SUMMARY STATEMENT

PROGRAM CONTACT: **(Privileged Communication)** ***Release Date:*** **11/09/2015**

Annette Rothermel

[redacted]

Application Number: **2 R01 AI089714-06A1**

Principal Investigator

FAUBION, WILLIAM A MD

Applicant Organization: MAYO CLINIC ROCHESTER

Review Group: **GMPB**
Gastrointestinal Mucosal Pathobiology Study Section

Meeting Date: **10/22/2015**
Council: **JAN 2016**
Requested Start: **07/01/2016**

RFA/PA: **PA13-302**
PCC: **I4A**
Dual PCC: **NLM DUAL**
Dual IC(s): **DK**

Project Title: **Inflammatory cascades disrupt Treg function through epigenetic mechanisms**

SRG Action: **Impact Score: 17 Percentile: 3**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**

Project Year	Direct Costs Requested	Estimated Total Cost
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

2R01AI089714-06A1 Faubion, William

RESUME AND SUMMARY OF DISCUSSION: This outstanding application from a well-established physician scientist is aimed at testing the hypothesis that histone methyltransferase EZH2, through epigenetic modification of Foxp3, plays a critical role in the homeostasis of Treg cells and that disruption of EZH2 function contributes to inflammatory bowel disease. During the previous period of funding, the principal investigator has been highly productive with important findings on EZH2-mediated transcriptional repression in Tregs. During a focused discussion, the reviewers noted numerous strengths of the application including the highly significant topic of research with clinical relevance and potential high impact on broad areas of autoimmune disease, the highly regarded and productive investigator, the innovative concepts regarding the epigenetic modifications of FoxP3 and cell autonomous mechanism of IL-6 in disrupting Treg function, the strong supportive preliminary data, the logically designed experiments with clear outcomes, as well as the exceptional research environment. Only minor concerns were noted and this application was viewed with high uniform enthusiasm.

DESCRIPTION (provided by applicant): The transcription factor FOXP3 is critical to the regulation of numerous debilitating human immune-mediated diseases. Very recently, the essential role for the histone methyltransferase (HMT) EZH2 in the epigenetic regulation and function of FOXP3 has been described. Inflammatory pathways modify EZH2 activity, and inflammatory signaling impairs Treg function in vivo and in vitro. The biological impact of the FOXP3-EZH2 pathway to IBD is unknown. Our long-term goal is to dissect epigenetic mechanisms regulating Treg cellular differentiation and function, particularly within the setting of GI inflammatory diseases. These discoveries will facilitate design of human cell therapy trials for IBD. The objective of this grant is to characterize the role for EZH2 in Treg suppressive function. The central hypothesis is that EZH2 plays a critical role in the homeostasis of Treg cells, and the disruption of EZH2 function by inflammatory signaling pathways contributes to IBD. Our rationale is that identification of the mechanism(s) to restore Treg suppressive function in the setting of intestinal inflammation will offer new therapeutic opportunities. Our specific aims will test the following hypotheses: (Aim1) Repression of immunoregulatory gene networks by FOXP3 requires the formation of a complex between this transcription factor and EZH2; (Aim 2) Inflammatory stimuli, such as IL6 lead to EZH2 phosphorylation and thereby disrupt the enzymatic activity of this epigenomic regulator; (Aim 3) Inhibition of the IL6 to EZH2 signaling pathway permits sustained Treg suppressive function in the setting of intestinal inflammation. Upon conclusion, we will understand the role for EZH2 in Treg loss of function in the setting of active inflammation. This contribution is significant since it will establish that several pathways targeted by available therapies (ie IL1β, IL6, TNFα) have the potential to regulate EZH2 HMT activity through post- translational modifications. Furthermore, current Treg cell therapy trials, while promising have not addressed the key issue of in vivo inflammation-induced disruption of Treg function. The proposed research is innovative because we investigate the effect of inflammatory signaling pathways on epigenetic complexes in Treg cells, a heretofore-unexamined process. Insight into epigenetic mechanisms is impactful as T cell progenitor cells inherit the parent transcriptional profile and unlike genetic change, they are modifiable by currently available therapy.

PUBLIC HEALTH RELEVANCE: The proposed research is relevant to the public health because IBD, increasing in prevalence, represents a major national cost measured by both patient suffering and economic burden; and despite significant advances in care, clinical trial data demonstrate remission rates at best of 40%. Upon conclusion, we will understand the role for EZH2 in Treg loss of function in the setting of active inflammation, and this discovery will stimulate the opening of a new avenue in therapeutics directed at stimulation of autologous Treg cells to function within the inflammatory milieu.

CRITIQUE 1

Significance: 2
Investigator(s): 3
Innovation: 3
Approach: 3
Environment: 2

Overall Impact: Dr. Faubion is an excellent physician-scientist who is an up and coming leader in the area of Treg biology related to GI diseases. He has published a number of very good manuscripts in the first funding period investigating the role of transcription factors and modulation of chromatin modifying complexes in Treg biology. In this application, he proposes to study the exciting area of epigenetic modulation of Treg suppressive function through the EZH2 signaling pathway. The area of investigation is considered highly significant. Globally, while studied by other leading investigators, pursuing regulation of epigenetic modifications of FoxP3 and Treg biology as a therapeutic approach for IBD is considered innovative. Enthusiasm for this application was somewhat dampened by the failure by the applicant to integrate and discuss the findings of three high profile recent papers that are directly related to this application (and suggest alternative mechanisms). In addition, the studies assessing the role of IL-6 related biology on the regulation of EZH2-mediated signaling would be strengthened by more preliminary data.

1. Significance:

Strengths

- Deciphering the role of epigenetic regulation of FoxP3 and Tregs has clear relevance to immune-mediated disease. Dr. Faubion's group made the initial discovery, confirmed by others in high impact journals, of a role for the histone methyl transferase EZH2 in the regulation of FoxP3.
- Inflammatory processes that potentially paralyze the HMT activity of EZH2 has relevance to Treg-targeted therapies.

2. Investigator(s):

Strengths

- Dr. Faubion is an excellent physician scientist. He is an Associate Professor of Pediatrics, Medicine and Immunology at the Mayo Clinic.
- He has published four senior authored manuscripts in the last five years in very good peer review journals (1 CMGH, 2 AJP, and 1 JBC) in the area of KLF regulation of Treg and lymphocyte biology.
- He is currently funded by the [redacted].

3. Innovation:

Strengths

- Directly investigating the role of epigenetic modifications on FoxP3 and Treg-mediated suppression and the role that inflammatory cytokines have in this process is considered innovative. As such, it is not surprising that this area has been extensively studied by a number of leading investigators (Bluestone, Rudensky, Laurence).

4. Approach:

Strengths

- The generation of conditionally targeted EZH2 mice (in FoxP3 positive cells) - $FOXP3^{\Delta EZH2}$ - that results in a lethal inflammatory disorder supports the hypothesis of a critical role of EZH2 in the epigenetic regulation of Tregs.

- Direct demonstration of interaction between EZH2 and FoxP3 support studies in Aim 1 which will investigate the critical domains required for functional activity. These experiments will yield clear results.
- Direct translation of these findings to EZH2 gene targets of relevance in IBD (RORA and IRF4) – both upregulated in CD – in reporter assays and ChIP assays with WT FOXP3/EZH2 and domain mutants are well outlined and focused (albeit perhaps too focused).
- Studies in Aim 2 to determine the role of the role of IL-6 on EZH-mediated suppression are likely to yield definitive and informative data. Similarly, experiments addressing the role of an EZH phosphomimetic Y641mutant and the non nonphosphorylatable Y641F mutant in vitro (Aim 2) and in vivo (Aim 3) are likely to yield informative data.

Weaknesses

- Defective function of Tregs in vitro contrasts with recent publications by Bluestone et al – suggesting normal in vitro function. These differences are not discussed and should since they may point different mechanistic functions. Indeed these differences are relevant to the in vitro suppression assays outlined in several sub aims.
- In addition to the unpublished worked presented in this proposal, data pointing to the role of EZH2/FoxP3 interactions in regulating colitis has been recently published by Laurence et al. These data due support the use of specific constructs to determine the precise interactions necessary to mediate EZH2-mediated suppression. However, the statement that “these exciting experiments will be the first to test a modifiable epigenetic mechanism in the treatment” of IBD is exaggerated.
- Rudensky et al has suggested that inflammatory signals induce the EZH2-Foxp3 mediated suppressive program. These data are counter to the hypothesis proposed and necessitates discussion.
- In this regard, the potential role of IL-6-driven and JAK2-mediated phosphorylation of EZH2 leading to inhibition of EZH2-dependent suppression while exciting would be strengthened markedly by preliminary data showing that IL-6 fails to suppress Treg function in the absence of EZH2.
- Studies investigating the role of blocking IL-6R in Tregs as a mechanism for treating colitis while potentially related to EZH2 may have many other possible mechanisms. The studies outlined, while potentially clinically relevant, do not support a direct role of IL-6R-activation in inhibiting EZH2 mediated suppression. Nonetheless, as noted above expression of the EZH phosphomimetic Y641mutant and the non nonphosphorylatable Y641F in Tregs will indirectly support a role of IL-6R activation in this process.

5. Environment:

Strengths

- Outstanding environment at the Mayo Clinic.

Protections for Human Subjects: Not Applicable (No Human Subjects)

Vertebrate Animals: YES, all five points addressed

Biohazards: Acceptable

Resubmission: Overall the applicant responded to the initial critiques. The applicant has added three new senior authored publications to his portfolio. He adequately addressed the extension of his original research project on KLF to study of EZH2.

Renewal: The applicant has published 10 peer review papers related to his initial project in very good (but not top) journals.

Budget and Period of Support: Recommend as Requested

CRITIQUE 2

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 1

Overall Impact: Goal of this revised competitive renewal R01 application is to further define the roles and mechanisms of FOXP3 and Treg cells in the pathogenesis of IBD, with particularly focusing on an epigenetic regulator histone methyltransferase (EZH2). Experiments outlined in the current proposal are natural extension of the PI previous works, but they are to further explore a new area by testing an interesting and novel hypothesis with considerable amounts of supporting preliminary results. The proposal is based on a strong rationale, well-prepared, and has a great potential impact in clinically important area of IBD. The productivity of the previous funding period is very good. The PI is a leader in this area and continuously successes in basic and translational research. All questions and concerns raised by previous study section have been nicely addressed by the PI, and some new preliminary results are also provided. Although there are still some minor concerns with the revised application, they don't affect overall enthusiasm to this proposal, based on PI track record and experience. The impact of this project is pretty high and it would provide crucial information about our understanding of EZH2 in IBD.

1. Significance:

Strengths

- Studies proposed in the application address key aspects of FOXP3 and Treg cells in the immune-response to inflammation in the gut mucosa and have great potential impact on the important area of IBD.
- To define biological role of EZH2 and its regulatory function on FOXP3 and Treg cells is novel and of significant.
- Many of the techniques proposed as well as recently generated new conditional knockout mice models are also novel.
- Experiments investigating EZH2 phosphorylation events during inflammation would provide significant information regarding gene regulatory cascade and it is also a potential new target of immunotherapy for patients with IBD.

Weaknesses

- Several previous studies have shown that IL-6 mediated disruption of Treg function is not totally dependent on EZH2.

2. Investigator(s):

Strengths

- The PI is an outstanding physician scientist with an excellent track record and particular expertise for the proposed experiments.
- The PI and this creative group are able to carry out all experiments outlined in the current application.

Weaknesses

The productivity of previous funding period is moderate.

3. Innovation:

Strengths

- Studies defining the mechanisms by which EZH2 modulates Treg cells and FOXP3 transcription factor in the setting of intestinal inflammation by using various genetically modified mouse models and state-of-the-art techniques are highly innovative.

Weaknesses

- Mechanisms underlying IL-6 mediated disruption of Treg cell function have been previously reported by many labs.

4. Approach:

Strengths

- Experiments are nicely and logically designed with appropriate controls proposed, and the protocol is easy to be read and followed.
- All necessary animal models and in vitro systems, functional and molecular biology assays for proposed studies are available and have been used on daily base for many years in the PI's lab. Alternative plan is also provided in the proposal.
- There are considerable amounts of preliminary results with the revised application, which support the hypothesis and verify the feasibility of methods.

Weaknesses

- The novelty of some experiments in Aim #2 needs to be improved.

5. Environment:

Strengths

- The environment is excellent at Mayo clinic.
- The lab and available facility of the PI are suitable for completing experiments proposed in the current application.

Protections for Human Subjects: Not Applicable (No Human Subjects)

Vertebrate Animals: YES, all five points addressed

Biohazards: Acceptable

Resubmission: All questions are addressed nicely by the PI, and some new preliminary results are also provided in the revised application. The proposal is improved significantly in general. Some technical concerns are minor and would be solved easily by the PI.

Resource Sharing Plans: Acceptable

Budget and Period of Support: Recommend as Requested

CRITIQUE 3

Significance: 1
Investigator(s): 1
Innovation: 1

Approach: 1
Environment: 1

Overall Impact: This A1 revised application proposes to investigate how inflammatory stimulus such as IL-6 disrupts EZH2-mediated transcriptional repression of FOXP3 target genes in IBD. In their last funding cycle, this group discovered that EZH2-mediated transcriptional repression is essential for Treg suppressor function. The previous review of this grant acknowledged the outstanding expertise of this investigator. The significance of the proposal was deemed quite strong, with possible translation into clinical setting and immunotherapy, and broad applicability in inflammatory diseases. The grant was considered high on innovation. Previous concerns were raised regarding the approach. Here, the investigator responds positively and is able to adequately address most of the concerns raised during the earlier review. This includes the addition of significant new data that supports their hypothesis and demonstration of feasibility. Additionally, some concerns were noted about publication record, which has been satisfactorily addressed by the investigator. Therefore, the overall impact of this outstanding proposal is now considered to be high.

1. Significance:

Strengths

- Concerns were noted in the last review regarding sufficiency of EZH2 in regulating Treg function. New data is presented demonstrating $FOXP3^{DEZH2}$ shows enhanced susceptibility to DSS-induced colitis. $FOXP3^{DEZH2}$ lymphocytes also show increased IFNγ and IL-17, and reduced IL10 production - perhaps by inhibition of a co-activator of IL-10 or indirectly in response to IFNγ and IL-17. Additionally, co-transfer of $FoxP3^{+}$ cells following inducible deletion of EZH2 did not confer protection in a T cell-transfer model of colitis.
- Published accounts of IL-6 mediated disruption of Treg function exists. Notwithstanding, this project appears unique in proposing a cell autonomous mechanism of I-L6 action on $FOXP3^{+}$ T cells.

2. Investigator(s):

Strengths

- While the publication record of the investigator was lauded, there were some concerns about paper with senior authorship and impact factor of journals published in. The concern was particularly raised in the backdrop of what was considered a change in direction (EZH2-focussed as opposed to KLF10-focussed). The investigator now lists 10 papers related to the project, including 6 as senior author. Additional 6 papers are listed outside of the focus of the prior grant. This raises the confidence in his ability to produce results. Additionally, the investigator now specifically points out a flow of logic linking KLF10 to EZH2. Therefore, it is felt that the investigator addressed this concern adequately.

3. Innovation:

Strengths

- The proposal centers on a novel, cell autonomous mechanism of IL-6 action in disrupting Treg function.

4. Approach:

Strengths

- Previously, a number of concerns were noted in this section. The investigator responded positively and now provide substantial amount of new data to support feasibility.

- It was enquired whether FOXP3$^{\Delta EZH2}$ mice shows spontaneous colitis. The investigator now demonstrates, albeit not spontaneous colitis, enhanced susceptibility to 1% DSS. This can be considered supportive of the investigators hypothesis. The occurrence of spontaneous colitis is somewhat rare such as in in genetic ablation of IL10, and other models of deletion of important anti-inflammatory molecules such as TAM RTKs show induced, but not spontaneous, colitis. In humans, while the etiology remains unknown, the incidence of colitis may not be spontaneous and may depend upon environmental factors.
- It was suggested that involvement of STAT3 be considered. The investigator now refers to EZH2-mediated methylation of STAT3 in glioblastoma in alternative approaches and proposes to isolate EZH2 complex after IL6 treatment to identify binding partners and substrates.
- Feasibility of neonatal cell transfer experiments was questioned. The investigator jettisoned those experiments in the revised proposal, thus alleviating this specific concern.
- Cytokine profiling of colonic supernatants is included in Aim 1.3 as was suggested by Previous Reviewer 1.
- Substantial amount of new data is provided in support of Aim 2. Phosphorylation site was identified and phosphomimetic and nonphosphorylatable mutants are described.
- Concerns about progress in the previous funding period along with lack of some proposed studies viz. using KLF10$^{flox/flox}$ raised doubts about the investigators ability. The new preliminary data provided by the investigator, including new tools such as inducible deletion of EZH2 and phosphosite studies mostly alleviates the concerns.
- In response to a question, the investigator includes new data on the expression of immunoregulatory molecules and IFNγ, IL17 and IL10 in FOXP3$^{\Delta EZH2}$ Tregs.
- Concerns about high levels of cytokine in KO and spontaneous inflammatory pathology can be addressed by inducible ablation.
- The investigator added new data on T cell-transfer model.
- The investigator was amenable to the recommendation to improve potential pitfalls and alternative approaches for Aim 3.

Weaknesses

- EZH2 action in other lymphocytes was indicated as an area of concern. This point could have been addressed better.
- The downregulation of IL10 following ablation of a repressive histone methyltransferase function remains a bit of conundrum not addressed by the investigator.

5. Environment:

Strengths

- Mayo clinic is an outstanding institution and provides the right environment to perform the proposed work.

Protections for Human Subjects: Not Applicable (No Human Subjects)

Vertebrate Animals: YES, all five points addressed

Biohazards: Not Applicable (No Biohazards)

Resubmission: The applicant has adequately addressed the previous comments.

Resource Sharing Plans: Acceptable

Budget and Period of Support: Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

VERTEBRATE ANIMAL (Resume): ACCEPTABLE
COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Gastrointestinal Mucosal Pathobiology Study Section
Digestive, Kidney and Urological Systems Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
GMPB
October 22, 2015 - October 23, 2015

CHAIRPERSON

COMINELLI, FABIO , MD, PHD
PROFESSOR AND CHAIR
DIVISION OF GASTROENTEROLOGY AND LIVER DISEASE
CASE WESTERN RESERVE UNIVERSITY
CLEVELAND, OH 44106

MEMBERS

BARRETT, TERRENCE A, MD
PROFESSOR AND CHIEF
DIVISION OF GASTROENTERLOGY
AND LIVER DISEASE
DEPARTMENT OF MEDICINE AND IMMUNOLOGY
UNIVERSITY OF KENTUCKY MEDICAL SCHOOL
LEXINGTON, KY 40536

CLAUD, ERIKA C, MD *
ASSOCIATE PROFESSOR
DEPARTMENT OF PEDIATRICS
UNIVERSITY OF CHICAGO
CHICAGO, IL 60637

DE PLAEN, ISABELLE G, MD
ASSOCIATE PROFESSOR
NEONATOLOGY DIVISION
DEPARTMENT OF PEDIATRICS
CHILDREN'S MEMORIAL HOSPITAL
CHICAGO, IL 60614

DUDEJA, PRADEEP K, PHD *
PROFESSOR OF PHYSIOLOGY IN MEDICINE
DEPARTMENT OF DIGESTIVE DISEASE AND NUTRITION
COLLEGE OF MEDICINE
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, IL 60612

GEWIRTZ, ANDREW T, PHD
PROFESSOR
INSTITUTE FOR BIOMEDICAL SCIENCES
CENTER FOR INFLAMMATION, IMMUNITY AND
INFECTION
GEORGIA STATE UNIVERSITY
ATLANTA, GA 30303

GHISHAN, FAYEZ KHALAF, MD *
PROFESSOR AND HEAD
DEPARTMENT OF PEDIATRICS
UNIVERSITY OF ARIZONA
TUCSON, AZ 85724

IVANOV, ANDREI IVANOVICH, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF HUMAN AND MOLECULAR GENECTICS
THE INSTITUTE OF MOLECULAR MEDICINE
SCHOOL OF MEDICINE
VIRGINIA COMMONWEALTH UNIVERSITY
RICHMOND, VA 23298

JABRI, BANA , MD, PHD *
PROFESSOR
DEPARTMENT OF MEDICINE AND PATHOLOGY
CANCER RESEARCH CENTER
UNIVERSITY OF CHICAGO
CHICAGO, IL 60637

JOBIN, CHRISTIAN , PHD
PROFESSOR
DEPARTMENT OF MEDICINE
DIVISION OF GASTROENTEROLOGY
UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE
GAINESVILLE, FL 32610

KAO, JOHN Y, MD *
ASSOCIATE PROFESSOR
DIVISION OF GASTROENTOLOGY
DEPARTMENT OF INTERNAL MEDICINE
UNIVERSITY OF MICHIGAN
ANN ARBOR, MI 48109

KESHAVARZIAN, ALI , MD
PROFESSOR AND DIRECTOR
DEPARTMENT OF GASTROENTEROLOGY
AND NUTRITION
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, IL 60612

KHAZAIE, KHASHAYARSHA , DSC, PHD *
PROFESSOR
DEPARTMENTS OF IMMUNOLOGY AND SURGERY
MAYO CLINIC
ROCHESTER, , MN 55905

KHURANA, SEEMA , PHD
PROFESSOR
DEPARTMENT OF BIOLOGY AND BIOCHEMISTRY
BAYLOR COLLEGE OF MEDICINE
UNIVERSITY OF HOUSTON
HOUSTON, TX 77204

LOZUPONE, CATHERINE , PHD *
ASSISTANT PROFESSOR
DEPARTMENT OF MEDICINE
UNIVERSITY OF COLORADO - DENVER
ANSCHUTZ, CO 80045

LUO, XIN M, PHD *
ASSISTANT PROFESSOR
DEPARTMENT OF BIOMEDICAL SCIENCE
AND PATHOBIOLOGY
COLLEGE OF VETRINARY MEDICINE
VIRGINIA TECH
BLACKSBURY, VA 24061

MANNON, PETER , MD *
PROFESSOR
DIVISION OF GASTROENTEROLOGY AND HEPATOLOGY
UNIVERSITY OF ALABAMA AT BIRMINGHAM
BIRMINGHAM, AL 35294

MAZMANIAN, SARKIS K, PHD
PROFESSOR
DEPARTMENT OF BIOLOGY AND BIOLOGICAL ENGINEERING
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA, CA 91125

NEWBERRY, RODNEY D, MD
PROFESSOR
DIVISION OF GASTROENTEROLOGY
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
SAINT LOUIS, MO 63110

OUKKA, MOHAMED , PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF IMMUNOLOGY
SEATTLE CHILDREN'S RESEARCH INSTITUTE
UNIVERSITY OF WASHINGTON
SEATTLE, WA 98101

POLK, D BRENT, MD
PROFESSOR AND CHAIR
DEPARTMENT OF PEDIATRICS
CHILDREN'S HOSPITAL, LOS ANGELES
LOS ANGELES, CA 90027

RIVERA-NIEVES, JESUS , MD
PROFESSOR
DEPARTMENT OF GASTROENTEROLOGY
UNIVERSITY OF CALIFORNIA, SAN DIEGO
SAN DIEGO, CA 920930063

ROTHLIN, CARLA , PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF IMMUNOBIOLOGY
YALE UNIVERSITY
NEW HAVEN, CT 06510

SNAPPER, SCOTT B, MD, PHD
ASSOCIATE PROFESSOR AND WOLPOW FAMILY CHAIR
DIVISION OF GASTROENTEROLOGY AND NUTRITION AND TRANSLATIONAL RESEARCH
CHILDREN'S HOSPITAL BOSTON
BOSTON, MA 02115

VERNE, G NICHOLAS , MD *
PROFESSOR AND CHAIRMAN
DEPARTMENT OF MEDICINE
SCHOOL OF MEDICINE
TULANE UNIVERSITY
NEW ORLEANS, LA 70112

WANG, JIAN-YING , MD, PHD *
PROFESSOR AND ASSOCIATE CHAIR FOR RESEARCH
DEPARTMENTS OF PATHOLOGY AND SURGERY
SCHOOL OF MEDICINE
UNIVERSITY OF MARYLAND
BALTIMORE, MD 21201

WILSON, JEAN M, PHD
PROFESSOR
DEPARTMENT OF CELLULAR AND MOLECULAR MEDICINE
COLLEGE OF MEDICINE
UNIVERSITY OF ARIZONA
TUCSON, AZ 85724

YUN, CHANGHYON CHRIS, PHD *
PROFESSOR
DIVISION OF DIGESTIVE DISEASES
SCHOOL OF MEDICINE
EMORY UNIVERSITY
ATLANTA, GA 30322

ZAVROS, YANA , PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MOLECULAR AND CELLULAR PHYSIOLOGY
UNIVERSITY OF CINCINNATI
CINCINNATI, OH 45267

MAIL REVIEWER(S)

NJAR, VINCENT COLLINS OFUKA, PHD
PROFESSOR OF MEDICINAL CHEMISTRY AND PHARMACOLOGY
DEPARTMENT OF PHARMACOLOGY
HEAD, MEDICINAL CHEMISTRY SECTION
CENTER FOR BIOMOLECULAR THERAPEUTICS
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE
BALTIMORE, MD 21201

SCIENTIFIC REVIEW OFFICER

ZHAO, AIPING , MD
SCIENTIFIC REVIEW OFFICER
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

EXTRAMURAL SUPPORT ASSISTANT

WASHINGTON, KELLIE L
EXTRAMURAL SUPPORT ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

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