

PROGRAM CONTACT:  
Diane Adger-Johnson

**SUMMARY STATEMENT**  
( Privileged Communication )

*Release Date:* 10/31/2016  
*Revised Date:*

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*Application Number:* 1 F31 AI131622-01

CONTRERAS,NICO  
ABOR, UNIVERSITY OF ARIZONA  
UNIVERSITY OF ARIZONA

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*Review Group:* ZRG1 F07-T (20)  
Center for Scientific Review Special Emphasis Panel  
Fellowships: Immunology  
*Meeting Date:* 10/20/2016  
*Council:* JAN 2017  
*Requested Start:* 04/01/2017

*PCC:* X79A D  
*Dual PCC:* RAJ DUAL  
*Dual IC(s):* DK

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*Project Title:* The Immunological Consequences of Mouse Cytomegalovirus on Adipose Tissue

*Requested: 3 Years*

*Sponsor:* NIKOLICH-ZUGICH, JANKO  
*Department:*  
*Organization:* UNIVERSITY OF ARIZONA  
*City, State:* TUCSON ARIZONA

*SRG Action:* Impact Score:17  
*Next Steps:* Visit [http://grants.nih.gov/grants/next\\_steps.htm](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

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## **1F31AI131622-01 CONTRERAS, NICO**

**RESUME AND SUMMARY OF DISCUSSION:** This new F31 application proposes to determine if adipose tissue acts as a reservoir for mouse cytomegalovirus (mCMV) replication and establishment of latency, and characterize the adipose tissue CD8 T cell response during mCMV infection. The applicant is the first in his family to attend college, and although undergraduate grades are average, there is a strongly positive academic trajectory since joining graduate school. The reference letters are uniformly laudatory and describe the applicant as strongly committed to a career in research. The sponsor is leader in the field of aging of the immune system, is well-funded, and the applicant and sponsor are clearly well-matched. The research plan is very well put together with excellent preliminary data, and appropriate consideration of pitfalls and alternate approaches. The strong training plan, which was tailored to the applicant, will provide outstanding training. Overall, the review committee expressed an exceptional level of enthusiasm for this application.

**DESCRIPTION (provided by applicant):** Adipose tissue has long been thought to simply be a site of lipid synthesis and energy storage. However, it has become increasingly clear that the inflammatory state of adipose tissue has profound effects on host immunity and metabolism. Recent reports have demonstrated that both viruses and parasites are capable of directly infecting the adipocytes and cellular constituents of adipose tissue. Furthermore, Human Immunodeficiency Virus (HIV) is capable of becoming latent within T cells found in adipose. Cytomegalovirus (CMV), a ubiquitous betaherpesvirus, results in a persistent lifelong infection and the holy grail of CMV research has been to identify sites of latency, but no study has demonstrated the extent to which adipose tissue is infected or harbors latent and persistent virus. CMV has a broad cellular and tissue tropism, and susceptible cells are all represented within the adipose tissue. Thus, it is necessary to investigate the consequences, if any, of CMV infection within adipose. In order to understand the consequence(s) of CMV infection on adipose we will employ the C57BL/6 mouse CMV (mCMV) model of infection. The goal of this proposal is to understand the functional consequences and mechanism of spread during mCMV infection within adipose tissue. The overall hypothesis of this proposal is that mCMV disseminates to adipose tissue, replicates, establishes latency, leading to an lifelong CD8 T cell response. We will address the hypothesis and achieve the goals of this proposal by first, determining the cell type(s) that are infected within adipose tissue during infection by qPCR, plaque assay, and flow cytometry. We will also determine if mCMV is capable of becoming reactivated from within adipose tissue. Second, we will determine the kinetic expansion and contraction of mCMV specific CD8 T cells. Investigation into infection of and the role of adipose tissue during an immune response is a new and growing field, thus this work, when completed, will represent a significant advancement in our fundamental base of knowledge regarding mCMV cell tropism and persistence. The findings of this proposal will call for the consideration of adipose tissue in the context of infection, which has far reaching impact on vaccinology, immunology, virology, and endocrinology.

**PUBLIC HEALTH RELEVANCE:** Cytomegalovirus (CMV) infects a majority of the world's population. There has been correlation between CMV infection and metabolic health decline, such as atherosclerosis. Our preliminary results expand this correlation and possibly mechanistically link CMV infection and a decline in metabolism, manifested as glucose intolerance and insulin resistance.

### **CRITIQUE 1:**

Fellowship Applicant: 1  
Sponsors, Collaborators, and Consultants: 1  
Research Training Plan: 2  
Training Potential: 2  
Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:** This is a new F31 proposal by an excellent predoctoral student who has shown strong scientific curiosity and motivation in the development as a scientist. The overall goal of this project is to determine whether adipose tissue represents a site for CMV replication and persistent in mice and how this might impact the ensuing CD8 T cell response overtime. This is a timely and important topic, and likely to have significant overall impact on our understanding of CMV biology and vaccine design. The two aims are each independent but have a strong common theme that draw upon the expertise of the sponsor in T cell memory, viral infection models, biology of aging, and vaccination. The general questions being addressed are important and investigating the role of adipose tissue during an anti-viral response is likely to lead to exciting new findings. There is good preliminary data to support the proposed experiments. In general, the proposed studies are well designed and feasible. A major strength of this application is the academic training plan. It is well tailored to the needs of the applicant. The facilities are all outstanding. The sponsor is well funded and highly productive. Overall, in spite of some minor concerns, I have a high level of enthusiasm for this application.

### **1. Fellowship Applicant:**

#### **Strengths**

- B.S. in Physiology (2012) and M.S. in Professional Sciences (2014) at the University of Arizona.
- Active in student advocacy programs.
- Student representative on the Department's Diversity Committee.
- Recipient of many scholarships and awards: Wildcat Excellence Award 2008-2012 (Tuition Scholarship); Roman DeSanctis Scholarship 2010-2011; University of Arizona Graduate College Dean's Tuition Award 2014.
- Candidate has very strong supportive letters: very hard-working, highly motivated, highly dedicated to his research; the best graduate student in the department; enormous potential as an independent investigator in the future.

#### **Weaknesses**

- None noted.

### **2. Sponsors, Collaborators, and Consultants:**

#### **Strengths**

- Direct sponsor: Dr. Nikolich-Zugich MD, PhD -- Department head of the University of Arizona Department of Immunology and Co-director of the Arizona Center on Aging; is a world-leading expert on aging of the immune system and is well published.
- The sponsor has trained and mentored 11 doctoral students (10 graduated with Ph.D., one with M.Sc.) and 20 postdoctoral trainees, and 5 junior faculty/clinical fellows with K or R awards.
- Evidence of success of past trainees; 11 former postdoctoral trainees hold faculty positions.
- Evidence of good research support for the proposed studies.
- Sponsor will be training one doctoral student, 2 postdoctoral trainees. There should be ample time for the mentor to address the needs of the applicant.

#### **Weaknesses**

- None noted.

### **3. Research Training Plan:**

#### **Strengths**

- The proposed research is a largely unexplored area- important and clinically relevant data could come from these studies.
- On the whole the experimental plan is highly feasible and well within the expertise of the PI.
- Preliminary data are strong and intriguing.
- All the required expertise is readily available.
- Expected outcomes and alternatives for each aim are well described.
- The sponsor indicates a clear expectation for research productivity including the number of papers and the frequency of data presentation at the regional and national level.
- The applicant will participate in formalized professional lectures and workshops that are highly relevant to his future development.
- Will be applying to attend the NIA Advanced Course on the Biology of Aging.
- Involved in outreach programs to promote STEM careers.
- The descriptions of the exact scientific meetings to be attended, the frequency of meetings is well described.

#### **Weaknesses**

- None noted.

#### **4. Training Potential:**

##### **Strengths**

- The applicant has identified a novel area in immunology and virology to pursue his training—the studies have a good chance of having an impact on the field.
- There are outstanding training opportunities (e.g. seminars, workshops, professional development opportunities) available for the applicant's development.
- The descriptions of the exact scientific conferences to be attended, the frequency of the group meetings and the regular communication of research results to the scientific community are well described.

##### **Weaknesses**

- Lack of plans to acquire new skills in cutting-edge cellular immunology techniques important for the career path he hopes to follow.

#### **5. Institutional Environment & Commitment to Training:**

##### **Strengths**

- The institutional environment for the applicant's scientific development is of high quality.

##### **Weaknesses**

- None noted.

#### **Vertebrate Animals:**

YES, all five points addressed

- The use of mice, numbers of animals, and procedures for immunization and infections are appropriate.

**Biohazards:**

Acceptable

- Mouse CMV is a BSL2 agent. The sponsor and his research team have extensive experience working with CMV infection models, there are no concerns.

**Training in the Responsible Conduct of Research:**

Acceptable

Comments on Format (Required):

- 9 hours of RCR instruction, comprised primarily of live workshops, presentations, academic coursework and/or face-to-face discussions.

Comments on Subject Matter (Required):

- Contains the NIH-required topics.

Comments on Faculty Participation (Required):

- Faculty participation is noted.

Comments on Duration (Required):

- Nine-week course session

Comments on Frequency (Required):

- Every week over the course of a semester.

**Resource Sharing Plans:**

Acceptable

**Budget and Period of Support:**

Recommend as Requested

**CRITIQUE 2:**

Fellowship Applicant: 1

Sponsors, Collaborators, and Consultants: 1

Research Training Plan: 2

Training Potential: 1

Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:** Outstanding applicant for the F31 diversity fellowship is paired with an excellent mentor who is working on T cell responses, aging and CMV infection. The applicant's research plan is based on solid preliminary results and rationale. Investigations of the adipose tissue as a site of CMV persistence and immune responses is a novel area and the findings may be important to understand CMV pathogenesis and the role of the adipose tissue in persistent infections. Overall this is an excellent application with great training potential.

**1. Fellowship Applicant:**

**Strengths**

- The scholastic performance of the applicant is very good in grad school, all As.
- The applicant earned a Professional Science Master's degree with a project developing assays detecting blood borne pathogens.
- He has received NIH funding through the Initiative to Maximize Student Diversity Award and currently sit on the Department of Immunobiology Diversity Committees.
- The applicant is first in his family to complete a Bachelor's degree and go to graduate school.
- He has done his course work, passed his qualifying exam and completed successful lab rotations.
- His recommendation letters are outstanding.

#### **Weaknesses**

- None noted.

### **2. Sponsors, Collaborators, and Consultants:**

#### **Strengths**

- Dr. Nolic-Zugic is a well-established scientist, he has studied T cell development, homeostasis, aging and the immune system and T cell responses to persistent infections such as cytomegalovirus.
- He has a long track record of successfully mentoring graduate students and postdocs.
- He has funding to support the applicant's research.

#### **Weaknesses**

- None noted.

### **3. Research Training Plan:**

#### **Strengths**

- The applicant's research plan focuses on persistent cytomegalovirus infection and the adipose tissue in a mouse model (mCMV). As immune responses in the adipose tissue have systemic consequences the goal is to define whether adipose tissue is a site of MCMV persistence, reactivation and immune responses. This is a novel topic.
- The rationale for the project is solid.
- The preliminary data form a logical starting point for the project.
- The experiments in Aim 1 are feasible and will be informative. Alternative outcomes of Aim 1 are discussed, the techniques and concepts are well described.
- In Aim2 CMV-specific CD8T cells will be enumerated in the adipose tissue and will be characterized with appropriate techniques.

#### **Weaknesses**

- A minor concern is that the ip infection is not a natural route, it would be interesting, and perhaps important to see whether by other routes of infection similar results are obtained.

### **4. Training Potential:**

#### **Strengths**

- The training plan is well described and thought through.

- It is very likely that the applicant will have a successful training and career and will also contribute to the enhancement of diversity in biomedical research.
- The sponsor and the applicant seem to form a good mentor mentee relationship, which allows the mentee to develop his creative potential with the careful guidance of the mentor.

#### **Weaknesses**

- None noted.

#### **5. Institutional Environment & Commitment to Training:**

##### **Strengths**

- The environment and institutional support is excellent.

##### **Weaknesses**

- None noted.

#### **Budget and Period of Support:**

Recommend as Requested

#### **CRITIQUE 3:**

Fellowship Applicant: 4

Sponsors, Collaborators, and Consultants: 2

Research Training Plan: 3

Training Potential: 2

Institutional Environment & Commitment to Training: 2

**Overall Impact/Merit:** This F31 application proposes training as a Ph.D. graduate student in the field of viral immunology at Department of Immunology, University of Arizona. It is from an applicant with a clear commitment on biomedical research for career development and an outstanding personal and professional goal. While his scholastic performance during undergraduate study and publication record during master thesis is moderate, this continuous PhD training will give him an opportunity to improve in these aspects with this fellowship support. The Sponsor, Dr. Nikolich-Zugich, Professor and Head of Department of Immunobiology, has substantial and relevant track records mentoring PhD students and has complementary expertise. The goal of this proposal is to understand the possibility of mCMV infection and functional consequences on host immunity and mechanism of spread during mCMV infection within adipose tissue. The applicant has made an interesting observation that he could recover CMV specific CD8 T cells from adipose tissues of persistently CMV infected animals. In addition, there has been correlation between CMV infection and metabolic health decline, manifested as glucose intolerance and insulin resistance. This proposal will address a simple question: how long-term infection with a persistent virus, such as CMV, impact inflammation and immunity in adipose tissue. With the two specific aims carefully prepared, he proposes to follow through on these experiments in as reasonable thoughtful manner. He will certainly generate interesting and important information regarding the functional linkage between persistent virus infection and host immune response in adipose tissue. This project will provide an ideal context in which the applicant to be trained in the field of viral immunology and, if successful, will likely lead to strong publications. The applicant will learn many new techniques and the sponsor provides a detailed description of technical and academic milestones for the applicant's training that are consistent with his goal of being an independent investigator. The institution has suitable equipment and facilities as well as other outstanding faculty and students with whom the applicant will interact. The clear goal of applicant, close engagement of the sponsor, and skill

development that will result from the proposed research and training mitigate the moderate weaknesses in the scholastic performance during undergraduate study and productivity in the phase of master thesis. Overall, it is likely that the activities described in this proposal will provide strong training to advance the potential of applicant's research independence.

**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.

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Footnotes for 1 F31 AI131622-01; PI Name: Contreras, Nico

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