AWARD NUMBER: W81XWH-19-1-0528

TITLE: Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)

PRINCIPAL INVESTIGATOR: Gary Hammer

CONTRACTING ORGANIZATION: University of Michigan
Ann Arbor, MI 48109-2200

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6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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14. ABSTRACT

We will assess the prospective utility of novel biomarkers in the clinical management of ACC. We hypothesize that serum steroids can specifically diagnose ACC, measure ACC burden, and detect recurrence; we also hypothesize that molecular biomarkers including tumor DNA methylation will predict ACC recurrence, progression, and selective response to adjuvant therapy.We will prospectively recruit ~200 participants with ACC or ACA from UM, A5, and ADIUVO-2. Diagnosis of ACC or ACA will be established by histology or imaging. Aim 1a: In patients with ACC or ACA, we will measure serum steroids by liquid chromatography-tandem mass spectrometry (LC-MS/MS) to identify ACC-specific steroid markers. Aim 1b: In patients with ACC, we will measure serum steroids as in Aim 1a with parallel imaging surveillance to identify steroid markers that predict recurrence. Aim 2a: In patients with ACC, we will measure tumor DNA methylation and determine if it predicts recurrence, progression, response to systemic therapies, and death. Aim 2b: In patients from ADIUVO-2, we will measure tumor DNA methylation and determine if it predicts adjuvant therapy-specific recurrence/survival. We will perform exome sequencing of paired tumor/germline DNA to prospectively identify genetic factors that predict response to adjuvant therapies.

15. SUBJECT TERMS

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1. Introduction

The adrenal glands are paired endocrine organs that produce steroid hormones and catecholamines critical for life. Adrenocortical carcinoma (ACC) is a rare cancer of these glands affecting ~1 individual/million/year worldwide. While ACC is rare, ~10% of the population bear benign adrenal lesions (largely adrenocortical adenomas [ACA]). Differentiating localized ACC from ACA is challenging, requiring extensive imaging workup. However, imaging often cannot rule out ACC, and exposes patients to collateral radiation. Half of all patients with ACC are diagnosed with surgically resectable localized disease. However, up to ~75% of all patients with ACC develop metastatic disease for which therapies are limited and prognosis remains dismal; <10% these patients survive 5 years after diagnosis. Early diagnosis of a recurrence is essential for appropriate management. Currently, mitotic activity in the primary tumor is the best predictor of recurrence, but aggressive disease course frequently observed among "low-risk" patients. Additionally, patients are usually surveilled with extensive imaging exams post-operatively, which is expensive and exposes patients to high doses of radiation. These statistics highlight significant gaps in the knowledge of optimal strategies for Diagnosis, Surveillance, and Prognosis of ACC. The goal of this proposal is to assess the prospective utility of novel biomarkers, including serum steroids and tumor DNA methylation, in diagnosis, risk stratification, and disease surveillance of patients with ACC This proposal will utilize samples prospectively obtained for the UM Endocrine Oncology Repository; the "American-Australian-Asian Adrenal Alliance" (A5), a large international collaborative network for adrenal research; and A5-initiated clinical trial ADIUVO-2 (NCT03583710), aiming to evaluate adjuvant therapies in patients with high grade ACC, randomized to receive mitotane alone or plus chemotherapy.

2. Keywords

adrenocortical carcinoma, ACC, DNA methylation, CIMP-high, steroidomics, LC-MS/MS, steroids, adjuvant therapy, adrenal cancer, adenoma, tumor, prospective, predictive, biomarker, adrenal, hormones

3. Accomplishments

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

- Specific Aim 1. Evaluating the use of steroid profiles in Diagnosis (Aim 1a) and Surveillance (Aim 1b) of adrenocortical carcinoma (ACC) patients. In patients with ACC or adrenocortical adenomas (ACA), we will measure serum steroids by liquid chromatography-tandem mass spectrometry (LC-MS/MS) to identify ACC-specific steroid markers (Aim 1a). In patients with ACC, we will measure serum steroids with parallel imaging surveillance to identify steroid markers that predict recurrence (Aim 1b).
- Specific Aim 2: Evaluating the use of tumor DNA methylation in stratifying ACC patients into risk groups (Prognosis). We will measure the methylation levels of a single locus, G0S2, and prospectively assess the utility of G0S2 hypermethylation in ACC risk stratification (Aim 2b), and in predicting response to different types of adjuvant therapy (Aim 2b).

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

- Specific Aim 1:
    - Major Task 1: Enrollment of 200 participants (ACA=100; ACC=100) and collection of relevant clinical data and biospecimens.
        - Subtasks 1 and 2 (also related to Specific Aim 2): Protocols review and approval by the University of Michigan IRBMED (approved on October 17, 2019) and by the USAMRMC Human Research Protection Office (approved on December 23, 2019)
        - Subtasks 3 and 4: Prospective enrollment of patients with ACC and ACA from the UM Endocrine Oncology Repository and American-Australian-Asian Adrenal Alliance (A5) that meet inclusion criteria for this study. To this date, we have consented 34 ACC patients and 26 ACA patients. Serum is available on a total of 35 patients out of 64 planned target for this reporting period due to COVID19 restrictions from

03/14/2020 to 07/08/2020 (see appendix). In addition, we received 72 samples from our collaborators at MD Anderson.

- Major Task 2: Serum steroid profiling by LC-MS/MS.
  - Subtask 1: Mass spectrometry assays have been modified with new internal standards for key analytes, improved sample preparation methods, and changes in drying procedures to minimize artifacts. We currently have performed serum steroid profiling of 72 samples received in collaboration. The LC-MS/MS analysis of University of Michigan samples is delayed due to COVID19 but is in the process of resuming.

- Specific Aim 2:
  - Major Task 1: Enroll 100 participants with ACC; collect relevant clinical data and biospecimens.
    - Subtask 1: See subtasks 3 and 4 from Major Task 1 (above).
    - Subtask 2: Due to lab access restrictions secondary to COVID-19, we have not started processing ACC samples for DNA extraction and determination of G0S2 methylation levels. However, we were able to develop an optimized protocol that enables the use of formalin-fixed paraffin-embedded (FFPE) samples to study DNA methylation, which will accelerate enrollment to this study and will enable supplementation with archival samples from our repository.

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 develop an improved technique for extracting DNA from FFPE tissue for DNA methylation analysis.

Dissemination of results to communities of interest:
Dr. Antonio Lerario was invited to give a 20-min oral presentation on the biomarker described in this proposal at the 2019 Adrenal Cancer Symposium in Clermont-Ferrand, FR. He discussed the preliminary data (now published) that has supported the ongoing studies described in this proposal and also shared our upcoming and ongoing DOD-supported studies with the adrenal cancer research community. The citation for his presentation is listed below:

Lerario AM. The role of G0S2 in ACC. Oral Presentation. ACC 2019 (Adrenal Cancer Symposium 2019), Clermont-Ferrand, France, on September 27-28, 2019

4. **Impact:** Nothing major to report at this time. However, our recent development of an improved technique to perform methylation profiling on FFPE tissue will now enable us to expand our study to include retrospective samples from University of Michigan and will enable us to include samples from investigators anywhere in the world. This represents a major advance in our ability to measure this biomarker.

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 from 03/14/2020 to 07/08/2020. As a result, we fell short of our target of 64 samples. However, we have received 72 serum samples from collaborators, and we are prepared to add additional samples that have been collected in our repository in the past.

6. **Products:** Nothing to report.

7. **Participants & Other Collaborating Organizations**

Individuals who have worked in this project during this reporting period are listed below. There are no changes from the previous submission of this information and no change in active or other support of the PD/PI or senior/key personnel since the last reporting period.

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 entire study and lead meetings with all members of the research team.

Name: Richard J. Auchus
Role: Partnering Principal Investigator
Research Identifier: https://orcid.org/0000-0001-6815-6181
Nearest person month worked: 1
Contribution to Project: Dr. Auchus has supervised his arm of the study and shared his expertise regarding LC-MS/MS analysis as we plan for sample acquisition during team meetings.

Name: Tobias Else
Role: Partnering Principal Investigator
Research Identifier: https://orcid.org/0000-0002-2262-0011
Nearest person month worked: 1
Contribution to Project: Dr. Else has supervised his arm of the study, facilitated acquisition of IRB approval, shared his expertise regarding serum sample analysis.

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 G0S2 methylation 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: 1
Contribution to Project: Ms. Mohan has worked with Dr. Lerario to optimize sample acquisition for G0S2 methylation analysis and evaluate study design, and has worked with Ms. Brand and Dr. Else to obtain IRB approval.

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.

Name: Patrick O'Day
Role: Technician
Research Identifier: N/A
Nearest person month worked: 1
Contribution to Project: Mr. O'Day has prepared and optimized mass spectrometer for measurement of steroid profiles from plasma samples.

Partner organizations which are collaborating with this project:

- Dr. Mouhammed Habra, MD (**MD Anderson Cancer Center**, Houston, TX).
- Dr. Anand Vaidya, MD **(Brigham and Women's Hospital** Boston, MA). (see appendices for supporting letters).

8. **Special Reporting Requirements:** Not needed.

9. **Appendices:**

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September 12, 2018

Gary D. Hammer, MD, PhD; Tobias Else, MD; Richard J. Auchus, MD, PhD
Floor B1 Reception A
1500 E Medical Center Dr SPC 5911
Ann Arbor, MI 48109-5911

Re: Letter of Support for CA180751 - "Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)"

Dear Drs. Hammer, Else, and Auchus,

It is a pleasure to support the proposed grant to the Department of Defense Peer Reviewed Cancer Research Program Translational Team Science Award, CA180751, entitled, "Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)." Your proposal seeks to improve strategies for diagnosis, surveillance, and prognosis of adrenal cancer using steroid and molecular biomarkers.

As an Associate Professor of Medicine in the Department of Endocrine Neoplasia and Hormonal Disorders, I am delighted to provide available adrenal tissue samples and serum/germline samples as part of the recently established American Australian Asian Adrenal Alliance (A5). The recently established study (Adjuvant therapy in high risk adrenal cancer patients-ADIUVO2) will provide prospectively collected biospecimens that can also be utilized to achieve the goals of your proposal. I estimate that we see ~40-50 new adrenal cancer patients per year and perform surgeries on at least 10 cases. This is in addition to numerous adrenal surgeries done for diagnoses other than adrenal cancer.

As such, I look forward to working with you and your team in this exciting study which will demonstrate the prospective value of serum steroid and tumor DNA methylation-based biomarkers in diagnosing adrenal cancer, measuring tumor burden, stratifying clinical outcomes, and predicting response to clinical interventions. Your study has great potential to refine approaches for clinical management of adrenal cancer, and to illuminate additional molecular alterations which may predict therapeutic response.

Best wishes,

Mouhammed Amir Habra, MD, FACP, FACE
Associate Professor, Department of Endocrine Neoplasia and Hormonal Disorders
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BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

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Director, Center for Adrenal Disorders
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September 13, 2018

Gary D. Hammer, MD, PhD; Tobias Else, MD; Richard J. Auchus, MD, PhD
Floor B1 Reception A
1500 E Medical Center Dr SPC 5911
Ann Arbor, MI 48109-5911

RE: Letter of Support for CA180751 - "Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)"

Dear Drs. Hammer, Else, and Auchus,

I write this letter to confirm my commitment to collaborate with you on the project that you have described in your proposal to the Department of Defense Peer Reviewed Cancer Research Program Translational Team Science Award, CA180751, entitled, "Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)." This proposal will prospectively evaluate the utility of novel serum steroid profiling techniques and molecular biomarkers in the diagnosis, surveillance, and prognosis of ACC.

As you know, I am the Director for the Center for Adrenal Disorders at Brigham and Women's Hospital. We are already engaged in several mutual collaborations and I look forward to collaborating on the proposed project as well. At Brigham and Women's Hospital, we see approximately 25-40 new patients with ACC, and 50-100 new patients with adrenocortical adenomas (ACA), every year. As you know, we are a member institution in the recently established American-Australian-Asian Adrenal Alliance (A5) Adrenal Network, which will facilitate our collaboration.

I look forward to contributing serum and tissue samples collected prospectively from participants with ACC and ACA for your proposal.

Sincerely,

Anand Vaidya, MD MMSc

UNIVERSITY OF MICHIGAN
eResearch.umich.edu
Medical School Institutional Review Board (IRBMED) • 2800 Plymouth Road, Building 520, Suite 3214, Ann Arbor, MI 48109-2800 • phone (734) 763 4768 • fax (734) 763 9603 • irbmed@umich.edu

To: Dr. Gary Hammer

From:

Michael Geisser
Alan Sugar

Cc:

Dipika Mohan
Tobias Else
Richard Auchus
Gary Hammer
Sarah Brand
Antonio Marcondes Lerario
Patrick ODay

Subject: Initial Study Approval for [HUM00166409]

SUBMISSION INFORMATION:
Study Title: Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)
Full Study Title (if applicable): CA180751 - Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)
Study eResearch ID: HUM00166409
Date of this Notification from IRB: 10/17/2019
Review: Full Committee
Initial IRB Approval Date: 10/17/2019
Current IRB Approval Period: **10/17/2019 - 10/16/2020**
Expiration Date:Approval for this expires at **11:59 p.m. on 10/16/2020**
UM Federalwide Assurance (FWA): FWA00004969 (For the current FWA expiration date, please visit the UM HRPP Webpage)
OHRP IRB Registration Number(s): IRB00001995
Supporting Documents: Letters of Support

Continuing Review Required: Yes

NOTICE OF IRB APPROVAL AND CONDITIONS:
The IRBMED has reviewed and approved the study referenced above. The IRB determined that the proposed research conforms with applicable guidelines, State and federal regulations, and the University of Michigan's Federalwide Assurance (FWA) with the Department of Health and Human Services (HHS). You must conduct this study in accordance with the description and information provided in the approved application and associated documents.

APPROVAL PERIOD AND EXPIRATION:
The approval period for this study is listed above. Please note the expiration date. If the approval lapses, you may not conduct work on this study until appropriate approval has been re-established, except as necessary to eliminate apparent immediate hazards to research subjects. Should the latter occur, you must notify the IRB Office as soon as possible.

RENEWAL/TERMINATION :
At least two months prior to the expiration date, you should submit a continuing review application either to renew or terminate the study. Failure to allow sufficient time for IRB review may result in a lapse of approval that may also affect any funding associated with the study.

IMPORTANT REMINDERS AND ADDITIONAL INFORMATION FOR INVESTIGATORS

APPROVED STUDY DOCUMENTS:
You must use any date-stamped versions of recruitment materials and informed consent documents available in the eResearch workspace (referenced above). Date-stamped materials are available in the "Currently Approved Documents" section on the "Documents" tab.

AMENDMENTS:
All proposed changes to the study (e.g., personnel, procedures, or documents), must be approved in advance by the IRB through the amendment process, except as necessary to eliminate apparent immediate hazards to research subjects. Should the latter occur, you must notify the IRB Office as soon as possible.

AEs/ORIOs:
You must inform the IRB of adverse events (AEs) and other reportable information and occurrences (ORIOs) according to your IRB's required reporting timetable (IRBMED and IRB-HSBS/Flint/Dearborn).

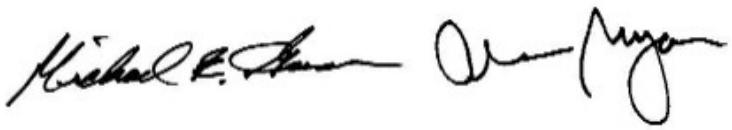
UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS (UPIRSOs or UaPs) :
Investigators must inform the IRB promptly of any potential Unanticipated Problems (UaPs or UPIRSOs) that come to the attention of the study team. Unanticipated Problems meet **all of the following criteria:**

1. **Unexpected** (in terms of nature, severity, frequency);
2. **Related or possibly related to participation in the research;** and
3. Suggests that the research places subjects or others at **a greater risk of harm** than was previously known or recognized.

See U-M HRPP Operations Manual Part 12.III.B.1.a.

SUBMITTING VIA eRESEARCH:
You can access the online forms for continuing review, amendments, and AEs/ORIOs in the eResearch workspace for this approved study (referenced above).

MORE INFORMATION:
You can find additional information about UM's Human Research Protection Program (HRPP) in the Operations Manual and other documents available at: http://research-compliance.umich.edu/human-subjects.



Michael Geisser **Alan Sugar**

E00954.1a - HRPO Approval Memorandum (HUM00166409, Proposal Number CA180751, Award Number W81XWH-19-1-0528)

Hammer, Gary

Mon 12/23/2019 9:27 AM

To: Marcondes Lerario, Antonio <alerario@med.umich.edu>; Mohan, Dipika <drmohan@med.umich.edu>; Lisa Byrd <lisakb@umich.edu>; La Pensee, Christopher <lapensee@med.umich.edu>;

Cc: Else, Tobias <telse@med.umich.edu>; Auchus, Richard <rauchus@med.umich.edu>;

From: Jessica Mendoza <jessica.l.mendoza19.civ@mail.mil>
Date: Monday, December 23, 2019 at 8:38 AM
To: Gary Hammer <ghammer@umich.edu>
Cc: Kimberly Odam <kimberly.l.odam.civ@mail.mil>, Jodi Bennett <jodi.h.bennett.civ@mail.mil>, "La Pensee, Christopher" <lapensee@med.umich.edu>, Lisa Byrd <lisakb@med.umich.edu>, Ismael Anoumatacky <namkpri.i.anoumatacky-akessepokou.ctr@mail.mil>, Lynell West <lynell.r.west.ctr@mail.mil>, Jessica Mendoza <jessica.l.mendoza19.civ@mail.mil>, Ashley Swanson <ashley.l.swanson2.ctr@mail.mil>, Darrell Beaver <darrell.l.beaver4.civ@mail.mil>
Subject: E00954.1a - HRPO Approval Memorandum (HUM00166409, Proposal Number CA180751, Award Number W81XWH-19-1-0528)

SUBJECT: Initial Approval for the Protocol, "Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)," Submitted by Gary D. Hammer, MD, PhD, University of Michigan, Ann Arbor, Michigan, HUM00166409, Proposal Log Number CA180751, Award Number W81XWH-19-1-0528, HRPO Log Number E00954.1a

1. The subject protocol was approved by the University of Michigan Institutional Review Board (IRB) on 17 October 2019. 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 accrual of adrenal tumors specimens from 250 Subjects.

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. **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. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 16 October 2020. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. 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.

d. 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), 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.

e. 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. Ismael Anoumatacky, DDS, Human Subjects Protection Scientist, at 301-619-3190/namkpri.i.anoumatacky-akessepokou.ctr@mail.mil.

8. The HRPO point of contact for post-approval oversight is Mrs. Lynell West, Human Subjects Protection Scientist, at 301-619-6247/lynell.r.west.ctr@mail.mil.

Ms. Jessica Mendoza
Human Subjects protections Scientist
Human Research Protection Office
USAMRDC Office of Research Protections (ORP)
Email: jessica.l.mendoza19.civ@mail.mil

Friday, September 27th

Registration & welcome coffee	**07:30-08:15**
Welcome address	**08:15-08:30**
Plenary Lecture	**08:30-09:15**

Pr Franck Pagès, HEGP, Paris, France
Immunoscore and immune modulation of Cancer

Basic Science in Adrenocortical Cancer	**09:15-11:00**

chairs : *Ono Meijer, Michaela Luconi*

Enzo Lalli, IPMC, Nice, France *09:15-09:35*
New markers of malignancy in ACC

Antonio Lerario, University of Michigan, Ann Arbor, USA *09:35-09:55*
The role of G0S2 in ACC

Nadia Cherradi, CEA, Grenoble, France *09:55-10:15*
The role of miRNAs in adrenocortical cancer pathogenesis

Alexandre Boyer, University of Montreal, Canada *10:15-10:35*
Hippo signaling in adrenal physiology

Laura-Sophie Landwehr, University of Würzburg, Germany *10:35-10:55*
Steroid hormones and cancer immunity in adrenocortical carcinoma

Coffee break	**11:00-11:30**
Genetics of Adrenal Tumors	**11:30-13:15**

chairs : *Jérôme Bertherat, André Lacroix*

Electron Kebebew, Stanford, USA *11:30-11:50*
Translating metastatic ACC OMICs analyses to new therapies

Emilia Pinto, St Jude Children's Hospital, Memphis, USA *11:50-12:10*
XAF1 as a modifier of P53 function and cancer susceptibility

Gareth Bond, Ludwig Institute for Cancer Research, Oxford, UK *12:10-12:30*
Genetic determinants of onset of ACC

Bill Rainey, University of Michigan, Ann Arbor, USA *12:30-12:50*
Novel driver genes in aldosterone producing adenomas

Dipika R Mohan, University of Michigan, Ann Arbor, USA *12:50-13:10*
DNA hypermethylation is directed to PRC2 targets and propagated independently of PRC2 in CIMP-high ACC

Invited Speaker

Name of presenting author: Antonio Marcondes Lerario

Email of presenting author: alerario@umich.edu

Laboratory / Hospital: University of Michigan

City: Ann Arbor, MI

Country: United States of America

Title of submission: The role of G0S2 in ACC

Authors list: Antonio Marcondes Lerario

Affiliations: Department of Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan, Ann Arbor, Michigan

Abstract: Adrenocortical carcinoma (ACC) is a rare, aggressive malignancy with few therapies. Surgery with adjuvant mitotane is standard of care for patients with locoregional disease. Despite this, up to 2/3 of patients recur with incurable metastases. While expert opinion recommends platinum-based adjuvant therapies for “high risk” patients, current cell proliferation-based prognostication strategies are often unreliable for individualizing therapeutic decisions. Recently, The Cancer Genome Atlas study on ACC (ACC-TCGA) identified that ACC is comprised of three distinct molecular classes (COC1-3), each driven by unique epigenetic, transcriptional, and somatic alteration signatures. Strikingly, the molecular features defining each class serve as independent predictors of clinical course, and patients with COC3 ACC almost invariably present with rapidly recurrent and fatal disease. Our work has focused on characterizing the molecular programs that define COC3, and – most recently – on developing strategies to translate this complex signature to clinic.

ACC-TCGA demonstrated that widespread CpG island hypermethylation (CIMP-high) is a hallmark of COC3. We recently demonstrated that binary hypermethylation and silencing of the gene G0S2 predicts CIMP-high status with 95% accuracy, and validated in an independent cohort of >100 adrenocortical tumors that G0S2 methylation identifies a subgroup of patients with CIMP-high disease kinetics (Mohan, Lerario et al. Clinical Cancer Research 2019). We also described a simplified restriction digest/qPCR strategy to accurately measure G0S2 methylation, enabling assignment of CIMP-high as early as 24 hours after surgery. G0S2 methylated/CIMP-high tumors account for 40% of ACC, nearly 70% of all recurrences, and >50% of deaths, highlighting a significant role for this marker in prognosticating ACC. Our current studies are directed to extending the application of this marker to prospective clinical trials (through A5 and additional platforms) so we may ultimately use G0S2 methylation status predictively, to guide therapeutic decisions for patients with COC3 ACC.

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.

From: Brand, Sarah
To: Brand, Sarah
Subject: FW: UMOR Human Research Activation Committee Approval
Date: Monday, August 10, 2020 10:18:23 AM

From: Brand, Sarah <sabrand@med.umich.edu>
Sent: Wednesday, July 8, 2020 1:07 PM
Subject: UMOR Human Research Activation Committee

From: U-M Human Research Activation Committee <human-research-activation@umich.edu>
Date: July 8, 2020 at 13:04:23 EDT
To: "Brand, Sarah" <sabrand@med.umich.edu>, "Hammer, Gary" <ghammer@med.umich.edu>
Subject: UMOR Human Research Activation Committee Approval

SENT ON BEHALF OF THE HUMAN RESEARCH ACTIVATION COMMITTEE

Date: July 8, 2020

Investigator: Gary Hammer

Project Title: The Michigan Endocrine Oncology Repository

Subject: UMOR Human Research Activation Committee Approval

The UMOR Human Research Activation Committee has completed the review of your study "The Michigan Endocrine Oncology Repository," HUM00024461. The outcome is shown below:

Review Decision:
This study is approved for Tier 1

This may or may not be the Tier you applied for when you submitted the Human Research Activation Checklist. It is your responsibility to refer to the Research Re-engagement website to determine which Tier(s) are open at any given time. It is also your responsibility to attend to changes regarding which Tier(s) are open at any given time.

If your Tier approval has conditions, those conditions are shown below. You must adhere to these conditions.

Reviewer conditions:

Per email with Sarah Brand these research samples will only be obtained if the subjects need to have samples drawn as part of their routine clinical care and she will use the daily health screen app before she picks up any samples at specimen processing.

If the reviewer had comments on your submission, they are shown below:

Important information:
You are responsible for obtaining regulatory approvals necessary to activate your study. Human Research Activation Committee approval is not Institutional Review Board approval.

You must notify your school/college leadership that you have been approved to activate your human research and adhere to any additional school/college requirements, including processes required to return to U-M space. This includes UM-Flint and UM-Dearborn.

Keep a record of the Tier to which this study was assigned and the approved Safety Plan. Different Tiers may need to be activated or deactivated in the future depending on the prevalence of COVID-19.

Please refer to the Research Re-engagement website for up-to-date information or email human-research-activation@umich.edu with questions about the activation process.

Thank you,

The Human Research Activation Committee