

AWARD NUMBER: W81XWH-19-1-0623

TITLE: Intra-Tumoral Steroid Production as a Mechanism of Immune Evasion in Adrenocortical Carcinoma (ACC)

PRINCIPAL INVESTIGATOR: Gary Hammer

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# REPORT DOCUMENTATION PAGE

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<b>14. ABSTRACT</b> Adrenocortical carcinoma (ACC) is a rare, aggressive cancer of the adrenal glands. Up to 75% of ACC patients will develop metastasis, but available therapies are ineffective and toxic. Immunotherapy has emerged as a promising strategy. The FDA accelerated approval of anti-PD-1 therapy for mismatch repair-deficient tumors including ACC, with rationale that genomically unstable tumors accumulate "neoantigens" that can be unmasked for immune clearance. However, therapy success relies on several factors including tumor immune infiltration, characteristically low in anti-PD-1-resistant tumors. In The Cancer Genome Atlas (TCGA) study on ACC, we observed ACC bears low expression of immune genes and is likely anti-PD-1-resistant. Paradoxically, the most aggressive ACC, with highest mutational burden, are the most immune poor. This ACC subset also exhibits pathologic cortisol excess and high expression of genes involved in steroid production. We <i>hypothesize</i> that in ACC, high concentrations of locally-produced steroids protect cancer cells from the immune system by impairing an anti-tumoral immune response. <u>Aim 1</u> - Characterization and quantification of ACC intra-tumoral steroidomics and the molecular phenotype of infiltrating immune cells. <u>Aim 2</u> - Functional characterization of the impact of ACC-secreted steroids on immune cell function and tumor immune infiltrate.					
<b>15. SUBJECT TERMS</b> NONE LISTED					
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## 1. Introduction

The adrenal glands synthesize and secrete a variety of hormones critical for life. Adrenocortical carcinoma (ACC) is a rare, aggressive cancer of these glands (5-year-survival ~35%). Up to 75% of ACC patients will develop metastasis, but available therapies are ineffective and toxic. ***There is an urgent need to identify novel therapies for advanced ACC that target tumor-specific vulnerabilities while limiting drug toxicity.*** Immunotherapy has emerged as a promising strategy for advanced cancers. The FDA accelerated approval of anti-PD-1 therapy for mismatch repair-deficient tumors including ACC, with rationale that genomically unstable tumors accumulate “neoantigens” that can be unmasked for immune clearance. However, therapy success relies on several factors including tumor immune infiltration, characteristically low in anti-PD-1-resistant tumors. In The Cancer Genome Atlas (TCGA) study on ACC, we observed ACC bears the lowest expression of immune genes of nearly all TCGA cancers, suggesting most ACC is likely anti-PD-1-resistant. Paradoxically, the most aggressive ACC, with highest mutational burden, are the most immune poor. This ACC subset also exhibits pathologic cortisol excess and high expression of genes involved in steroid production. Given the well-known immunosuppressive actions of glucocorticoids, these observations suggest intra-tumoral steroid production may be a novel mechanism of immune evasion in ACC. Our overall objective is to characterize a novel mechanism by which cancer cells evade the immune system, which will enable the development of improved therapeutic strategies to target ACC and other malignancies using immunotherapy. We hypothesize that in ACC, high concentrations of locally-produced steroids protect cancer cells from the immune system by impairing an anti-tumoral immune response.

## 2. Keywords

Adrenocortical carcinoma, ACC, immunotherapy, steroids, intra-tumoral steroids, tumor, orthotopic xenograft, transcriptome, steroidomics

## 3. Accomplishments

The major goals of this project, as stated in two Specific aims in the SOW, are:

- Specific Aim 1 – Characterization and quantification of ACC intra-tumoral steroidomics and the molecular phenotype of infiltrating immune cells. We will measure tissue concentrations of steroid hormones in frozen ACC samples from the University of Michigan Endocrine Oncology Repository by liquid chromatography-tandem mass spectrometry (LC-MS/MS). We will characterize the spectrum of infiltrating immune cells (including T cells) present in each sample by immunohistochemistry, and evaluate cytokines, immune signatures, and steroidogenic programs differentially expressed across ACC by RNA-seq. Through integrated analyses, we will characterize the immune cell signature associated with a given steroid profile and transcriptional program.
- Specific Aim 2 – Functional characterization of the impact of ACC-secreted steroids on immune cell function and tumor immune infiltrate. We will characterize secreted steroidomics of ACC-derived cell lines by LC-MS/MS. We will treat CD8+ T cells with conditioned media from ACC-derived cell lines +/- a variety of steroidogenesis inhibitors to evaluate impact of secreted steroids on T cell function in vitro. We will test if disrupting steroid receptor signaling using pharmacological antagonists of steroid receptors on T cells reverse these effects, and will extend findings to co-culture experiments with T cells and ACC cell lines. We will treat a steroidogenic, syngeneic xenograft mouse model of metastatic ACC with PD-1 inhibitors +/- inhibitors of steroid production/action, and measure impact on tumor burden and immune infiltrate.

For this reporting period, pertinent tasks as proposed in the SOW and **accomplishments** are described below:

- Specific Aim 1:

- Major Task 1 (months 1-10): Collect frozen human ACC samples; collect relevant clinical data.
  - Subtask 1: Protocol review and approval by the University of Michigan IRB. **(approved 06/23/2019, see appendix)**
  - Subtask 2: Protocol review and approval by the USAMRMC Human Research Protection Office **(initial approval 08/27/2019, see appendix)**
  - Subtask 3: Select 50 frozen ACC samples from the UM Endocrine Oncology Repository (MEOR); collect relevant clinical and demographic data. **(38/50 samples identified)**
  - Subtask 4: Quality-control checking of samples by histological assessment (will be performed by the Hammer Lab team, UM). We will evaluate sample quality by inspecting for areas of extensive necrosis or acellular material.
- Major Task 2 (months 10-14): Measure intra-tumoral concentrations of steroid hormones, precursors, and metabolites in human ACC samples by LC-MS/MS. **This task has not begun due to COVID-19 restrictions (see 5. Changes/Problems).**
  - Subtask 1: Harvest 200 mg of the 50 selected frozen ACC samples using a cryotome (will be performed by the Hammer Lab team, UM). Tissues will be harvested for LC-MS/MS steroid profiling (which will be performed in the next subtask) and for immunohistochemistry/immunofluorescence (will be performed in Major Task 3).
  - Subtask 2: Homogenize tissues and extract steroids for LC-MS/MS steroid profiling (will be performed by the Auchus Lab team, UM).
  - Subtask 3: Perform intra-tumor steroid profiling in collected samples (will be performed by the Auchus Lab team, UM) to measure the concentrations of intra-tumoral steroids present in each patient sample. LC-MS/MS data will be analyzed as in Rege et al. JCEM 2018.
- Major Task 4 (months 10-12): Characterize steroidogenic and immune-related transcriptional programs in human ACC samples by RNA-seq. **This task has not begun due to COVID-19 restrictions (see 5. Changes/Problems).**
  - Subtask 1: Extract RNA from the 50 ACC frozen samples (will be performed by the Hammer Lab team, UM).
- Specific Aim 2:
  - Major Task 6 (months 1-6): Characterize spectrum of ACC-secreted steroids in mouse and human models of ACC in vitro (Y1, NCI-H295R, SW13 cell lines). All experiments in this task will be performed in four biologically independent replicates. **These studies started late and are ongoing but have not been completed due to COVID-19 restrictions.**
    - Subtask 1: Measure steroids from conditioned media of ACC cell lines (these cell lines are available at the Hammer Lab; protocols for measuring steroids by mass spectrometry in conditioned media are established in the Auchus Lab).
    - Subtask 2: Treat cell lines with the following steroidogenesis inhibitors: metyrapone, trilostane, ketoconazole, etomidate, and abiraterone (this task will be performed in the Hammer Lab).
    - Subtask 3: Compare steroids in the conditioned media before and after treatment with steroidogenesis inhibitors. Each experiment will be performed in quadruplicates (each drug versus vehicle-treated cells). Changes in steroid production will be assessed by t-tests.
  - Major Task 7 (months 6-14): Measure the impact of ACC-secreted steroids on CD8+ T cell function in vitro. All experiments in this task will be performed in four biologically independent experiments in Dr. Keshamouni's lab, using conditioned media or cells from ACC cell lines maintained in Dr. Hammer's lab. For all experiments, statistical significance for differences in steroid production will be evaluated by Student's t-test for pairwise

comparisons or ANOVA with post-hoc tests for greater than pairwise comparisons. **We are currently developing a protocol to isolate CD8+ T cells from mice and these studies are on going, but have not been completed due to COVID-19 restrictions.**

- Subtask 1: Treat CD8+ T cells with conditioned media from ACC cell lines before and after treatment with steroidogenic inhibitors and steroid receptor inhibitors.
  - Subtask 2: Perform CD8+ T cells activation assay to measure changes in T cell proliferation after exposure to conditioned media.
  - Subtask 3: Perform CD8+ cells chemotaxis assay to measure changes in T cell migration after exposure to conditioned media by flow cytometry.
  - Subtask 4: Perform CD8+ apoptosis assay to measure changes in T cell apoptosis after exposure to conditioned media by TUNEL.
  - Subtask 5: Perform CD8+ cytokine production assay to measure changes in T cell cytokine production by ELISPOT.
  - Subtask 7: Perform co-culture experiments with ACC cell lines and CD8+ T cells and measure changes in ACC cytotoxicity after exposure to different steroidogenesis inhibitors by measuring changes in CD8+, NR5A1+ cells by immunocytochemistry and apoptosis by TUNEL.
- Major Task 8 (months 1-14): Characterize the metastatic potential, tumor dynamics, and steroidogenesis profile of a syngeneic, orthotopic xenograft model of ACC (this is a study utilizing cell lines engrafted in an animal model, which will be performed in the Hammer Lab). **This task has barely begun and is far from complete due to the substantial delays associated with obtaining ACURO approval (see below) and COVID-19 restrictions (see 5. Changes/Problems).**
- Subtask 1: Obtain ACURO approval for all the studies involving experimental animals. **(approval received 05/28/20, see appendix)**
  - Subtask 2: Cross male AHe/J mice and female C57L/J mice to generate LAF1 mice **(male AHe/J mice will need to be cryorecovered. See 5. Changes/Problems)**
  - Subtask 3: Perform US-guided orthotopic injection of Y1 cells in LAF1 mice – pilot study with 20 mice. 10 will be sacrificed 30 days after injection to measure steroid serum levels and IHC characterization of tumors. The US-guided Y1 cells orthotopic injection will be performed by Dr Erica A. Newman in her Lab, which Dr. Hammer's lab has access to.
  - Subtask 4: Perform steroid profiling in tumors originating from Y1 injection in 10 mice (serum steroids will be measured by mass spectrometry in the Auchus Lab) to evaluate if orthotopic xenografts are steroidogenic as predicted.
  - Subtask 5: IHC characterization of immune cell infiltration of Y1-derived tumors in 10 mice to determine if immune cells infiltrate orthotopic xenografts. **(we are now optimizing antibodies to detect immune cells by IHC in mouse tissue)**
  - Subtask 6: Characterization of the xenografts at the predetermined endpoint or death: evaluation of local tumor growth and metastatic potential. This study will be performed in the 10 remaining mice.

#### **Training opportunities and professional development:**

Graduate student research assistant Dipika Mohan has trained with members of Adrenal Research Group at the University of Michigan to learn how to extract steroids from media and tissue. Dipika is also training a rotating graduate student who is aiming to become core personnel on this project. When this student joins the lab and becomes core personnel, she will be added to the Participants section of all reports.

#### **Dissemination of results to communities of interest:**

Dr. Gary Hammer was invited to participate in a round table discussion focused on the future of ACC treatment/clinical trials at the 2019 Adrenal Cancer Symposium in Clermont-Ferrand, FR. He shared our upcoming and ongoing DOD-supported studies with the adrenal cancer research community. The citation for his contribution to the round table discussion is listed below:

Hammer GD (participant). Round Table on Clinical Trials/ACC Treatment. ACC 2019 (Adrenal Cancer Symposium 2019), Clermont-Ferrand, France, on September 27-28, 2019

4. **Impact:** Nothing major to report at this time. However, this subject is of increasing interest to the adrenal cancer research community and we expect this work when completed will have high impact.
5. **Changes/Problems:** We are experiencing a significant delay in patient enrollment, sample collecting and processing due to lockdowns and access restrictions to facilities related to COVID-19. All human subjects research and the Michigan Endocrine Oncology Repository (MEOR) was shut down from 03/14/2020 to 07/08/2020 (see appendix). All basic science research was shut down beginning 03/20/2020 (see appendix). On 05/26/2020, Wave 1 reactivation began for essential basic science research only. Wave 2 reactivation began on 06/17/2020 and Wave 3 reactivation began subsequently. As a result, we have not been able to process human samples, perform in vitro experiments, or perform in vivo experiments. However, we are adding additional personnel to this project (See 3. Accomplishments, Training opportunities...) and hope to accelerate our productivity in the next year. Additionally, AHe/J mice required for generation of LAF1 mice for orthotopic xenograft experiments are not readily available and will need to be cryorecovered from The Jackson Laboratory. This will lead to an additional 3-4 month delay in beginning xenograft studies.
6. **Products:** Nothing to report at this time.

## 7. Participants & Other Collaborating Organizations

Name: Gary D. Hammer

Role: Initiating Principal Investigator

Research Identifier: <http://orcid.org/0000-0001-6843-3628>

Nearest person month worked: 1

Contribution to Project: Dr. Hammer has supervised the study and lead meetings with all members of the research team.

Name: Richard J. Auchus

Role: Co-Investigator

Research Identifier: <https://orcid.org/0000-0001-6815-6181>

Nearest person month worked: 1

Contribution to Project: Dr. Auchus has shared his expertise regarding LC-MS/MS analysis of intra-tumoral and secreted steroids in frozen tissue samples and cell lines (respectively) during team meetings.

Name: Venkateshwar Keshamouni

Role: Co-Investigator

Research Identifier: <https://orcid.org/0000-0003-1947-791X>

Nearest person month worked: 1

Contribution to Project: Dr. Keshamouni has shared his expertise regarding in vitro and in vivo immune/tumor cell studies in team discussions.

Name: Antonio M. Lerario

Role: Co-Investigator

Research Identifier: <https://orcid.org/0000-0002-8336-6432>

Nearest person month worked: 1

Contribution to Project: Dr. Lerario has worked on optimizing sample acquisition for RNA-seq analysis and has shared bioinformatics expertise to evaluate study design and number and type of samples required for biological/clinical significance during team meetings.

Name: Dipika R. Mohan

Role: Graduate Student

Research Identifier: <https://orcid.org/0000-0002-6334-9416>

Nearest person month worked: 2

Contribution to Project: Ms. Mohan has worked with Dr. Lerario to optimize sample acquisition for RNA-seq analysis and evaluate study design, and has worked with Ms. Brand to obtain IRB approval. Ms. Mohan has also worked on extraction of ACC cell line secreted steroids with members of Dr. Auchus's team. Finally, Ms. Mohan has completed mouse training and helped with submitting amendments for the University of Michigan IACUC protocol and ACURO.

Name: Sarah Brand

Role: Coordinator of A5

Research Identifier: N/A

Nearest person month worked: 1

Contribution to Project: Ms. Brand has led submitting and obtaining IRB approval, and will also assist in enrolling and consenting patients at the University of Michigan and managing clinical data.

## 8. Special Reporting Requirements: Not applicable.

**9. Appendices:** Please see subsequent pages in the appendix for the following information –

Notice of HRPO approval (08/27/2019)

Notice of ACURO approval of animal studies (05/28/2020)

Notice that human subjects research will be stopped for COVID-19 research shutdown (03/14/2020)

Notice that all basic science research will be stopped for COVID-19 research shutdown (03/18/2020)

# E00965.1a - HRPO Approval Memorandum (Proposal Number CA180750, Award Number W81XWH-19-1-0623)

Nancy Englar <nancy.e.englar.civ@mail.mil>

Tue 8/27/2019 5:04 PM

To: Gary Hammer <ghammer@umich.edu>;

Cc: Kimberly Odam <kimberly.l.odam.civ@mail.mil>; Jodi Bennett <jodi.h.bennett.civ@mail.mil>; Margaret Frederick <margaret.m.frederick.ctr@mail.mil>; Mohan, Dipika <drmohan@med.umich.edu>; Katelyn Gibbs <katelyn.d.gibbs.ctr@mail.mil>; Nancy Englar <nancy.e.englar.civ@mail.mil>; Ashley Swanson <ashley.l.swanson2.ctr@mail.mil>; Darrell Beaver <darrell.l.beaver4.civ@mail.mil>;

SUBJECT: Initial Approval for the Protocol, "Intratumoral Steroid Production as a Mechanism of Immune Evasion in Adrenocortical Carcinoma (ACC)," Submitted by Gary Hammer, MD, PhD, University of Michigan, in Support of the Proposal, "Intratumoral Steroid Production as a Mechanism of Immune Evasion in Adrenocortical Carcinoma (ACC)," Submitted by Gary Hammer, MD, PhD, University of Michigan, Ann Arbor, Michigan, Proposal Log Number CA180750, Award Number W81XWH-19-1-0623, HRPO Log Number E00965.1a

1. The subject protocol was approved by the University of Michigan Medical School. Institutional Review Board (IRB) on 23 June 2019. The IRB determined that consistent with the 2018 Common Rule that no continuing review is required. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subjects protection requirements.
2. This no greater than minimal risk study is approved for the use of banked specimens and data from up to 100 adult subjects diagnosed with ACC.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRDC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
4. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to [usarmy.detrick.medcom-USAMRDC.other.hrpo-cr-documents@mail.mil](mailto:usarmy.detrick.medcom-USAMRDC.other.hrpo-cr-documents@mail.mil). Failure to comply could result in suspension or termination of funding.
  - a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRDC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution (Note: HRPO review and approval of institution is required), elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.
  - b. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.
  - c. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email ( [usarmy.detrick.medcom-USAMRDC.other.hrpo@mail.mil](mailto:usarmy.detrick.medcom-USAMRDC.other.hrpo@mail.mil)), by facsimile (301-619-7803), or mail to the U.S. Army Medical Research and Development Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.
    - (1) All unanticipated problems involving risk to subjects or others.
    - (2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.
    - (3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

d. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

5. Please note: The USAMRDC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract or grant/cooperative agreement funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds by notice of official award documentation. It is recommended that you contact the appropriate contract/grants specialist or Contracting/Grants Officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this study is Dr. Margaret Frederick, Human Subjects Protection Scientist, at 301-619-7418/margaret.m.frederick.ctr@mail.mil.

8. The HRPO point of contact for post-approval oversight is Ms. Katelyn Gibbs, Human Subjects Protection Scientist, at 301-619-7839/katelyn.d.gibbs.ctr@mail.mil.

Ms. Nancy Englar, MHL, CIP  
Human Subject Protections Scientist  
Human Research Protection Office  
USAMRDC Office of Research Protections (ORP)  
Email: nancy.e.englar.civ@mail.mil



**DEPARTMENT OF THE ARMY**  
HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
810 SCHREIDER STREET  
FORT DETRICK, MD 21702-5000  
May 28, 2020

Director, Office of Research Protections  
Animal Care and Use Review Office (ACURO)

Subject: Approval of Proposal Number CA180750, Award Number W81XWH-19-1-0623 entitled, "Intratumoral Steroid Production as a Mechanism of Immune Evasion in Adrenocortical Carcinoma (ACC)"

Gary Hammer  
University of Michigan  
Ann Arbor, MI, US

Dear Gary Hammer:

Reference: (a) DOD Instruction 3216.01, "Use of Animals in DOD Conducted and Supported Research and Training"  
(b) US Army Regulation 40-33, "The Care and Use of Laboratory Animals in DOD Programs"

In accordance with the above references, ACURO protocol CA180750.e001 entitled, "Renewal The Cooperation of MYCN and the DNA Damage response in Neuroblastoma in Vivo," IACUC protocol number PRO00008248, Protocol Principal Investigator Erika Newman, is approved by ACURO as of 05/28/2020 for the use of mice and will remain so until modification, expiration or cancellation. This protocol was approved by the University of Michigan IACUC on 03/26/2018; IACUC approval expires 03/26/2021.

**Required Actions:**

**A. Submit to ACURO for review and approval prior to implementing:**

- IACUC-approved de novo reviews of the protocol
- IACUC-approved significant changes to this protocol (see guidance document)

**B. Notify ACURO within 5 business days of any of the following:**

- Any noncompliance, suspensions or adverse events (see guidance document)
- Receipt of notification that the institution is under investigation by USDA
- AAALAC, International accreditation status change

For further assistance, please contact ACURO at (301) 619-6694, FAX (301) 619-4165, or via e-mail: [usarmy.detrick.medcom-usamrnc.other.acuro@mail.mil](mailto:usarmy.detrick.medcom-usamrnc.other.acuro@mail.mil).

***NOTE: Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer or Grant Officer can authorize expenditure of funds. It is recommended that you contact the appropriate Contract Specialist or Contracting Officer regarding the expenditure of funds for your project.***

Sincerely,

Dawn C. Fitzhugh, VMD, MPH, DACLAM  
Colonel, US Army  
Director, Animal Care and Use  
Review Office

Copies Furnished:

Erika Newman  
Dr. William King  
Dr. Daniel Myers  
Ms. Colleen L. Vogler  
Dr. Dipika Mohan  
Dr. Ray Martell  
Dr. Ashley L. Swanson  
Dr. Donna Kimbark



Dear Faculty and Research Staff,

The continued health and wellbeing of our entire University of Michigan community remains paramount. In an effort to minimize the risk of contracting or spreading COVID-19 in human participant research interactions and to preserve personal protective equipment for clinical care, the university is placing temporary restrictions on human subjects research effective Saturday, March 14, and continuing through Friday, May 1. We will continue to reevaluate this timeframe.

1. All research studies that currently require direct person-person interactions, but do not offer direct therapeutic (drug and device) benefit to subjects must immediately pause new enrollment and discontinue in-person interactions unless study procedures can be modified to use alternative methods of gathering study data (e.g., telephone interviews, email, etc.). Studies involving no direct person-person interactions with participants may continue (e.g., secondary data analysis, remote or online contact, etc.).
2. Studies that involve the administration of drugs or monitoring of devices that provide therapeutic benefit to study participants may continue, but study teams should consider alternatives to having the participant be on-site for all study visits (e.g., electronic monitoring and/or data collection, as possible). Study teams also should evaluate how illness and absences, drug shortages, facility closures, or lack of required personal protective equipment may impact treatment delivery or monitoring.
3. IRB review of new studies that are not essential for managing COVID-19 circumstances may be delayed.

Principal investigators, schools, colleges and units will partner with their research staff, students and graduate student research assistants who are impacted by this pause in work to identify an appropriate plan moving forward, including any financial ramifications this may pose. Faculty principal investigators should actively work to communicate this change to the teams.

Thank you again for your continued support of the U-M research enterprise. I encourage you to visit our [COVID-19: Research Operations at U-M page](#), which includes the latest information and resources so that our campus community can best manage their research and scholarship activities. This webpage will be updated regularly and will be the source of ongoing guidance in this evolving situation.

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With this enewsletter, the [Medical School Office of Research](#) is shifting from the monthly publication of "Research News" to a weekly edition. Please bookmark the important links below and consider setting up email alerts to stay abreast of the latest information not only from our organization, but from UMOR.

Events around us are continuously evolving, and our team is committed to keeping you informed and supporting our research community to the utmost of our ability.


**UMOR Research Operations**

**UMMS Office of Research**

## News Affecting Your Research Operation

### Prepare to Ramp Down by 5pm on Friday, March 20

Earlier today, Rebecca Cunningham, M.D., U-M Interim Vice President for Research, sent a message to the research community that announced the following:

*"In an effort to protect the health and safety of the University of Michigan community amid the rapidly changing COVID-19 situation, researchers across all three campuses should ramp down all noncritical research laboratory activities by 5 p.m. on Friday, March 20. We will continue to assess the situation at regular intervals.*

*Faculty, staff and students must ramp down all on-campus laboratory research activities, with the exception of research related to COVID-19. The university will maintain minimal access to laboratories so that critical activities, including the maintenance of animals, unique reagents, and essential equipment and materials, along with research related to COVID-19, can continue. Research and scholarship (e.g., analyzing data, writing and reviewing manuscripts, preparing presentations, developing new grant proposals, convening online discussions with students and lab staff, etc.) that can occur remotely should continue."*

Please visit the [UMOR Research Operations](#) web page to learn more details about Dr. Cunningham's announcement. Additionally, on that page under the tab labeled "Research Facilities/Laboratory Safety," you'll find downloadable links for:

- [Medical School Laboratory Shutdown Guidelines](#)
- [UMOR Laboratory Shutdown Guidelines](#)
- [Abbreviated Continuity of Operations Plan \(COOP\)](#)

These are very serious times, and the health and safety of our researchers and staff is of utmost importance. If you have questions, visit the [Medical School Office of Research's COVID-19](#) webpage, or please don't hesitate to reach out to the Medical School Office of Research at [ummsresearch@umich.edu](mailto:ummsresearch@umich.edu).

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## Guidance from the Facilities Team

[Medical School Facilities](#) has posted a webpage dedicated specifically to FAQs that might develop around the ramp down of biomedical research operations. [CLICK HERE](#) to learn more about:

- Emergency contacts
- Utilities such as power and water will remain on
- Continuity of services such as cleaning, maintenance, and dining
- Delivery and receiving
- And more.

Questions? Contact Medical School Facilities at [med.school.facilities@umich.edu](mailto:med.school.facilities@umich.edu).

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## Donate Supplies to Help Keep Healthcare Workers and Our Community Safe

This morning the clinical enterprise sent an email requesting needed supplies. Unopened materials needed include:

- Face Masks (e.g. loops around ears)
- N95 Masks (branded for medical or construction use)
- Safety eye wear (goggles) (branded for medical or construction use)
- Powered Air-Purifying Respirators (PAPRs)
- PAPR Hoods

### Who to Contact

Please e-mail : [umh-dock-receivingteam@med.umich.edu](mailto:umh-dock-receivingteam@med.umich.edu) to let them know that you will be dropping off supplies

### Where to Take Supplies

Michigan Medicine  
1500 East Medical Center Drive, Dock 5  
Ann Arbor, Michigan 48109

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## Guidance from the Animal Care & Research Program

On March 16, 2020, all individuals on an active animal use protocol [received an email](#) from the [Animal Care & Use Program](#) Leadership Team outlining several important updates and recommended changes for how PIs and their laboratories should organize research projects involving animals amid the rapidly changing COVID-19 situation.

In a [follow-up email](#) to the entire animal care and use community on March 17, 2020, U-M's Attending Veterinarian provided additional clarification on several pieces of guidance, including:

- Continuity of routine daily husbandry and veterinary care
- Ongoing experiments using animals
- Cessation of breeding as it pertains to commercially-available species/strains
- Animal identification
- Placing orders for animals and other medications/supplies
- ULAM Training Core classes
- IACUC protocol reviews
- And many more.

Please review [this information](#) carefully to determine appropriate actions on how to best safeguard your research during this time. Ongoing guidance, information, FAQs, and other updates regarding research involving animals will be posted to the [UMOR Research Operations webpage](#).

Perhaps more than most, we are accustomed to maintaining our poise and carrying out our responsibilities during unusual circumstances. Please know that our entire animal care team remains committed to supporting your research, your staff, and the animals within our care, however possible. With this in mind, please continue to reach out to our team with any questions and concerns at [acuoffice@umich.edu](mailto:acuoffice@umich.edu); we are here to help safeguard and support your research activities.

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## Proposal Submissions and Award Management

The [Grant Services & Analysis](#) team wants to remind our research community to review two important sections of the [UMOR Research Operations](#) webpage. The "**Proposal Submission and Award Management**" section on that page includes information about:

- Proposal deadline extensions
- How the NIH is responding to the COVID-19 situation
- When to seek prior approval from a sponsoring agency
- What happens if the COVID-19 situation slows or halts progress on a project
- And more.

And the "**Costs During the COVID-19 Health Crisis**" section on the page addresses:

- U-M's recommendations on the approach to charging of salaries when no work is performed due to COVID-19
- Getting reimbursed for the costs incurred during the pause on NIH-funded human subjects research
- Whether a grant will pay for project-related costs, such as animal per diem, incurred during a ramp down
- And more.

Please don't hesitate to contact us at [msgrants@umich.edu](mailto:msgrants@umich.edu) if you have questions.

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## Study-Specific Planning Guidance

[IRBMED](#) has posted information on a Study-Specific Planning Guidance web page, including info about:

- Initiating new human subject research related to COVID-19
- Study team procedures for continuity of operations
- How to submit study-specific questions to the IRBMED staff owner identified for the study in eResearch
- And more.

Questions? Contact [irbmed@umich.edu](mailto:irbmed@umich.edu).

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## Temporary Restrictions on Human Subject Research

The [Clinical Trials Support Office](#) has created a specific webpage to address issues unique to our clinical research community. Visit the [CTSO-Specific COVID Updates](#) page for updates, including details about:

- Temporary restrictions on human subjects research
- MCRU activities regarding participants and community engagement
- Study monitoring visits
- Research Pharmacy FAQs

Please don't hesitate to contact us with questions at [ctsogroup@umich.edu](mailto:ctsogroup@umich.edu).

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## Resources for Remote Working

This is a reminder that HITS has posted a web resource "[Tech Guide to Working Remotely](#)," which includes helpful info about:

- Operating systems
- Internet connectivity
- VPN access and Duo preferences
- Collaboration tools
- And more.

Also, ITS Central Campus announced yesterday that the university now has an agreement with Zoom, a video conferencing service that offers options for online meetings, chat rooms, webinars, and mobile collaboration. [CLICK HERE](#) to learn more.

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## BlueJeans Dial-In Temporary Change

### If you're dialing in from off campus, new numbers are required

ITS Central Campus sent a message earlier this week indicating that BlueJeans is experiencing a degradation in service, and asking that staff and students stop using the university on-campus number – 763-1841 – immediately, if working off campus.

[CLICK HERE](#) to view the alternative numbers, and additional updates. ITS instructs that if you are working on campus, you should still connect to BlueJeans through 3-1841 to minimize the load on outbound calling volume.

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## Updates from the Medical School Office of Research

### Biomedical Research Core Facilities

In an effort to protect the health and safety of the University of Michigan community amid the rapidly changing COVID-19 situation and in compliance with directive from the UMOR, [Biomedical Research Core Facilities](#) (BRCF) will switch from normal to emergency operations.

As part of emergency operating procedures, all non-essential activities will be suspended, keeping only critical activities operational. Please visit our [website](#), contact Core Directors for updates regarding specific core access, or contact us at [brcf-umms@umich.edu](mailto:brcf-umms@umich.edu).

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### Calendar Review & Analysis Office

The [Calendar Review and Analysis Office](#) will remain open and conduct business consistent with the most current guidance from the university. We will handle immediate issues that arise on a case-by-case basis and follow prevailing guidance. In recognition of the benefits of social distancing in slowing the potential spread of COVID-19, CRAO staff are working remotely.

The University has released temporary restrictions on human subjects research in an effort to minimize the risk of contracting or spreading COVID-19 in human participant research interactions and to preserve personal protective equipment for clinical care. You can visit the [UMOR Research Operations](#) page under "Research Involving Human Subjects" to learn the full details.

[CLICK HERE](#) for our staff directory that includes email and phone numbers, or contact us at [cr2-ao@med.umich.edu](mailto:cr2-ao@med.umich.edu).

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### Central Biorepository

In compliance with the directive from UMOR that all labs should ramp down operations, the [Central Biorepository](#) (CBR) will switch from normal to emergency operations, no later than March 20, 2020. Non-essential activities will be suspended, keeping only critical activities operational, including:

- Maintenance of a safe work environment
- Control of in-transit biospecimens
- Maintenance of biospecimen temperatures
- Maintenance of the LabVantage database

CBR has already made arrangements to receive most, if not all, in-transit biospecimens and accession them into the appropriate long-term storage environment. Thank you for your partnership in communicating your needs and working with our team to send samples to CBR. **If you have not yet made arrangements for CBR to receive your samples, please do so now, so that we may receive and accession them by March 20, 2020.**

[CLICK HERE](#) for more details about CBR operations relative to the COVID-19 situation, or contact us at [cbr.requests@umich.edu](mailto:cbr.requests@umich.edu).

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## Clinical Trials Support Office

The [Clinical Trial Support Office](#) (CTSO) and its units will remain open and conduct business consistent with the most current guidance from the university. We will handle immediate issues that arise on a case-by-case basis and follow prevailing guidance. [CLICK HERE](#) to visit our COVID-19 web page, and please don't hesitate to contact us with questions at [ctsogroup@umich.edu](mailto:ctsogroup@umich.edu).

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## Data Office

In alignment with the U-M's policy encouraging telecommuting, the [Data Office](#) team is currently working from home. We will continue to be available by phone and email, individually and as a unit (click here: <https://doctrjira.med.umich.edu/service/portal/1>) so you should continue to experience the service you have come to expect across all our service areas.

Please watch return emails in the event a specific member of the team is out, and if needed, redirect your inquiry here: <https://doctrjira.med.umich.edu/service/portal/1> to be assisted.

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## Fast Forward Medical Innovation

The [Fast Forward Medical Innovation](#) team is currently working from home, in alignment with the U-M's policy encouraging telecommuting. We will continue to shepherd the biomedical research enterprise's business development, commercialization, and innovation education remotely, so you should not experience any disruption in the services we provide, but we encourage you to contact us via email with any concerns. [CLICK HERE](#) for our staff directory that includes email and phone numbers, or contact us at [ffmioffice@umich.edu](mailto:ffmioffice@umich.edu).

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## Grant Services & Analysis

Grant Services & Analysis team members are available by phone and email, individually and as a unit ([msggrants@umich.edu](mailto:msggrants@umich.edu) or [CLICK HERE](#)) so you should continue to experience the service you have come to expect across all our areas. Please watch return emails in the event a specific member of the team is out, and if needed, redirect your inquiry to [msggrants@umich.edu](mailto:msggrants@umich.edu).

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## IRBMED

IRBMED encourages study teams to monitor the [IRBMED website](#) for any changes in workflows and for additional guidance (especially IRBMED procedures for urgent amendments and study conduct during the research pause).

The [UMOR Research Operations](#) site also contains important responses to frequently asked questions that relate to clinical research at Michigan Medicine. Check that website frequently as questions are updated daily.

General questions for IRBMED can be submitted to [irbmed@umich.edu](mailto:irbmed@umich.edu). The email inbox will be monitored during normal business hours and over the weekend. Responses will be provided within one business day.

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## Unit for Laboratory Animal Medicine

The [Unit for Laboratory Animal Medicine](#) (ULAM) will maintain mechanisms for providing continued daily care to all animals housed on campus in the event of a natural disaster or other events that may interrupt normal business, including the COVID-19 situation.

This includes veterinary medical care; assessment of animal health and wellbeing; provision of food, water and clean cages; and maintenance of appropriate environmental conditions. All animal care staff (veterinarians, veterinary technicians, husbandry and housing, etc.) are considered mission-critical staff and report to work to ensure the continued health and well-being of all animals.

Questions? Contact us at [ulam-questions@umich.edu](mailto:ulam-questions@umich.edu).

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## Event & Scheduling Changes

Changes regarding events hosted or co-sponsored by units within the Medical School Office of Research.

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The [IRBMED](#) team has sent an update indicating that all their courses will be moved to BlueJeans and some dates will change. Registered participants will be notified via email, and registration will remain open. Visit the [IRBMED website](#) for their latest news, or contact [irbmed@umich.edu](mailto:irbmed@umich.edu) with questions.

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The [Fast Forward Medical Innovation](#) fastPACE final presentation event scheduled for **March 20** has been changed to a virtual event. [CLICK HERE](#) for details.

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The "Working with Industry" event hosted by the [Clinical Trial Support Office](#) and scheduled for **March 24** has been shifted from in-person to a virtual event. [CLICK HERE](#) for more details and the blue jeans login information or contact [ctsogroup@umich.edu](mailto:ctsogroup@umich.edu) with questions.

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The [Data Office](#) Lunch & Learn on **March 25** at NCRC has been canceled. The presentations scheduled for this session will be moved to the September installment, and a new date and location will be announced at a later time. Questions or concerns about the event? Email Michelle at [michbo@med.umich.edu](mailto:michbo@med.umich.edu).

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The [Central Biorepository](#) has canceled the Open House of their facility scheduled for **March 26**. The event will be rescheduled at a later date.

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[Fast Forward Medical Innovation's](#) "Pharmaceutical Industry: Trends, Opportunities, & Challenges" event featuring Paul Hudson, CEO of Sanofi, and scheduled **April 2** has been postponed and will be rescheduled at a later date. Please [CLICK HERE](#) for more details.

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The "International Mock Board Examination and Laboratory Animal Seminar Series" scheduled for **April 15-17** has been postponed. [CLICK HERE](#) for more details.

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The "Fifth Annual Science of Enrichment Symposium" scheduled for **April 22** has been postponed. [CLICK HERE](#) for more details.

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Looking for additional information about changes to training & events? Visit...

- [Medical School Office of Research Events & Workshops](#)
- [Faculty Development Workshops](#)
- [Michigan Medicine Events](#)



To better navigate the complexities of the U-M biomedical research enterprise, visit the [Research Project Lifecycle](#) . This interactive tool provides an overview of the resources available to you, not only within the Medical School Office of Research but also across the University. The "stops" along this lifecycle are highlighted above, and more information is available [online](#) .



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