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TITLE: Biomarker-Based Prediction Models for Response to Treatment in Systemic Sclerosis-Related Interstitial Lung Disease

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14. ABSTRACT

Systemic sclerosis (SSc-Scleroderma) is associated with substantial morbidity and mortality. Interstitial lung disease (ILD) is the leading cause of disease-related mortality. Response to immunosuppression is highly variable in patients with SSc related ILD. The currently available clinical markers are inadequate for identifying the likely responders. The utilized treatments are also associated with potentially serious adverse events, and their use should be reserved for highly responsive patients, further underscoring the critical need for development of reliable prediction tools. Our goal is to develop prediction tools using a combination of serum biomarkers and whole blood/skin gene expression data with potential clinical predictors. As the first step, the baseline serum samples of the Scleroderma Lung Study II (SLS II) were examined. The related analysis has been completed. We are currently confirming the candidate cytokine predictors in the GENISOS cohort. We are currently confirming our protein and transcript level data in an independent cohort.

15. SUBJECT TERMS

Systemic sclerosis – scleroderma – interstitial lung disease - biomarker

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1. **Introduction:**

Systemic sclerosis (SSc-scleroderma) is associated with substantial morbidity and mortality. Interstitial lung disease (ILD) is the primary cause of disease related death. Immunosuppressive agents such as mycophenolate mofetil and cyclophosphamide are used for treatment of SSc-ILD. However, response to these treatments is highly variable and the clinical predictors cannot reliably identify the likely responders. In this project, we use the valuable samples collected in the Scleroderma Lung Study II (SLSII) clinical trial and the observational cohort, GENISOS to identify and verify molecular predictors of response to treatment. For this purpose, novel technologies and analytic approaches will be used to determine key serum protein levels and transcript signatures in whole blood and skin samples collected in the SLSII study. The identified candidate molecular predictors in the SLSII will be verified in the GENISOS cohort during the last year of study period.

2. Keywords:

Systemic sclerosis – scleroderma – interstitial lung disease – biomarker

3. **Accomplishments:**

Major Task 1 : Institutional Review Board (IRB) and DOD Human Research Protection Office (HRPO) – 1 to 4 months
- Milestone Achieved #1: HRPO Approval was obtained on 1/9/2017

Major Task 2: Specific Aim 1: To determine the predictive significance of the peripheral blood type-I IFN signature – 5 to 24 months
- The Whole blood RNA samples have been extracted. Gene expression data have been generated. We are currently determining the candidate transcripts for the validation step. The goal is to write a separate whole blood gene expression manuscript after the manuscript on the serum protein predictors has been submitted.

Major Task 3: Specific Aim 2: To define the predictive significance of the skin immune dysregulation transcript signature for response to treatment – 5 to 24 months
- The skin biopsy samples were obtained from UCLA Pathology Repository and initial analysis on marker of fibrosis has been completed. However, several new candidate biomarkers have been identified (see Tasks 1 and 4). We are currently discussing with Dr. Browning the possibility of performing additional staining for these candidate biomarkers. These results will be published with the above mentioned gene expression manuscript.

Major Task 4: Specific Aim 3: To characterize the predictive significance of key Th2 plasma cytokines for response to immunosuppression in SSc-ILD – 5 to 18 months
- As expected from the timeline, the experimental part of this task has been completed. This task has led to discovery of five novel predictive biomarkers in both treatment arms (see below). The related results will be shown as an oral presentation at the upcoming American College of Rheumatology Annual Scientific Meeting.
- We are awaiting the validation/confirmation of the above important results in the GENISOS cohort before submitting a manuscript because high-impact journals require the confirmation of study results in an independent cohort.

Major Task 5: Specific Aim 4: To develop and validate multivariable prediction tools for SSc-ILD with identified clinical and molecular predictors – 25 to 36 months
- The candidate proteins and transcripts identified in the above aims will be examined in the GENISOS cohort.

What was accomplished under these goals?

HRPO approval: HRPO approval has been maintained at the study sites (University of Texas Health Science Center Houston and University of California Los Angeles) by providing continuing review to local Institutional Review Boards (IRBs) and obtaining the necessary approvals.

SLSII sample repository: A data base that tracks all obtained and stored samples in SLSII has ensured that all utilized samples for the above experiments are tracked. Specifically, thaw/freeze cycles, remaining volumes, and the name of project have been recorded. This will ensure that the valuable resource of the SLSII biorespository remains available for future studies.

Identification of candidate predictive biomarkers in the SLSII:

We have focused on transcript and serum protein based predictive biomarkers for response to treatment (cyclophosphamide or mycophenolate mofetil) in SSc-ILD. The transcript level data are currently undergoing further analysis and the identified biomarkers will be validated in the GENISOS cohort. The analysis of the serum protein data has been completed. Major efforts have been focused on the completion of serum protein project because serum proteins are easily obtained during routine clinical practice and validated serum protein predictive biomarkers can change the clinical care and study design in SSc-ILD. Below, we summarize the already generated important results:

We determined levels of serum proteins involved in the immune pathways. Specifically, 37 serum proteins were measured in all available 134 baseline samples (samples were collected before initiation of treatment) of the SLSII. This panel included known potential inflammatory biomarkers such as IL-6, CCL2 (MCP-1), and B-lymphocyte chemoattractant (BLC). Next, we investigated whether the investigated cytokines can predict response to treatment. For this analysis, the primary outcome was serially obtained forced vital capacity (FVC) obtained between month 3 and month 12 visits. FVC is the only validated outcome measure for SSc-ILD. Similar to the main clinical study, an analytic approach was pursued that accounts for missing non-random follow-up data such as respiratory failure, drop outs, and death. The analysis was also adjusted for the baseline FVC value. In this analysis, three cytokines showed predictive significance for <u>better response in both treatment arms after adjustment for multiple comparisons</u>. Specifically, Chemokine (C-X-C motif) ligand 9, CXCL9 was predictive of higher serially obtained FVC (b=0.99; pFDR=0.039 and b=0.39; pFDR<0.001 in the CYC and MMF arms, respectively). Similarly, Chemokine (C-X-C motif) ligand 10, CXCL10 was predictive of higher serially obtained FVC (b=0.57; pFDR<0.001 and b=0.40; pFDR=0.034, in the CYC and MMF arms, respectively). Similarly, Vitamin D Binding Protein (VDBP) predicted better response to treatment in both treatment arms (b=0.001, p=0.024; b=0.004, p=0.006 in the CYC and MMF arms, respectively). Of note, general inflammatory markers such as CRP was not associated with better response.

CXCL9 and CXCL10 are both interferon-inducible chemokines. We have shown in our global gene expression studies that an interferon signature is the most prominent gene expression profile in the peripheral blood of patients with systemic sclerosis. Therefore, there is biological plausibility for our finding, indicating that SSc patients with a pro-fibrotic inflammatory profile (i.e. interferon signature) are more likely to respond to immunosuppression. This was the primary hypothesis of this project I as mentioned in our original grant application.

VDBP is a not a strong correlate of CXCL9 and CXCL10 (r=0.22 and r=0.39, respectively). Therefore, we believe VDBP can be also an independent predictor of response. While VDBP has vitamin D binding properties, it can also activate macrophages. Figure 1 shows the course of FVC in the patient groups that have been dichotomized based on the median value of baseline VDBP levels.

CYC group, by median of VDBP   MMF group, by median of VDBP
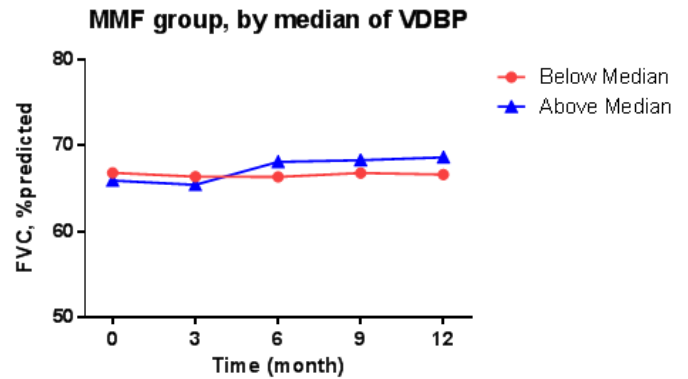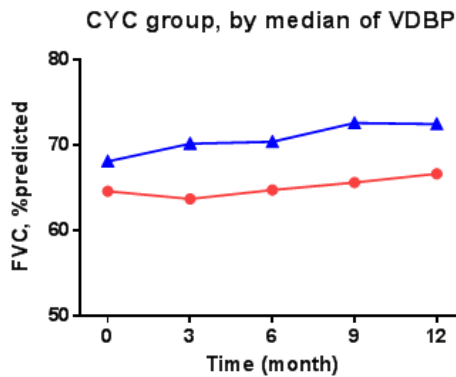
We also investigated whether two specific pneumoproteins, Krebs von den Lungen-6 [KL-6] and CC chemokine ligand 2 [CCL18]) predict response to immunosuppression with cyclophosphamide (CYC) and mycophenolate (MMF) in SSc-ILD. CCL18 was assayed by commercially available ELISA while KL-6 was measured using antibody coated latex microbeads and an automated analyzer.

Baseline serum KL-6 and CCL18 correlated with extent of ILD. KL-6 levels correlated. After adjusting for baseline disease severity, higher baseline KL6 levels predicted progression of ILD as measured by the course of the FVC (CYC/MMF: Estimate -0.31/-0.74; P=0.024/<0.001) and DLCO (CYC/MMF: Estimate -1.30/-1.29; P<0.001/<0.001) over 1 year for both treatment arms. Similarly, higher baseline CCL18 levels predicted progression of ILD as measured by the course of the FVC (CYC/MMF: Estimate -1.24/-0.35; P<0.001;0.007) and DLCO (CYC/MMF: Estimate -1.87/-1.24; P=0.001/0.002) over 1 year for both treatment arms. These results indicate that Patients with higher baseline KL-6 and CCL18 levels were more likely to experience disease progression despite treatment with CYC and MMF. These results will be presented at the upcoming American College of Rheumatology Annual Scientific Meeting this month.

We are currently investigating the predictive significance of above mentioned candidate biomarkers in the GENISOS cohort in order to have an independent replication cohort. A manuscript combining the results from the GENISOS and SLSII cohorts will be submitted this year.

4. Impact:

What was the impact on the development of the principal discipline(s) of the project?

Given that ILD is the most common cause of disease-related death in SSc, a clinically-useful, robust prediction algorithm that includes the above cytokines for immunosuppressive treatment response represents substantial progress over the current "one-size fits all" approach. It is conceivable that SSc-ILD patients with low CXCL9, CXCL10, VDBP and high KL-6 and CCL18 levels might benefit from other treatment modalities such as anti-fibrotic agents. Ultimately, these predictive biomarkers can transform the clinical care for SSc patients with ILD and improve outcomes by enabling more focused and effective treatment approaches.

What was the impact on other disciplines?

Our predictive biomarkers might be also useful for predicting response to immunosuppression in other connective-tissue disease related ILD such as rheumatoid lung disease and polymyositis related ILD.

What was the impact on technology transfer?
Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

5. Changes/Problems:
None

6. Products:
Two manuscripts on the above mentioned proteomic data are under preparation and will be submitted for publication this year.

Another manuscript on the predictive significance of KL-6 and CCL18 in the GENISOS cohort was published this year:

- Salazar GA, Kuwana M, Wu M, Estrada-Y-Martin RM, Ying J, Charles J, Mayes MD, Assassi S. KL-6 But Not CCL-18 Is a Predictor of Early Progression in Systemic Sclerosis-related Interstitial Lung Disease. J Rheumatol. 2018 Aug;45(8):1153-1158

The above mentioned KL-6 and CCL18 results will be shown in an oral presentation at the upcoming American College of Rheumatology Annual Scientific Meeting this month:
 - Elizabeth R. Volkmann, Donald P. Tashkin, Masataka Kuwana, Ning Li, Julio Charles, Faye N. Hant, Galina S. Bogatkevich, Tanjina Akter, Michael Roth, Hyun J. Grace Kim, Jonathan Goldin, Dinesh Khanna, Philip J. Clements, Daniel E. Furst, Robert Elashoff, Rick Silver and Shervin Assassi. Specific Pneumoproteins Predict Progression of Interstitial Lung Disease in Systemic Sclerosis Patients Undergoing Treatment with Immunosuppression. Abstract Number: 1877.

7. Participants:

Dr. Shervin Assassi (PI; UTHealth):	No change
Dr. Wenjin Zheng	No change
Julio Charles (Research Associate; UTHealth):	No change
Dr. Robert Elashoff (Co-I; UCLA):	No change
Dr. Ning Li (Biostatistician-UCLA):	No Change
Dr. Jeffrey Browning (Co-I, Boston University)	No Change

Participants:

Name:	Shervin Assassi
Project Role:	PI
ORCID ID:	
Person month worked:	3.0
Contribution to Project:	Oversee all project related activities
Funding Support:	

Name:	Wenjin Zheng
Project Role:	Co-I
ORCID ID:	
Person month worked:	2.16
Contribution to Project:	Conduct the analysis of high through-put gene expression data
Funding Support:	

Name:	Jeffrey Browning
Project Role:	Co-I
ORCID ID:	0000-0001-9168-5233
Person month worked:	0.36
Contribution to Project:	Performed immunohistological staining, analysis and report
Funding Support:	

Name:	Robert Elashoff
Project Role:	Principal Investigator
ORCID ID:	
Person month worked:	2.5
Contribution to Project:	Statistical data analysis
Funding Support:	

Name:	Ning Li
Project Role:	Biostatistician
ORCID ID:	
Person month worked:	2.15
Contribution to Project:	Statistical data analysis
Funding Support:	

PREVIOUS, CURRENT AND PENDING SUPPORT

ASSASSI, SHERVIN

PREVIOUS

1K23AR061436
Title: Molecular Markers for Progression of Pulmonary Fibrosis in Systemic Sclerosis
Role: PI
Time Commitment: 3.60 calendar months
Supporting Agency: NIH/NIAMS
Point of Contact: Teresa Do, 301-594-3512, dote@mail.nih.gov
Performance Period: 8/15/2011 - 6/30/2015 (NCE until 6/30/16)
Level of Funding: $493,922
Brief Description of Project Goals: The aim of this study is to identify gene expression and interferon induced chemokines that correlate/predict the course of pulmonary fibrosis in an observational SSc cohort.
Specific Aims:
1) To identify peripheral blood cell gene expression patterns predictive of ILD progression. RNA isolated from monocytes and lymphocytes of SSc patients will be investigated by DNA microarrays and the predictive significance of transcripts for progression of ILD will be examined. Subsequently, the findings will be confirmed in whole blood samples of an independent group of patients by qPCR.
2) To identify skin gene expression patterns predictive of ILD progression. RNA isolated from skin samples will be examined by DNA microarrays and the predictive significance of skin transcripts for ILD progression will be investigated.
3) To ascertain the extent of correlation between gene expression patterns of the concomitantly collected skin and peripheral blood samples of SSc patients.
4) To examine the predictive significance of IFN inducible chemokines for ILD progression in the GENISOS cohort. The serum IFN inducible chemokine levels will be determined by multiplex assays and their predictive value will be investigated in a multivariate model after inclusion of other known predictors.

Title: Molecular Changes following Treatment with Cyclophosphamide or Autologous Hematopoietic Cell Transplantation in Patients with SSc
Role: PI
Time Commitment: No Salary Support during NCE
Supporting Agency: Karen Brown Scleroderma Foundation
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:
Michael Brown, The Karen Brown Scleroderma Foundation, P.O. Box 261671 Encino, CA 91426-1671
Performance Period: 9/1/2012-12/31/2015 (NCE)
Level of Funding: $96,548 (direct costs)
Brief Description of Project Goals: The aim of this study to identify the molecular changes at the gene expression and cytokine levels resulting from treatment with autologous stem cell transplantation in comparison to cyclophosphamide in SSc patients.

5U01AI09090-05
Title: Studies of HLA Region Genomics in Systemic Sclerosis and Ankylosing Spondylitis
Role: Co-investigator
Time Commitment: No Salary Support*
Supporting Agency: NIH/NIAD
Point of Contact: John A. Villella, 301-402-6489, vilellaja@mail.nih.gov
Performance Period: 07/15/2010 – 06/30/2015
Level of Funding: $2,669,206
Brief Description of Project Goals: Aims to identify sequence variations of HLA and non-HLA disease-associated genes within the MHC region in SSc and AS in three different ethnic groups, and

subsequently distinguish true causal disease associations from associations due to linkage disequilibrium (LD).

Specific Aims: 1) identify genotypes of the HLA genes in association with scleroderma and ankylosing
spondylitis; 2) determine specific genotypes in association with disease severity of scleroderma and ankylosing
spondylitis.

* Dr. Assassi did not receive any salary support for this project because of the budgetary requirement in his K23 award. Effort is concurrent with K23.

NO1-AI05419 (Sullivan)
Title: A randomized, open-label, phase II/III multicenter study of high-dose immunosuppressive therapy using total
body irradiation, cyclophosphamide, ATGAM, and autologous transplantation with auto-CD34+HPC versus
intravenous pulse cyclophosphamide for the treatment of severe systemic sclerosis
Role: Co-I
Time Commitment:
Supporting Agency: Duke University/NIAD
Point of Contact: Office of Research Contracts, 919-668-1759, orcfed-foundationcontracts@dm.duke.edu
Performance Period: 4/2005-10/2017
Level of Funding: $73,500
Brief Description of Project Goals: Dr. Assassi's role in this project was to identify the molecular changes at the gene expression and cytokine level resulting from treatment with immunoablation/autologous stem cell transplantation in comparison to cyclophosphamide in SSc patients enrolled in the SCOT trial.

CURRENT

Title: Biomarker-Based Prediction Models for Response to Treatment in Systemic Sclerosis-Related Interstitial Lung Disease
Role: PI
      Time Commitment: 3.60 calendar months
Supporting Agency: United States Army Medical Research
Point of Contact: Susan Dellinger, 301-619-2090; susan.m.dellinger.civ@mail.mil
Performance Period: 9/15/2016-09/14/2019
Level of Funding: $362,782 (annual direct cost)
Brief Description of Project Goals: The ultimate goal of this proposal is to develop and validate prediction tools for response to treatment in SSc related ILD using multi-level clinical and molecular data.
Specific Aim 1: To determine the predictive significance of the peripheral blood type-I IFN transcript signature for response to immunosuppression in SSc-ILD and to examine its treatment related changes.
Specific Aim 2: To define the predictive significance of the skin immune dysregulation transcript signature for response to treatment.
Specific Aim 3: To characterize the predictive significance of key Th2 plasma cytokines for response to immunosuppression in SSc-ILD and to determine the longitudinal changes of these cytokines.
Specific Aim 4: To develop and validate multivariable prediction tools for SSc-ILD with identified clinical and molecular predictors.

Title: Longitudinal analysis of SSc skin morphology and correlation to gene expression signatures

Role: PI
Time Commitment: 0.60 calendar months
Supporting Agency: Biogen MA, Inc
Point of Contact: Jo Viney, VP – Immunology Research, 225 Binney St, Cambridge, MA 02142
Performance Period: 10/5/15 – 10/4/18
Level of Funding: $25,091 (annual direct cost)
Brief Description of Project Goals: The major goals of this project is to investigate the correlation between SSc skin morphology and gene expression signatures

Title: To gain a better understanding of global gene regulation in systemic sclerosis (SSc) and the role of specific targets (CD226, ATX) and mechanisms (EndoMT) in disease pathogenesis
Role: PI
Time Commitment: 1.20 calendar months
Supporting Agency: Boehringer-Ingelheim Pharmaceuticals, Inc
Point of Contact: Bruce Butler, VP – Research and Technology, Binger Strasse, 55216 Ingelheim am Rhein
Performance Period: 2/15/18 – 8/14/19
Level of Funding: $84,722 (annual direct cost)
Brief Description of Project Goals: The major goals of this project is to study and assess the mechanism of SSc global gene regulation and the role of CD226, ATX and the mechanisms of EndoMT in disease pathogenesis.

Title: CONQUER Registry Study
Role: Site PI
Time Commitment: 1.20 calendar months
Supporting Agency: Scleroderma Research Foundation
Point of Contact: Luke Envin, 220 Montgomery St, Ste 484, San Franscisco, CA 94104
Performance Period: 3/20/18 – 3/19/20
Level of Funding: $65,421 (annual direct cost)
Brief Description of Project Goals: The major goals of this project is to create a prospective national registry of early systemic sclerosis patients. The study is based on 12 specialized scleroderma centers in the USA. All prospectively collected serum, RNA, and DNA samples will be stored at the CONQUER Biorepository located in our divisional laboratory.

PENDING

Title: CFIm25 mediated alternative polyadenylation regulates fibrosis in systemic sclerosis
Role: PI
Time Commitment: 2.40 calendar months
Supporting Agency: National Institutes of Health, NIAMS
Point of Contact: Andrew Jones; 301-435-0610; jonesan@mail.nih.gov
Performance Period: 4/1/19-3/31/24
Level of Funding: $266,740 (annual direct cost)
Aim I: Define the fibroblast specific contribution of CFIm25 depletion in dermal fibrosis murine models. This aim will elucidate the downstream effects of CFIm25 depletion on key fibrotic pathways.
Aim II: Determine the mechanisms for CFIm25 downregulation and assess their potential as therapeutic targets in dermal fibrosis. The mechanisms for TGFβ mediated miR-203 downregulation and subsequent CFIm25 repression by miR-203 will be elucidated. This aim will characterize the upstream events leading to CFIm25 depletion and will identify potential therapeutic targets. **Aim III: Characterize CFIm25 in SSc human skin/fibroblasts and identify fibrotic genes dysregulated by APA.** Serial dermal fibroblasts and skin samples from patients with early SSc and

matched controls will be examined using a novel RNA sequencing technology. This aim will provide for the first time an unbiased, longitudinal view of CFIm25 mediated APA profile in a fibrotic disease.

OVERLAP
None

Browning, Jeffrey

CURRENT

Title: "Preclinical assessment of dimethylfumarate (Tecfidera) as a novel therapeutic for systemic sclerosis associated pulmonary arterial hypertension"
Role: Co-investigator
Time Commitment: 0.6 Calendar Months
Supporting Agency: Boston University School of Medicine (PI: M. Trojanowska)/ National Scleroderma Foundation (SCORES Grant)
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:
Performance Period: 4/1/2017-3/31/2019
Level of Funding: $11,900 per year (direct)
Brief Description of Project Goals: Develop preclinical package in support of a clinical trial of dimethylfumarate in scleroderma associated pulmonary arterial hypertension.
Overlap: None

Title: "Modulation of protein export pathways as targets in lupus nephritis"
Role: PI
Time Commitment: 0.2 Calendar Months
Supporting Agency: Boston University School of Medicine /Hoffman La Roche Exploratory Research Grant
Name and Address of the Funding Agency's Procuring Contracting/Grants Officer:
Performance Period: 7/1/2017-6/30/2019
Level of Funding: $65,000 per year direct costs ($100,000 total/year)
Brief Description of Project Goals:
Explore protein export pathways as potential targets for the treatment of lupus nephritis
Overlap: None, exploration of inhibitors of protein trafficking processes.

ELASHOFF, R.

ACTIVE

Title: "Barber-Pharmacist Coordination to Improve Blood Pressure Management in Black Men"
Role: Subaward PI
Time Commitment: 1.2 Calendar Months
Supporting Agency: UCLA
Performance Period: 4/1/2014-3/30/2019
Level of Funding: $400,000 per year direct costs
Brief Description of Project Goals:
This highly significant application will examine the impact of an intervention on systolic BP assessed in the barbershops after barbers refer their customers with high blood pressure to trained community-

based clinical pharmacists who, with doctors' approval and oversight, will provide specialty-level healthcare.

Title: "Base Unit Core Program, UCLA Cancer Center Support Grant"
Role: Co-I
Time Commitment: 2.4 Calendar Months
Supporting Agency: NCI
Performance Period: 12/1/2002-11/30/2018
Level of Funding: $1,408,000
Brief Description of Project Goals:
The major goal of this project is to support the Cancer Program at UCLA by providing support by shared resources, faculty, salaries, and new development programs.

Title: "Protocol Review/Monitoring System Core Program, UCLA Cancer Center Support Grant"
Role: Co-I
Time Commitment: 1.2 Calendar Months
Supporting Agency: NCI
Performance Period: 12/1/2002-11/30/2018
Level of Funding: $462,165
Brief Description of Project Goals:
The major goal of this project is to support the Cancer Program at UCLA by providing protocol review and monitoring services.

Title: "UCLA Clinical and Translational Science Institute"
Role: Co-I
Time Commitment: 2.4 Calendar Months
Supporting Agency: NCRR
Performance Period: 6/1/2011-6/30/2021
Level of Funding: $462,165
Brief Description of Project Goals:
The UCLA CTSI is an academic-clinical-community partnership designed to accelerate scientific discoveries and clinical breakthroughs to improve health in the most populous and diverse county in the US.

Title: "Multicenter Selective Lymphadenectomy Trial (MSLT II) in Melanoma"
Role: Co-I
Time Commitment: 0.6 Calendar Months
Supporting Agency: NIH
Performance Period: 9/23/2014-8/23/2019
Brief Description of Project Goals:
Subjects must be diagnosed with melanoma. All subjects receive sentinel lymphadenectomy. If the subject
is sentinel node positive and meets study requirements, the subject is randomized to receive either (1)
completion lymphadenectomy (2) observation with nodal ultrasound. Subjects are then followed for 10
years

PENDING:

None