultimately intended to facilitate and accelerate the benefits to society, in terms of improved quality of life as well as improved health status. The Committee used a very broad view of health of the public that encompasses all types of translation, products, and outcomes as the basis for developing a Model of Research Translation (Figure 1, Chapter 5). This Model of research delineates the scope of research translation for NIAMS within the larger context of translation from basic science to improved health of the public. The adequacy of SCOR was considered in the context of this Model as was that of possible new mechanisms.

In its consideration of SCOR as a part of the future direction of NIAMS, the Committee evaluated the history and current status of NIAMS SCOR as well as abstracts of funded SCOR, and responses to a Survey sent by the Committee to current and former SCOR Directors. The Committee also reviewed information about other center mechanisms funded within the NIH and NIAMS that include clinical research and research translation as priorities.

B. Committee Evaluation of SCOR

The NIAMS SCOR Program has set the stage for future research translation in that SCOR developed new mechanisms for synergistic and productive interactions between basic and clinical researchers. SCOR brought together scientists who would not have otherwise interacted, breaking down silos; SCOR attracted scientists beyond the PIs of the projects it funded; and SCOR was able to make positive and long-lasting changes in the research culture of the home institution. The SCOR Administrative Core and Scientific Cores were absolutely essential to the establishment and maintenance of these desirable changes in scientific interactions, research teams, and institutional culture. Another important lesson learned from SCOR is that the disease focus is critical to unifying the goals of basic and clinical researchers. These elements of the SCOR Program need to be incorporated into future center mechanisms directed towards research translation.

Despite these positive attributes of SCOR, the Committee felt that retaining or changing the SCOR Program is not the best approach to establishing a funding mechanism for research translation within NIAMS. The Committee noted that, although some transformation of basic to clinical knowledge and research did occur in SCOR, translation was not the predominant contribution of SCOR. While the Committee concurs that a single five year round of funding may not be long enough for translation, translation did not emerge as a significant theme even for SCOR that were funded for more that one cycle. This is understandable in that SCOR did not have translation as its stated aim. But the experience with SCOR demonstrates that having the critical elements in place for the translation process is not sufficient for translation to emerge as the major theme. The Committee agreed that specific and overriding goals for translation are essential to the realization of basic to clinical research translation as the dominant outcome. SCOR has a distinct and well known identity that has been established and honed over many years; the Committee decided that it would be very difficult to transform this identity into one that reflects research translation as the priority. Also, since SCOR has lost some of its appeal for many reasons, including low funding caps, it was determined that it would be difficult to use SCOR as the mechanism to attract scientists to a new goal of translation. Thus, the Committee considered options that are alternatives to SCOR to meet the future needs of NIAMS.

C. Proposed Center for Research Translation (CORT)

1. *CORT Structural Framework*

In considering the future direction of NIAMS in translational research and the process of research translation, the Committee determined that a mechanism of centers of excellence was the best approach. The Committee recommends that the proposals for this type of center be solicited through Requests for Applications in targeted areas and developed using the new model for these Centers.

The Committee developed the framework for a new translation-focused center mechanism: the Center of Research Translation (CORT). The proposed CORT is grounded in the Committee's conceptual model (Figure1, Chapter 5) and re-creates elements from SCOR that are relevant to the translation process, such as the combination of basic and clinical researchers and projects focused on a common disease theme, scientific cores, and the coordinating functions of an administrative core. Two major features distinguish CORT from SCOR: 1) the overarching aim of disease-specific research translation from basic to clinical, and 2) the inclusion of resources and a new administrative structure to facilitate research translation. CORT is designed to create a center of research excellence that brings together resources and individuals in an administrative structure that facilitates disease-specific research translation. The resources are research (i.e., scientific projects and scientific cores), as well as administrative. In addition to a central Administrative Unit, CORT includes in its administrative structure both a Scientific Advisory Group (SAG) and a

Translation Advisory Group (TAG), each charged with oversight, coordination, and communication. SAG's role is related to rigor, conduct of the research, and scientific interactions and TAG's role is related to translational progress, innovative approaches, lay/advocacy group participation, and new outside partnerships. Thus the role of TAG is completely new and TAG members should include lay persons and representatives from advocacy organizations as the primary members along with health care professionals, scientists, and industry representatives who share an interest in the specific disease and translation related to it.

The organizational framework of the CORT is depicted in Figure 2.

PROPOSED CENTER OF RESEARCH TRANSLATION (CORT)

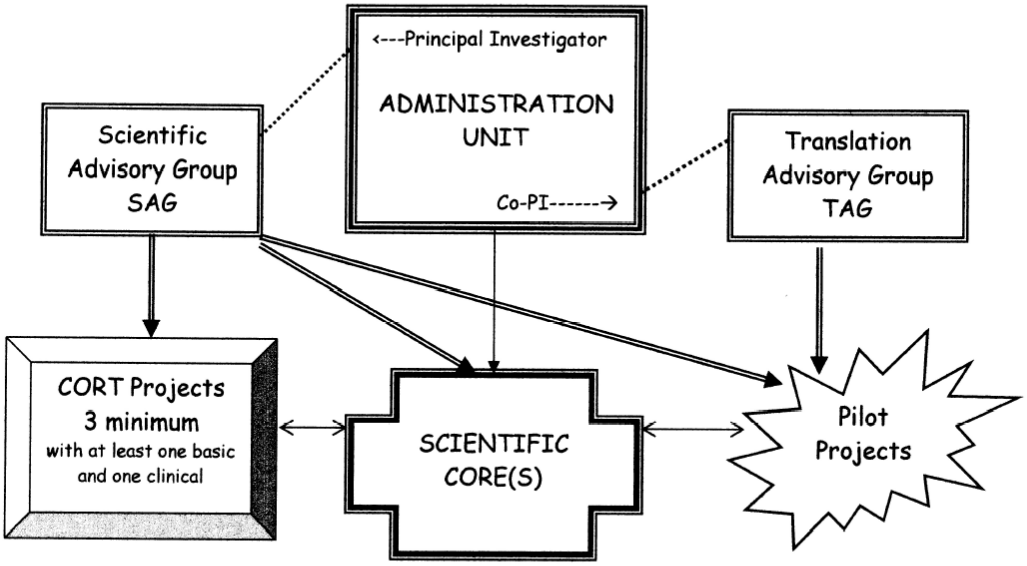


Figure 2

CORT has a centralized Administration Unit. There are two Advisory Groups: 1) Scientific Advisory Group (SAG) and 2) Translation Advisory Group (TAG). There are three research units: 1) CORT Projects, 2) Scientific Core(s), and 3) Pilot Projects.

2. Administration Unit

The Administration Unit is led by the CORT PI as Center Director. The Administration Unit is the core of the organizational structure and responsible for

oversight and coordination of all aspects of CORT, including the co-ordination of the roles of SAG and TAG.

3. *Scientific Advisory Group (SAG)*

SAG has as its membership senior scientists from within and outside the institution; the PI of CORT is the primary liaison to SAG and meets with them at least annually. SAG provides scientific oversight for all active research studies, including CORT Projects and Pilot Projects. Although SAG has primary responsibility for deciding the acceptability of proposed Pilot Projects in terms of scientific merit, SAG does not make the final selection as to which pilots are to be funded.

4. *Translation Advisory Group (TAG)*

The selection of Pilot Projects for CORT funding, from among those deemed scientifically meritorious by SAG, is the responsibility of the TAG. TAG will look for the most cogent translational issues presented in the proposed pilot projects and make the final choice of those to be funded as Pilot Projects. TAG is charged with facilitating the translational process in general, including communication with lay public and advocacy group constituents; creation of partnerships with outside organizations and agencies; and generation of supplemental resources. TAG can address translation beyond the confines of mechanism of the disease and its prevention and treatment and into the realm of ameliorating the negative impact of the disease on the lives of those affected by it. TAG has lay members who are knowledgeable and committed to translation of knowledge to benefit persons affected by the disease of the particular CORT. The co-PI of CORT serves as the primary liaison to TAG, which meets at a minimum annually. In addition to their separate meetings, SAG and TAG have one joint annual meeting with all CORT participants to discuss the progress of the science as well as the progress of the translation.

The Committee created TAG as an essential component of CORT for three major reasons. First, the Committee determined that the goal of translation is new and the mechanisms that facilitate it are in a discovery stage; TAG is needed to pioneer this effort and to keep it on track in the midst of a scientific endeavor that is likely to be attracted to developing primarily basic science knowledge. Second, each CORT needs to be continuously informed of the lay perceptions of the meaning of improved health relative to the specific disease, in order assure that translation can occur beyond the realm of traditional medical care; members who represent persons affected by the disease are needed as members of TAG. There may be particular aspects of a disease that diminish quality of life of persons affected that could be ameliorated independently from the treatment or cure of the pathology. Examples are physical exercise for amelioration of pain and decreased mobility in persons with arthritis and management of debilitating symptoms (i.e., pain, fatigue) in fibromyalgia. Third, TAG is needed to create partnerships and liaisons with individuals, agencies, and groups that are beyond the usual research circles; the members of TAG must be connected to these groups.

5. *CORT Projects*

The Committee recommends that each CORT have at least three separate funded research projects linked to a common disease focus. Referring to the Model of Research Translation in Figure 1 (Chapter 5), at least one of these projects should be directed basic science and at least one should be clinical research. This will assure that at least one basic scientist and one clinical researcher are coordinating their research and creating the vehicle for the translation of basic science into clinical research and knowledge.

6. *Scientific Cores*

The Scientific Cores are intended to provide centralized services (e.g., assays, analysis, and data repositories) for the CORT Projects and the Pilot Projects to enhance the quality and the progress of the research. The Scientific Cores can also be a source of technique innovation. Based upon the experience of SCOR, the Committee viewed the Scientific Cores as assets that can be used to attract additional researchers (funded by other mechanisms) to CORT.

7. *Pilot Projects*

The Pilot Projects are an essential component of CORT in that they are intended as the means to allow faster reaction to new ideas, testing of hypotheses that are risky, and gathering of pilot data for submission of a larger proposal to an external funding source. The Committee views this mechanism as critical to the facilitation of basic to clinical translation and building of the research infrastructure for research translation. This mechanism is intended in part to make CORT a starting point for translational researchers of the future.

C. Recommendations of the Committee

1. Discontinue NIAMS SCOR at the end of its Current Funding Cycle.

The Committee recommends funding through the full award period of currently funded SCOR.

2. Create a new research center mechanism specifically for translation and consistent with CORT.

The organizational structure and functional components of CORT are proposed as the means for moving forward with research translation within the scope of funding opportunities of NIAMS. CORT offers the opportunity of engaging persons other than scientists and clinicians, including lay and advocacy group representatives, in the translation process.

2a. Institute 5 year award periods for CORT with competitive review criteria that take into account progress in the direction of translation.

The Committee agreed that the time period needed for significant translation manifested as improved health is likely to be longer than 5 years. Thus, interim goals indicating directional progress (i.e., basic knowledge into clinical) in research translation should be used as the basis for renewals of CORT awards for additional funding cycles.

2b. Create a mechanism for sharing translational progress across funded CORTs and adaptation of CORT over time.

Since a directed effort towards research translation is new, CORT should be viewed as a pioneering effort that will need revision over time to achieve the desired outcomes. Sharing among CORT PIs will allow the most effective approaches and mechanisms to be incorporated over time. The Committee also viewed the gathering of CORT PIs at least annually as a means of creating translational synergy that parallels the basic-clinical synergy of the scientific interactions.

2c. Create flexibility in the implementation of the CORT Translational Advisory Group.

In its discussions, the Committee considered how TAG might be created and came to the conclusion that it might not be wise to fully engage outside partners until a CORT is actually funded. It is recommended that CORT applications be reviewed with a plan for constituting TAG with letters of agreement to be obtained after the CORT is funded. However, the plan for TAG in the proposal should be fully formulated including goals, methods, and short and long-term measurable outcomes. It is expected that TAG members will be put in place quickly since the CORT cannot fund any Pilot Projects until this advisory group is in place (see 2d).

2d. Provide adequate funding for CORT.

The funding level for SCOR would be inadequate for CORT, especially in view of the expanded structure, functions, and translational aims of CORT. The Committee recommends a minimum of $1.0 million for each CORT to cover all aspects CORT except funding of the Pilot Projects. Each CORT should be eligible for an additional $200,000 per grant year to internally fund Pilot Projects at a level of $50K each per year for up to two years per pilot. These Pilot Projects are screened for scientific merit by SAG and selected for funding by TAG. TAG must be fully implemented before the CORT becomes eligible to fund Pilot Projects.

2e. Create a special review process for CORT that weights the quality of the overall translational plan as the highest priority, recognizing that research projects must be scientifically sound.

The Committee recommends that the group constituted to review CORT, or any other type of application for research translation funding, be given careful instructions as to their determination of scientific merit of the CORT Projects. Traditionally, reviewers factor in contribution to a particular field of science as a part of their merit score. While this is appropriate for R01 type applications, it needs to be adjusted for CORT. The scientific review for CORT is recommended to be limited to feasibility and rigor of each CORT Project; the value of the contribution of each proposed project to the overall aim of research translation should be substituted for contribution to an area of science. CORT applications need to be evaluated as to the combination of research projects, scientific cores, advisory groups, and administration as the means for achieving specific aims for research translation. Each CORT proposal should include translational aims and methods for achieving them in addition to the specific aims for each component research project and the scientific cores.

2f. Foster partnerships between CORT and lay/advocacy groups and foundations invested in the disease-specific translation.

The Committee encourages NIAMS to assist funded CORTS to engage in partnerships with interested lay/advocacy groups for the purposes of broadening the perspective of improved health of persons affected by the disease and generating additional resources for translation.

APPENDICES

A --- NIAMS SCOR Program Review Committee Roster

B --- Biographical Sketches of Committee Members

C --- Agendas of the SCOR Review Meetings

D --- Budget History of SCOR

E --- Table 1: History of SCOR Applications by Disease

F --- Chart 1: Total Number of Active NIAMS SCOR Programs

G --- Chart 2: Applications for NIAMS SCOR in Rheumatoid Arthritis (RA)

H --- Chart 3: Applications for NIAMS SCOR in Osteoarthritis (OA)

I --- Chart 4: Applications for NIAMS SCOR in Osteoporosis (OP)

J --- Chart 5: Applications for NIAMS SCOR in Lupus (SLE)

K --- Chart 6: Applications for NIAMS SCOR in Scleroderma (SSc)

L --- Chart 7: History of SCOR Applications by Year, Disease

APPENDIX A

NIAMS SCOR PROGRAM REVIEW COMMITTEE ROSTER

PEGGY CROW, M.D.
Professor of Medicine
Hospital for Special Surgery
New York, New York

HOWARD B. DICKLER, M.D.
Senior Associate Dean for Research and Graduate
Studies and Professor of Medicine
University of Maryland School of Medicine

SUE K.DONALDSON, Ph.D. (Chair)
Professor of Physiology and Nursing
School of Nursing
The Johns Hopkins University

THOMAS A. EINHORN, M.D.
Chairman and Professor
Department of Orthopaedic Surgery
Boston University Medical Center

BRIAN L. KOTZIN, M.D.
Professor of Medicine and Immunology
University of Colorado Health Sciences Center

LAWRENCE G. RAISZ, M.D.
Professor of Medicine
Director, UConn Center for Osteoporosis
University of Connecticut Health Center

JOHN R. STANLEY, M.D.
Milton B. Hartzell Professor
Department of Dermatology
University of Pennsylvania

SHARON F. TERRY, M.A.
Executive Director of PXE International, and
President of the Genetic Alliance
Washington, DC

NIAMS Staff Who Assisted the Committee:

Steven J. Hausman, Ph.D., Deputy Director
Cheryl Kitt, Ph.D., Director of the Extramural Programs
Julia Freeman, Ph.D. Centers Program Director
Helen M. Simon, M.S., Chief of Program Planning

APPENDIX B

BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS

MARY K. CROW, M.D.

Dr. Crow is Professor of Medicine at Weill Medical College of Cornell University and Senior Scientist and Director of Rheumatology Research at Hospital for Special Surgery in New York City. She also directs the Immunology Program in the Graduate School of Biomedical Science at Cornell and is Co-Director of the Mary Kirkland Center for Lupus Research. Dr. Crow received her M.D. at Cornell and Internal Medicine and Rheumatology subspecialty training at New York Hospital. She is on the Board of Directors of the American College of Rheumatology and is active in the Arthritis Foundation and The S.L.E. Foundation.

Dr. Crow's earliest research experience was in the laboratory of Dr. Marc Weksler, where she first learned about the spectrum of immunological alterations that characterize patients with systemic lupus erythematosus. While in Dr. Weksler's laboratory, she observed the activation of T lymphocytes by autologous cells and characterized the immunosuppressive T cell function that was generated in the setting of this autologous mixed lymphocyte response. She received further training in the laboratory of Dr. Henry Kunkel at Rockefeller University where she was among the first to characterize and study the functional properties of human dendritic cells.

At Hospital for Special Surgery, Dr. Crow has studied the effects of superantigens on T cell-dependent immune responses; characterized the oligoclonal T cells that comprise the cellular infiltrate in the rheumatoid synovium; studied the functional consequences for B lymphocytes of cognate help from T cells; and demonstrated the altered regulation of CD40 ligand in lupus T cells. Dr. Crow continues to investigate the underlying triggers of autoimmunity in the prototype rheumatic diseases, SLE and rheumatoid arthritis, and the cellular and cytokine mediators of uncontrolled immune system activation in those disorders.

HOWARD B. DICKLER, M.D.

Dr. Dickler received his B.A. from the Johns Hopkins University and his M.D. from the George Washington University School of Medicine where he was first in his class. Following training in internal medicine at the New York Hospital – Cornell Medical Center, he did fellowships in immunology at the Rockefeller University under Henry G. Kunkel and at the National Cancer Institute under William D. Terry. He then joined the Immunology Branch of the National Cancer Institute as a Senior Investigator in 1974. His laboratory focused on the characterization of cell surface molecules on lymphocytes and mononuclear cells, the interactions of these molecules on the cell surface, and their role in regulating the immune response. He has authored 57 peer-reviewed publications.

In 1989 Dr. Dickler was appointed Chief of the Clinical Immunology Branch of the National Institute of Allergy and Infectious Diseases, leading a $90 Million extramural research program where he more than doubled research funding supported by the branch and more than tripled support for set-aside initiatives during a time period when support for NIAID programs other than AIDS grew by less than half. He pioneered multi-Institute cooperative funding of initiatives, developed accelerated review and funding mechanisms, and helped to initiate intervention trials in individuals at risk for developing Insulin Dependent Diabetes Mellitus, patients with systemic vasculitis, and patients with immunodeficiency diseases. Since 1999, Dr. Dickler has been the Associate Dean for Research and Graduate Studies and Professor of Medicine at the University of Maryland School of Medicine. In this position he has primary responsibility for the school's research enterprise, which generated $241.7 Million in research grants and contracts in FY 2002. This represented 50.5% of the School of Medicine budget, and an increase in three years of 75% from the $138.1 Million in funding that was achieved in FY 1999 prior to his arrival. This level of research growth outpaces the increase in the NIH budget during this period, and was achieved without increasing the number of faculty.

As Associate Dean, he is responsible for the Office for Research and Graduate Studies (ORAG); which currently has 10 reporting units: the Human Subjects Protection Program (including the IRBs); the Animal Subjects Protection Program (including the IACUC); Veterinary Resources; the MD/PhD program; the Center for Clinical Trials; the General Clinical Research Center; the Genomics and Biopolymer Core Facility; the Transgenic Core Facility, the Bioinformatics Core Facility, and the Biosafety Level 3 Containment Core. Dr. Dickler reorganized and enhanced the 1st four programs, and he initiated and brought online the latter six programs. His initiatives have secured in excess of $20 Million in NIH funding.

Dr. Dickler is a member of the American Society for Clinical Investigation, has served as a Councilor of the Clinical Immunology Society, is on the Steering Committee of the GRAND group of the American Association of Medical Colleges, and continues to teach medical students and residents as an Attending Physician on the general medicine wards.

SUE KAREN DONALDSON, PhD, RN, FAAN*

Sue K. Donaldson is Professor of Nursing, School of Nursing and Professor of Physiology, School of Medicine, at the Johns Hopkins University, Baltimore, MD (1994-present). She also currently holds a joint appointment in Oncology, School of Medicine and the Johns Hopkins Hospital.

From 1994 to 2001 she was Dean of the School of Nursing, Johns Hopkins University. Dr. Donaldson received BSN (1965) and MSN (1966) degrees from Wayne State University, Detroit, MI and the PhD in Physiology and Biophysics (1973) from University of Washington, Seattle, WA.

Previously, she was a faculty member at the University of Washington, Seattle, WA (1973 – 1978) and Rush University, Chicago, IL (1978- 1984). Dr. Donaldson also was Professor of Physiology, School of Medicine and Professor of Nursing, School of Nursing at the University of Minnesota, Minneapolis, MN (1984 -1994). While at the University of Minnesota she was the Cora Meidl Siehl Chair for Nursing Research and the founding Director of the Center for Long-Term Care of the Elderly.

She serves as a consultant to the National Institutes of Health (NIH), USPHS and to other research organizations and academic institutions. Dr. Donaldson is a pioneer in nursing research and internationally known for her basic science research in cellular skeletal and cardiac muscle physiology. She has held leadership positions in the Biophysical Society and the American Heart Association. In 1992, Dr. Donaldson was inducted as a Fellow in the American Academy of Nursing (*FAAN). Dr. Donaldson was elected to the Institute of Medicine, National Academy of Sciences in 1993. She currently serves as a member of the Special Medical Advisory Group (SMAG), U.S. Department of Veteran's Affairs and was recently a member of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Advisory Council, NIH (1998-2003). Dr. Donaldson is currently the American Academy of Nursing (AAN) representative to the National Coalition for Health Professional Education in Genetics (NCHPEG) and a member of the AAN Expert Panel on Genetics, a group that she chaired 2001-2002. Dr. Donaldson is also currently Chair of the Genetics Committee, Southern Regional Education Board, Council on Collegiate Education in Nursing.

THOMAS A. EINHORN, M.D.

Thomas A. Einhorn, M.D. is Chairman of the Department of Orthopaedic Surgery and Professor of Orthopaedic Surgery and Biochemistry at Boston University School of Medicine.

A graduate of Rutgers University and Cornell Medical College, he completed his internship at the Hospital of the University of Pennsylvania, orthopaedic residency at St. Luke's - Roosevelt Hospital in New York City, and a fellowship at the Hospital for Special Surgery.

His professional interests include research on the repair and regeneration of bone and cartilage, reconstructive surgery of the hip and knee, and the treatment of metabolic bone disease. He has served as Chairman of the Orthopaedics and Musculoskeletal Study Section of the National Institutes of Health, President of the Orthopaedic Research Society, President of the International Society for Fracture Repair and Chairman of both the Committee on Examinations and the Council on Research and Scientific Affairs of the American Academy of Orthopaedic Surgeons. Currently, he serves on the Board of Trustees of the Orthopaedic Research and Education Foundation and the National Osteoporosis Foundation. His awards include the *American British Canadian Traveling Fellowship, Marshall R. Urist Award*, and *Kappa Delta Award* . He is Deputy Editor for Current Concepts Reviews for *The*

Journal of Bone and Joint Surgery, and serves on the Editorial Boards of *The Journal of Bone and Mineral Research* and *Bone*. Since 1997, he has been listed by Woodward/White as one of *The Best Doctors in America.* An author of over 100 scientific articles, his future goals are dedicated to exploring the role of molecular medicine in orthopaedic surgery.

BRIAN L. KOTZIN, M.D.

Brian L. Kotzin is Professor of Medicine and Immunology at the University of Colorado Health Sciences Center (UCHSC) and is Head of the Division of Clinical Immunology in the Department of Medicine. He is an active member of the faculty of the Department of Medicine, Department of Immunology, and Human Medical Genetics Program at UCHSC. He also is Director of the Denver Autoimmunity Center of Excellence. Dr. Kotzin received his M.D. at Stanford University, completed medicine residency at the Beth Israel Hospital in Boston, MA before his subspecialty training in immunology and rheumatology at Stanford University. His research training was in the laboratory of Samuel Strober at Stanford University.

Dr. Kotzin has served on a number of committees relevant to rheumatology, clinical immunology, autoimmunity, and immunology. For example, he has served as chairman of the Immunological Sciences Study Section (NIH), member of the Board of Directors of the American College of Rheumatology (ACR), member of the National Research Committee of the Arthritis Foundation, chairman of the FASEB Conference on Autoimmunity, scientific program chairman for the annual meeting of the American College of Rheumatology, councilor and annual meeting program chairperson for the Clinical Immunology Society (CIS), member and chairman of the American Association of Immunologists (AAI) Clinical Immunology Committee, block (clinical immunology) chairperson for AAI Annual Meetings, section editor for the *Journal of Immunology*, associate Editors for various journals including *Journal of Clinical Investigation* and *Arthritis and Rheumatism*, councilor, secretary-treasurer, and president of the Western Society of Clinical Investigation as well as representative to numerous other organizations, workshops, and meetings related to studies of systemic lupus and other autoimmune diseases. Dr. Kotzin has also been active in the Immune Tolerance Network (ITN) as a member of the Autoimmunity Subcommittee, and recently served as chairman of the Central Steering Committee for the Autoimmunity Centers of Excellence (ACE. Dr. Kotzin has served on many study sections at NIH and has been an ad-hoc member of NIAMS Board of Scientific Counselors and NIAID Council.

Dr. Kotzin's research has been primarily directed to the genetic basis of systemic lupus erythematosus, particularly in animal models of this disease, and the role of T cells in the pathogenesis of human autoimmune diseases. Recent studies in mouse lupus have uncovered interferon-induced genes as major candidate lupus-susceptibility genes. Recently, he has also been active in the design of clinical trials relevant to rheumatoid arthritis and systemic lupus.

LAWRENCE G. RAISZ, M.D.

Dr. Raisz is Professor of Medicine at the University of Connecticut Health Center and Director of the UConn Center for Osteoporosis. He was Program Director of the Lowell P. Weicker, Jr. General Clinical Research Center from 1993-2002 and head of the Division of Endocrinology from 1974-1997. Dr. Raisz graduated from Harvard Medical School in 1947 and received his clinical and research training at the Boston City Hospital, the Boston VA Hospital, New York University Medical School, Strangeways Research Laboratory in Cambridge England and the National Institutes of Health. Prior to joining the faculty at University of Connecticut in 1974 he was head of the Division of Clinical Pharmacology at the University of Rochester.

Dr. Raisz was the second President of the American Society for Bone and Mineral Research and the founding Editor of the Journal of Bone and Mineral Research. His honors include the Edwin B. Astwood Lecture Award of the Endocrine Society and the William F. Neuman Award and the Shirley Hohl Service Award and the Louis V. Avioli Lectureship Award from the American Society for Bone and Mineral Research. He holds an Honorary Doctorate from the University of Umea in Sweden. Dr. Raisz is Chair of the Scientific Advisory Board of the National Osteoporosis Foundation and a member of its Board of Trustees. He is a Scientific Editor of the Surgeon General's Report on Osteoporosis and Bone Health. He is the author of over 400 publications on clinical and basic research on bone metabolism and co-editor of "Principles of Bone Biology" with Drs. John Bilezikian and Gideon Rodan.

JOHN R. STANLEY, M.D.

Positions

1981-1983	Assistant Professor of Dermatology, Department of Dermatology, Uniformed Services University of the Health Sciences
1983-1985	Associate Professor of Dermatology, Department of Dermatology, Uniformed Services University of the Health Sciences, 430l Jones Bridge Road, Bethesda, Maryland 208l4
1986-1994	Professor of Dermatology, Uniformed Services University of the Health Services
1985-1994	Senior Investigator, Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD
1995-Present	Professor and Chair, Department of Dermatology, University of Pennsylvania, Philadelphia, PA

Honors

1988	Election to American Society for Clinical Investigation
1990	Election to the American Dermatological Association
1992	Alfred Marchionini Prize, international prize given by a German foundation for outstanding research in dermatology
1993	Elected Honorary Foreign Member, Société Française de Dermatologie et de Vénéréologie

1993	Elected member of the German Dermatologic Society (Deutsche Dermatologische Gesellschaft).
1994	Society for Investigative Dermatology, Montagna Award
1997	Elected to the Association of American Physicians
2001	Marion B. Sulzberger Memorial Award Lecturer, American Academy of Dermatology

Dr. Stanley's laboratory is studying the molecular pathophysiology of pemphigus and bullous impetigo/staphylococcal scalded skin syndrome. He has characterized the autoantigens in pemphigus as desmogleins, cell adhesion molecules in the desmosome by immunochemical methods and molecular cloning. He defined the molecular pathophysiology of these diseases so as to explain the localization of blisters both in different epithelia (e.g. mucous membrane or skin) and different levels of the epithelia. His data led to the conclusions that autoantibody-induced loss of function of desmogleins causes blister formation in the epidermis in pemphigus, and has confirmed these conclusions by genetic means with both transgenic and knockout mice. He is now addressing the fundamental question of what actually causes the antibody response in pemphigus, by examining the antibody response in humans through phage display and by characterizing the immune response against desmogleins in military personnel who have received the anthrax vaccine (some of whom have developed pemphigus vulgaris). Dr. Stanley's laboratory has also characterized the molecular pathophysiology of bullous impetigo/staphylococcal scalded skin syndrome, in which exfoliative toxins cause a blister identical to that caused by the anti-desmoglein 1 antibody in pemphigus foliaceus. He has shown that exfoliative toxin is a serine protease with exquisite specificity for cleaving desmoglein. Current studies are addressing the molecular mechanism of exfoliative toxin cleavage of desmoglein.

SHARON TERRY, M. A.

Sharon is President of the Genetic Alliance and the founding Executive Director of PXE International, a lay advocacy group for the genetic condition pseudoxanthoma elasticum (PXE). Following the diagnosis of their two children with pseudoxanthoma elasticum (PXE) in 1994, Sharon, a former college chaplain, and her husband, Patrick, founded and built a dynamic organization that fosters ethical research and policies and provides support and information to members and the public. She is also the founding president of the Genetic Alliance BioBank, a repository that provides archiving for lay advocacy organization owned and managed biological samples and clinical data. She is at the forefront of consumer participation in genetics research, services and policy and serves as an Ethical Legal and Social Implications Research Advisor of NHGRI/NIH, and a member of many of the major governmental advisory committees on medical research. She is a member of the board of directors of the Biotechnology Institute and the advisory board of the Johns Hopkins Genetics and Public Policy Center funded by the Pew Charitable Trusts. She has co-authored numerous papers including two papers on the discovery of the PXE gene, published back-to-back in Nature Genetics, June 2000. As a co-inventor of the

gene associated with PXE (ABCC6), she has filed a patent application for the invention. She directs a 19-lab research consortium and manages 52 offices worldwide for PXE International.

Sharon feels strongly that consumers, working together and partnering with professionals and industry, can generate the energy and mechanisms necessary to realize the promise of basic research. Her work with the Genetic Alliance over the past few years has included working on international and national committees, particularly focused on genetic literacy, research protections, biosample repositories, technology translation, accessible services and youth issues. Sharon is committed to facilitating technical assistance to lay advocacy groups, so that each group benefits from the wisdom of the other.

Sharon lives with Patrick and their two children in Maryland.

APPENDIX C

AGENDAS OF THE SCOR REVIEW MEETINGS

REVIEW OF THE NIAMS SPECIALIZED CENTERS OF RESEARCH AGENDA FOR THE FIRST MEETING

August 6, 2003

6:30	Meet for Dinner: Introductions and Overview of the Process	

August 7, 2003

8:30	Welcome and Introductory Remarks	Sue Donaldson
8:45	Charge to the Group	Steve Katz
9:00	Historical Perspective of SCOR	Julia Freeman
10:00	Break	
10:15	Program Perspective on the SCOR Program	Joan McGowan
10:45	Program Perspective on the SCOR Program	Susana Serrate-Stein
11:30	Methods, Tools, and Data from the NHBLI SCOR Review – an Example	Gail Pearson
12:00	Lunch	
12:30	Discussion of major aspects of SCOR to be reviewed/sections of the Committee's Report and scope/nature of recommendations in the Committee's Report to Dr. Katz	Sue Donaldson
1:00	Discussion as to information and data needed to evaluate the SCOR program and to make recommendations as to future NIAMS funding opportunities	Sue Donaldson
2:00	Review of existing NIAMS outcome data for funded SCOR and formulation of methods and additional data gathering tools that will be used by the Committee	Sue Donaldson
4:00	Adjourn	

REVIEW OF THE NIAMS SPECIALIZED CENTERS OF RESEARCH
AGENDA FOR THE SECOND MEETING

September 30, 2003

8:30 AM	Welcome and Brief Overview of the Work of the Committee to Date	Sue Donaldson
8:45	Review of the U54 Mechanism	Julia Freeman
9:15	Experience with the New U54 Muscular Dystrophy Centers	Richard Lymn
10:15	Break	
10:30	Discussion of Materials Sent and Issues Raised	All
12:00	Lunch	
1:00	Discussion of the Responses from Current and Former SCOR Directors and Translation into Summary/Collective Content for the Report	All
3:00	Formulation of Major Recommendations for the Report	All
5:00	Adjourn	

October 1, 2003

8:30	Delineation of Key Points to be in the Prose Discussion Specific to Each Major Recommendation for the Report	All
10:15	Break	
10:30	Outline of the Major Sections of the Report	All
12:00	Lunch	
1:00	Finalize the Executive Summary of the Report	All
3:00	Identify Other Resources (Additional Information or People) that the Committee Would Like to Invite to Have Available at the November Meeting	All
4:00	Adjourn	

REVIEW OF THE NIAMS SPECIALIZED CENTERS OF RESEARCH
AGENDA FOR THE THIRD MEETING

November 18, 2003

8:30 AM	Status of the Work of the Committee to Date	Sue Donaldson
8:45	Overall Comments from Committee Members on the Draft Report	All
10:15	Break	
10:30	Discussion of the Report Recommendations and the Rationale for Each	All
12:00	Lunch	
1:00	Discussion of Cores for Translation Centers	All
3:00	Reports from the 2 Working Subgroups	
5:00	Adjourn	

November 19, 2003

8:30	Continue Detailed Analysis of All Sections of the Report to Determine Consensus	All
10:15	Break	
10:30	Complete the Recommendations of the Report and the Supporting Rationale	All
12:00	Lunch	
1:00	Continued Discussion of Outstanding Issues and Identification of Additional Materials for the Committee	All
1:30	Post Hoc Report Writing and Review Assignments to Finalize Report	All
2:00	Adjourn	

APPENDIX D

BUDGET HISTORY OF THE SCOR PROGRAM

Fiscal Year	Total Extramural Research Funding*	# SCOR	Total SCOR Funding**	SCOR % of Total Extramural Research Funding
1987	$127,948	9	$7,661	5.99%
1988	133,677	9	6,989	5.23%
1989	144,560	9	6,750	4.67%
1990	148,990	9	6,930	4.65%
1991	169,895	9	6,967	4.10%
1992	178,128	7	6,048	3.40%
1993	184,495	9	7,942	4.30%
1994	194,712	9	7,959	4.09%
1995	201,538	9	7,855	3.90%
1996	213,890	9	7,723	3.61%
1997	224,399	6	5,494	2.45%
1998	240,289	8	7,905	3.29%
1999	267,151	8	7,787	2.91%
2000	303,813	8	8,389	2.76%
2001	341,564	9	9,033	2.64%
2002	381,510	10	10,446	2.74%

All dollar amounts are in thousands.

* Excludes Research Management & Support (RMS)

** Specialized Centers of Research (P50)

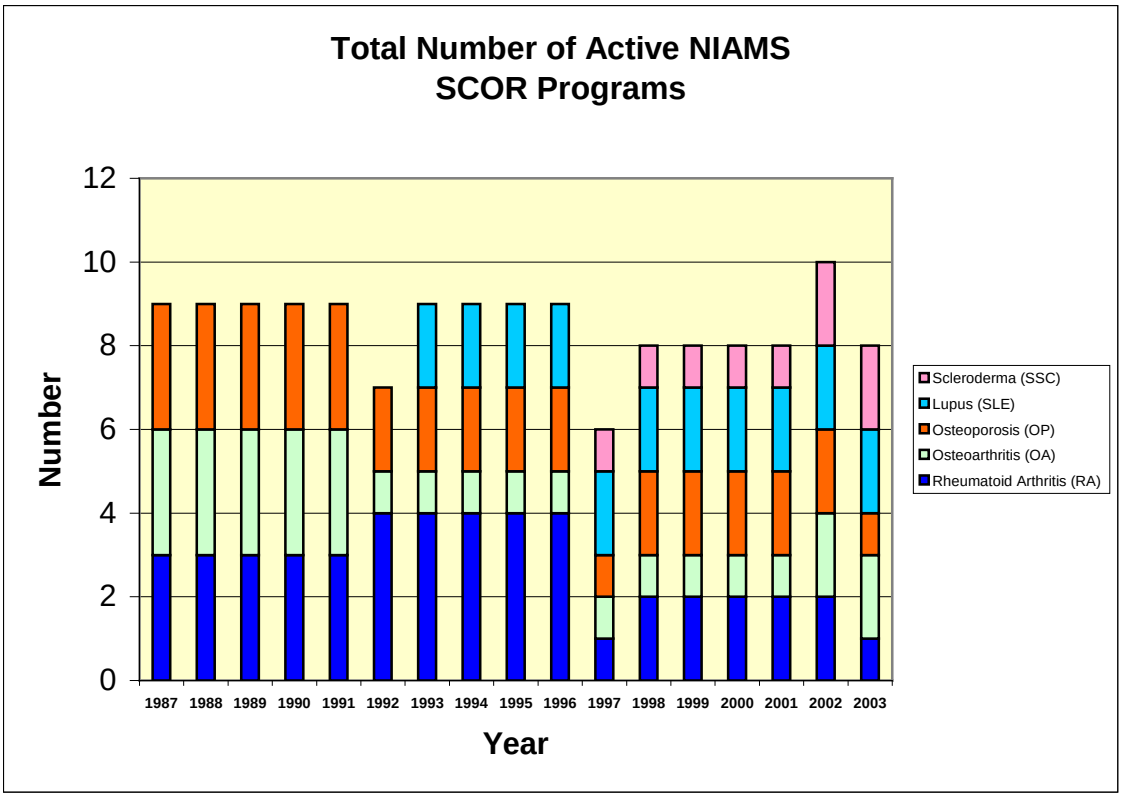
APPENDIX E

Table 1: History of SCOR Applications by Disease

Disease	Year	Applications Received	Applications Funded
Rheumatoid Arthritis			
	1987	7	3
	1992	5	4
	1997	9	1 (four years)
	1998	6	1
	2001	3	1
	2003	3	0
Osteoarthritis			
	1987	11	3
	1992	4	1
	1998	5	1
	2002	4	2
Osteoporosis			
	1987	15	3
	1992	4	2
	1997	11	1 (four years)
	1998	5	1
	2001	1	1 (four years)
	2003	2	0
Lupus			
	1993	14	2
	1998	11	2
	2002	8	2
Scleroderma			
	1997	9	1 (four years)
	1999	3	0
	2001	4	2

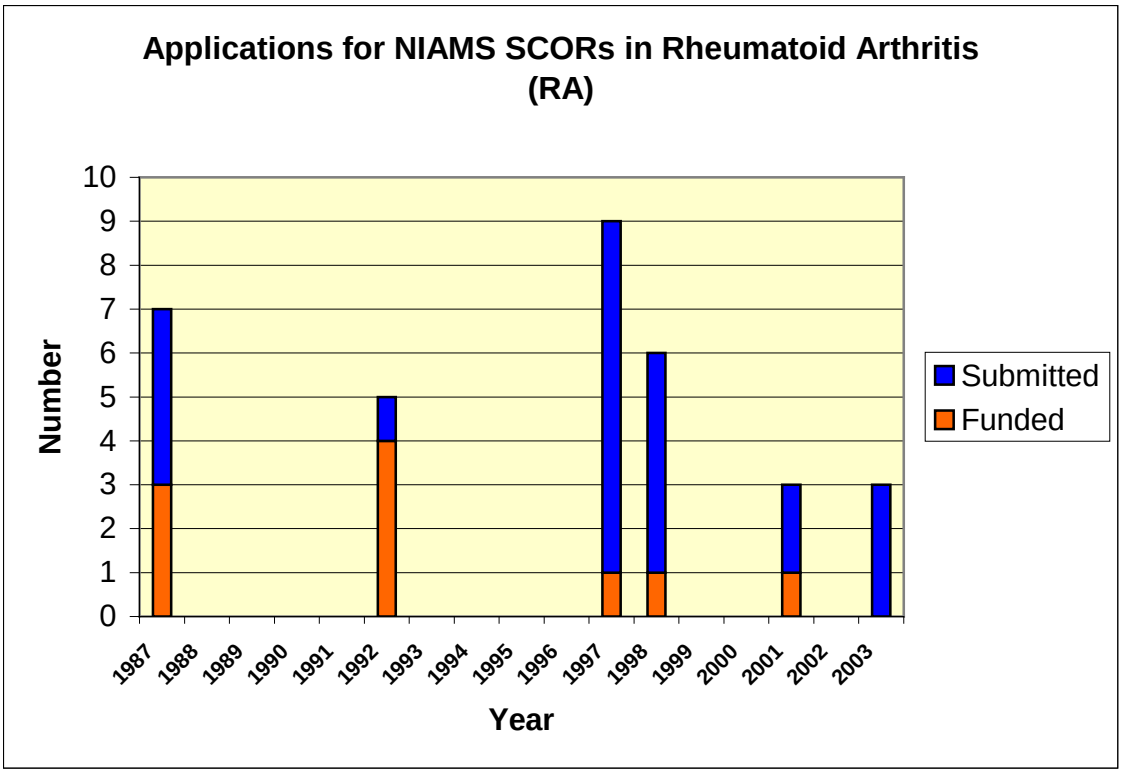
APPENDIX F

Chart 1



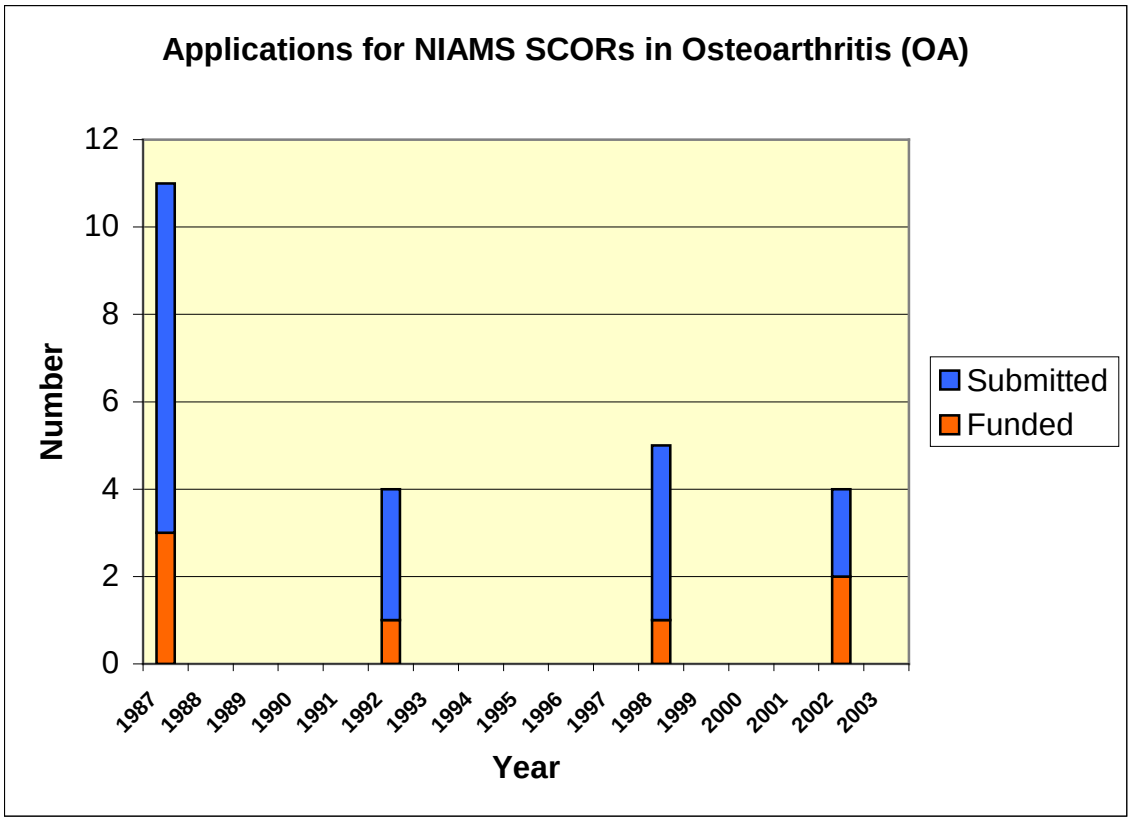
APPENDIX G

Chart 2



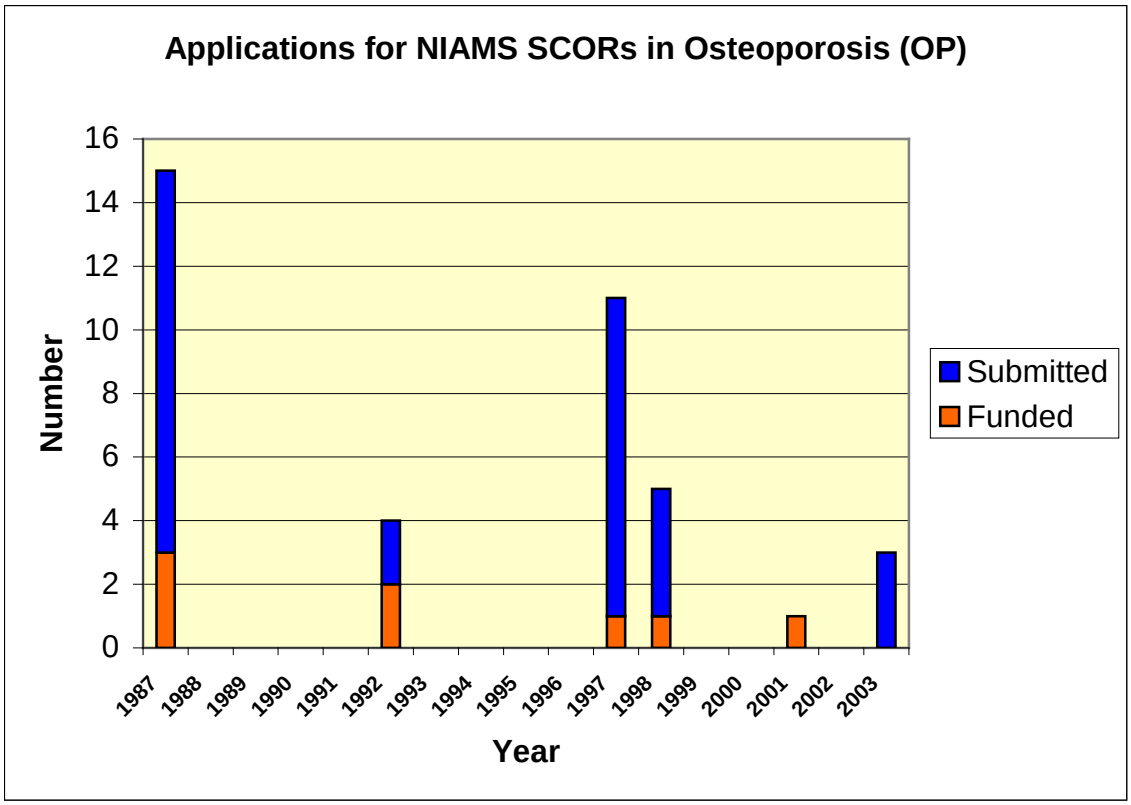
APPENDIX H

Chart 3



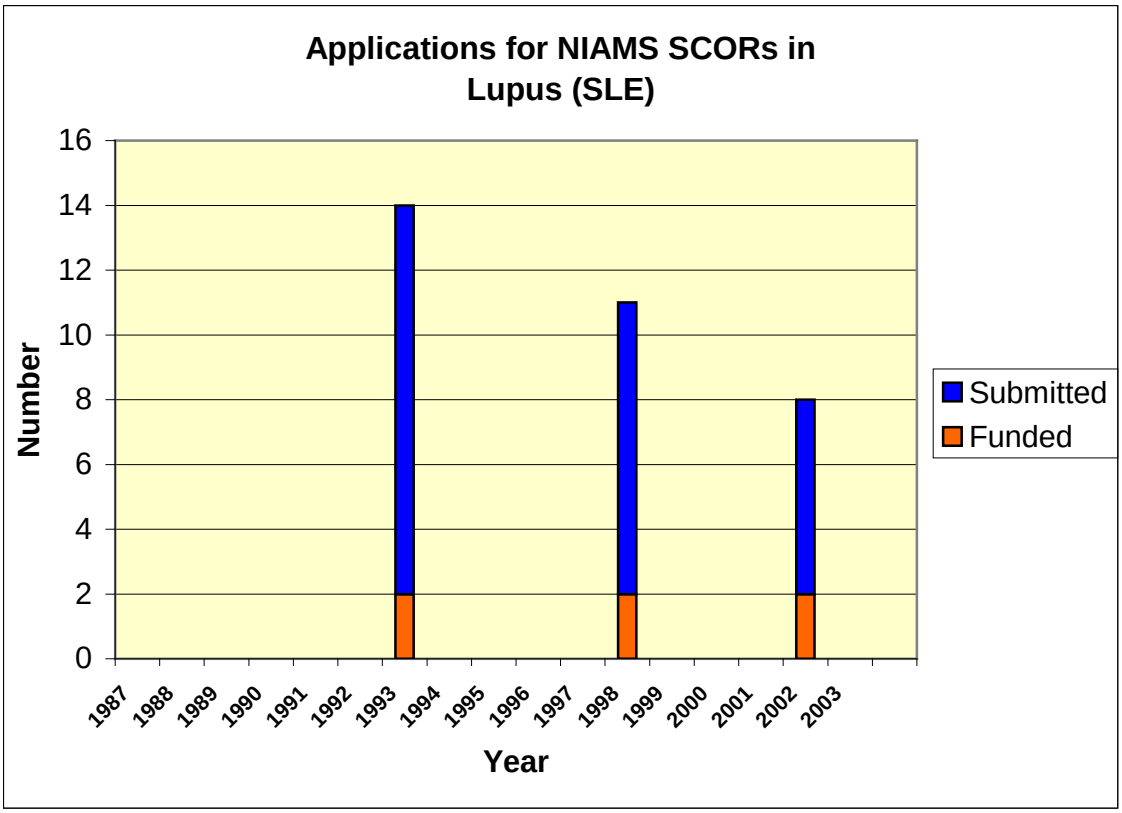
APPENDIX I

Chart 4



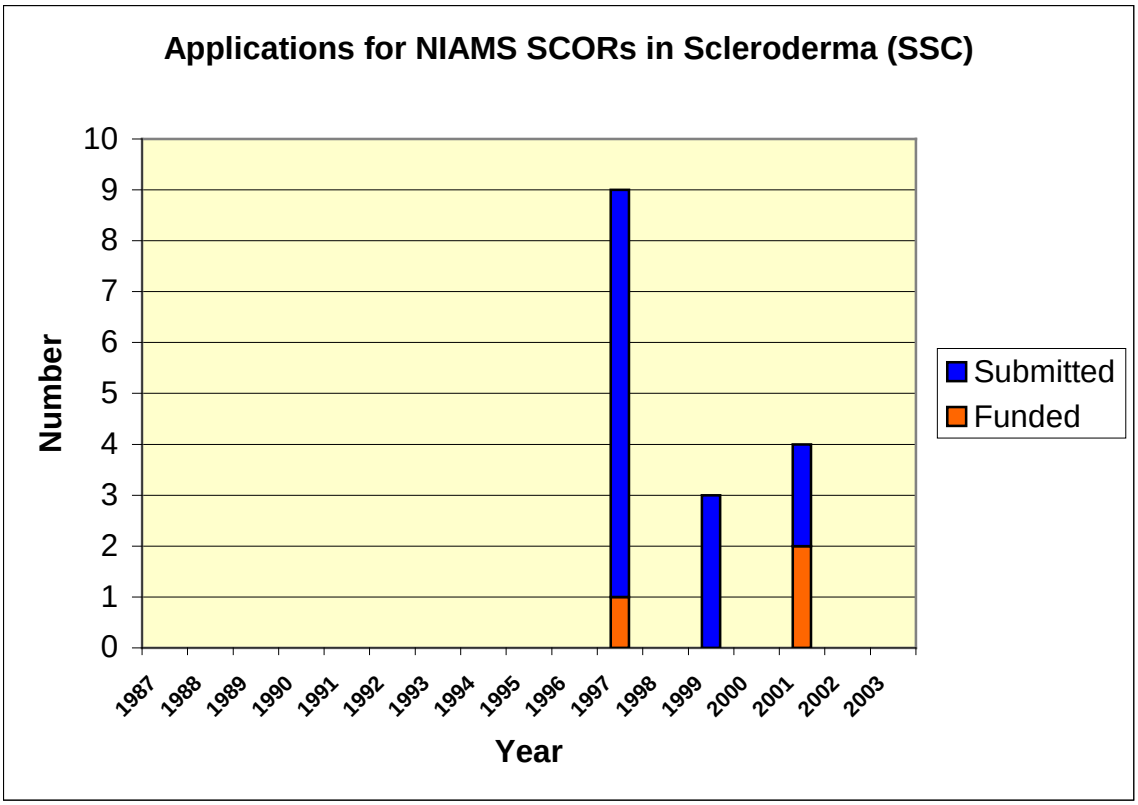
APPENDIX J

Chart 5



APPENDIX K

Chart 6



APPENDIX L

Chart 7

History of SCOR Applications by Year, Disease