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TITLE: Salivary Proteomic and microRNA Biomarkers Development for Lung Cancer Detection

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Introduction

This is a lung cancer biomarker development project to test the hypothesis that there are discriminatory proteomic and miRNA biomarkers in saliva that can detect lung cancer with the aim to reduce the number unnecessary diagnostic workups (bronchoscopy) in patients with suspicious chest symptoms. Preliminary data is in place to support that our salivary biomarker technologies can discover and validate lung cancer biomarkers in saliva. The major goal is to perform a properly powered biomarker discovery and definitive validation of salivary proteomic and miRNA biomarkers for detection of lung cancer based on PProBE design principles (prospective-specimen-collection and retrospective-blinded-evaluation). The outcome of this three-year proposal will be a panel of definitively validated non-invasive saliva-based proteomic and micro-RNA biomarkers for detection of lung cancer.

Body

The first year of this lung cancer biomarker development project was spent in the obtainment of regulatory (IRB) approvals from the two performance sites of the project, University of California Los Angeles and the Greater Los Angeles VA (GLA-VA), as well as with the Human Research Protection Office (HRPO) at the US Army Medical Research and Materiel Command (USAMRMC). These lengthy regulatory procedures unfortunately caused a year of setbacks that we still have not been able to initiate our translational research study to develop salivary biomarkers for lung cancer detection. We are regretful of the setbacks. As of August 22 2013 we received a HRPO approval memorandum (Appendix 1) that indicated initial approval of the subject protocol. We are now waiting for the VA to approve the requested changes and then will forward them to DoD for review and final approval. The following is a detailed chronology of the events that occurred during the past year of the steps taken and transpired between UCLA, GLA-VA and the USAMRMC.

We were contacted by Brian Garland as our HRPO representative, on October 24, 2012. It should be noted that our lung cancer IRB approval at the GLA-VA was obtained on December 16, 2009. It was approved as an additional arm under an existing approved IRB at the GLA-VA titled "Salivary Biomarker Development for Oral Cancer Detection".

When we were informed of DoD funding of the lung cancer salivary biomarker project, we submitted the approved GLA-VA lung cancer IRB to UCLA to amend it under our approved "umbrella" biorepository IRB. It was at that time that we realized that the approved GLA-VA IRB for this lung cancer project retained the Oral Cancer in its title and did not include Lung Cancer. This was flagged by our administrative staff at UCLA. We informed and requested the GLA-VA to change the title of the GLA-VA approved IRB for our study to include lung cancer. The GLA-VA concurred and initiated the title changing. Upon this request, the GLA-VA decided to change the consent and required UCLA to obtain a waiver of Off-site Banking from VA Headquarters. This set us back further in addition to vacation and furloughs that we were experiencing at that time. The final GLA-VA approval came on February 8, 2013, six months after UCLA flagging the incorrect inclusion of oral cancer in the title of the approved GLA-VA IRB.

On April 3, 2013 Dr. Sheila Rowe from USAMRMC contacted us on the status of IRB documents. Our clinical project manager, David Akin submitted the approved GLA-VA IRB and Wang Banking Memo to Dr. Sheila Rowe on April 15, 2013. David Akin followed up on the status of documents on April 29th and Dr. Rowe confirmed that documents were forwarded to HRPO and that we should expect to receive correspondence from HRPO shortly. On May 8th, we were contacted by Tykisha Roberson, introduced herself as our new HRPO representative and requesting additional documentation including the UCLA IRB approval, UCLA IRB application, and all VA approval documents (including consent, HIPAA Authorization, ORD approval, etc). Supporting documents including the UCLA IRB approval, training certificates, and GLA-VA supporting documents were submitted to Tykisha Roberson on May 16, 2013.

While these regulatory approvals were ongoing between GLA-VA and USAMRMC, UCLA migrated its IRB applications from paper to electronic format. My research group was informed by UCLA IRB that the GLA-VA lung cancer project should be converted to a stand alone IRB rather than part of an "umbrella" biorepository protocol. We were completely caught off guard by this new UCLA policy. This process was immediately initiated and the study was approved by UCLA IRB on 7/31/2013. All documents were resubmitted to Tykisha Roberson on July 31, 2013, with the DOD project on its own UCLA IRB approval.

These requested changes for the informed consent and HIPAA required resubmission back to the GLA-VA for review and approval, this was done on 8/22/2013.

In addition, while this was being completed at UCLA, the GLA-VA Contracts and Grants informed us that because of another funding agency (University of California Tobacco Related Disease Research Program TRDRP) on the same GLA-VA lung cancer salivary biomarker study, we would have to change the PI-ship from Dr. Marilene Wang to Dr. Tina Chang. This transfer was initiated on July 19, 2013 and has now been approved as of 8/28/2013. The requested consent changes were incorporated into the consent and will be forwarded to Tykisha Robertson for review.

We are now waiting for the GLA-VA to provide us with an approved consent with the requested changes and then will forward them to DoD for review and approval.

Based on the email from USAMRMC on August 22 (Appendix 1), upon approval of the informed consent changes, the HRPO of USAMRMC will approve the use of human subjects of this lung cancer biomarker development study.

We should have final approval in 1-2 weeks. Our project can begin at that time.

Key Research Accomplishments

Not applicable.

Reportable Outcomes

Not applicable.

Conclusion

Not applicable.

References

Not applicable.

Appendices

Appendix 1: USAMRMC email dated August 22, 2013.

Subject: A-17632.a HRPO Approval Memorandum (Proposal Log Number LC110207, Award Number W81XWH-12-1-0330)

Date: Thursday, August 22, 2013 12:26:43 PM Pacific Daylight Time

From: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US)

To: dtww@ucla.edu

CC: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US), Drake, Carrie E CTR USARMY MEDCOM (US), Rowe, Sheilah S CTR USARMY MEDCOM CDMRP (US), jcastellon@dentistry.ucla.edu, Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US), Katopol, Kristen R CTR USARMY MEDCOM (US), silverio.santiago@va.gov, Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US), Deener, Chasen N CIV USARMY MEDCOM USAMRAA (US), Roberson, Tykisha L CTR USARMY MEDCOM (US), 'ocga7@research.ucla.edu'

SUBJECT: Initial Approval for the Protocol, "Salivary Proteomic and microRNA Biomarkers Development for Lung Cancer Detection," Submitted by David T. Wong, DMD, University of California, Los Angeles, Los Angeles, California, Proposal Log Number LC110207, Award Number W81XWH-12-1-0330, HRPO Log Number A-17632.a

1. The subject protocol was initially approved by the University of California, Los Angeles (UCLA) Institutional Review Board (IRB) on 30 July 2013. This protocol was reviewed by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, US Army, and USAMRMC human subjects protection requirements.
2. This no greater than minimal risk study is approved for the UCLA use and analysis of 300 saliva samples collected at the Los Angeles VA Hospital.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC 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 following are reporting requirements and responsibilities of the Principal Investigator to the HRPO. Failure to comply could result in suspension 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 USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, 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. All unanticipated problems involving risk to subjects or others must be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

c. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

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.

e. A copy of the continuing review approval notification by the UCLA IRB must be submitted to the HRPO as soon as possible after receipt of local IRB approval. According to our records, it appears the next continuing review by the UCLA IRB is due no later than 29 July 2014. Please note that the HRPO also conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

f. The final study report submitted to the UCLA 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.

g. 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; the issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any regulatory agencies including legal or medical actions; and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the HRPO.

5. Please note: The USAMRMC 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 USAMRMC 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 funding. Only the Contracting Officer/Grants 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.

7. The HRPO point of contact for this study is Mrs. Tykisha Roberson, MBA, Human Subjects Protection Scientist, at 301-619-1030/Tykisha.L.Roberson.Ctr@mail.mil.

KIMBERLY L. ODAM, MS, CIP
Human Subjects Protection Scientist
Human Research Protection Office
Office of Research Protections
US Army Medical Research and Materiel Command

Note: The official copy of this memo is housed with the protocol file at the Office of

Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.