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CONTRACTING ORGANIZATION: Florida, University of, Gainesville, FL

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14. ABSTRACT Malignant peripheral nerve sheath tumors (MPNSTs) are very rare cancers that carry a poor prognosis. About half occur in the context of neurofibromatosis type 1 (NF1), an autosomal dominant syndrome that affects approximately 1/3000 individuals world-wide. NF1 patients develop multiple slow-growing benign Schwann cell tumors (neurofibromas) throughout life, anywhere on the peripheral nervous system, from spinal nerve roots to nerve endings in the skin. Neurofibromas affecting larger nerves are called plexiform, which are thought to be congenital in origin and have an 8-13% risk of transformation to MPNST, which may not be detected until an existing tumor becomes painful. Because of MPNST rarity, there is no evidence-based treatment protocol. Rather, each institution manages cases uniquely, choosing from treatment modalities, with variable results. In addition, as the World Health Organization 2016 classification indicates, "Clinically validated and reproducible grading systems for MPNST are generally lacking" (Reuss et al., 2016), so neuropathologists have less-than-optimal tools for diagnosis and prognosis. Complicating progress in MPNST clinical care is heterogeneity at several levels. Although most cases are seen in major medical centers, there are fewer than 20 retrospective studies in the literature, and these report somewhat different therapies, outcomes and prognostic factors. At a molecular level, MPNSTs are also very heterogeneous, contributing to the lack of validated histopathology assays and defying simple						
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1. Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are very rare, with a five-year survival rate below 50%. About half occur in the patients with neurofibromatosis type 1 (NF1), an autosomal dominant tumor syndrome in which patients develop slow-growing benign Schwann cell tumors (neurofibromas) throughout life, anywhere on the peripheral nervous system, from spinal nerve roots to nerve endings in the skin. Neurofibromas affecting larger nerves are called plexiform, which carry an 8-13% risk of transformation to MPNST. Because of MPNST rarity, there is no evidence-based treatment protocol, so institutions manage patients with variable modalities. In addition, neuropathologists lack advanced tools for diagnosis and prognosis. The goal of this work is twofold: (1) to gather retrospective chart review data on MPNST cases treated at the University of Florida (UF) College of Medicine (Aim 1), and (2) study MPNST sections for immunostaining of two antigens (Aim 2). The purpose of the first Aim is to provide data to the field about therapeutic approaches and success at UF. The purpose of the second Aim is to test for relationships between immunostaining results for two proteins of interest, with prognosis/survival: H3K27me3 and HMGA2. All MPNST cases treated at the University of Florida College of Medicine, for which sufficient data and samples exist, will be studied. This involves retrospective chart review and analysis of existing specimens.

2. **Keywords:** malignant peripheral nerve sheath tumor (MPNST), neurofibromatosis type 1 (NF1), epigenetics, H3K27me3, HMGA2, immunohistochemistry, retrospective chart review.
3. **Accomplishments:** specifics are presented per the Statement of Work below.

Major Task 1. Analyze retrospective clinical data from UF MPNST cases (Aim 1).

Subtask 1. Search UF databases to identify MPNST cases (anticipate 50-80), gather clinical information (months. 1-6)

Results: Data on a subset of 20 cases (treated through Orthopaedics) was initially gathered as part of a medical student project, coming in to this study. The statistical analysis has now been completed, and a manuscript reporting this work was written and submitted to the journal *Sarcoma*. It was accepted last week. This paper reports that the patients in this cohort had an outstanding five-year survival rate of 70% overall, including 60% for patients with metastatic disease. These patients were treated almost exclusively with surgery and radiation, not chemotherapy, even in patients with metastasis. It was also observed that MPNSTs lacking S100B immunostaining were significantly associated with worse survival. The paper also reports some other data generated previously by the medical student (Daniel Knewitz, first author) examining NF1 germline mutations in a set of different MPNST patients. He found an excess of whole-gene deletion mutations (three-fold the usual incidence) in NF1 families with one or more members who developed MPNST. Procurement of clinical data from the additional UF MPNST cases has only recently begun, and is anticipated to be completed by end of December 2021.

Subtask 2. Perform statistical analysis on Subtask 1 data to identify clinical factors affecting patient survival. (months 7-12)

Results: Analysis of the subset mentioned above (medical student study) was completed; analysis of the additional UF MPNST cases from across the institution will be performed once the data are collected.

Major Task 2. Collect and analyze data from MPNST tissue from the Aim 1 patients (Aim 2). (up to 80 samples, FFPE blocks)

Subtask 1. Find FFPE blocks in Pathology Department for Aim 1 patients. (months 1-6)

Results: the list has been produced and the paperwork is being processed to request FFPE blocks available from MPNSTs. These should be in hand by the end of November 2021.

Subtask 2. Cut 4 slides from each FFPE block (months 2-8)

Results: Anticipated to begin in Nov. - Dec. 2021.

Subtask 3. Stain 1 MPNST slide each with hematoxylin and eosin. (months 2-7)

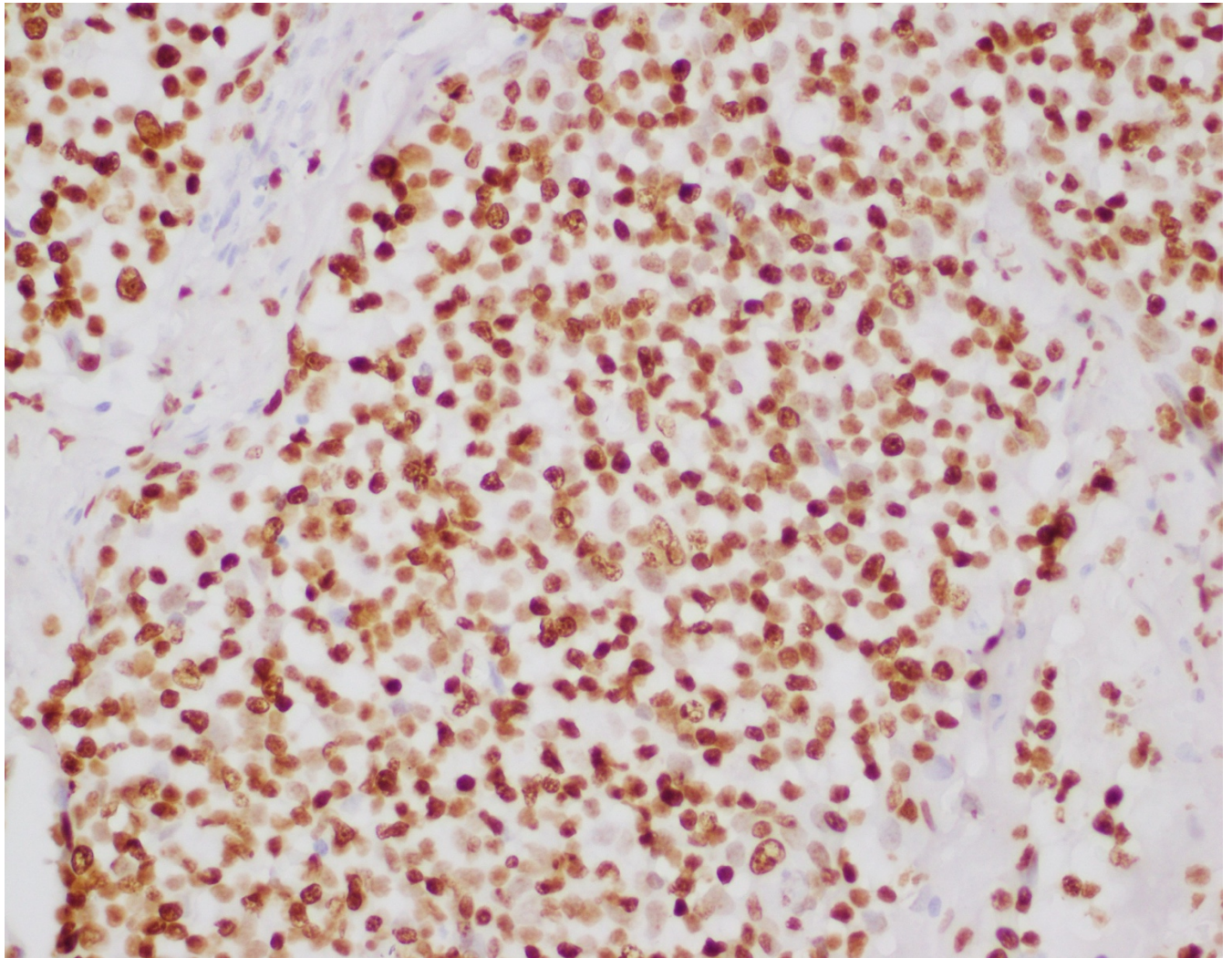
Results: Anticipated to begin in Nov.-Dec. 2021 depending on speed at which blocks are provided.

Subtask 4. Optimize H3K27me3 staining protocol and stain 1 MPNST slide each. (months 2-7)

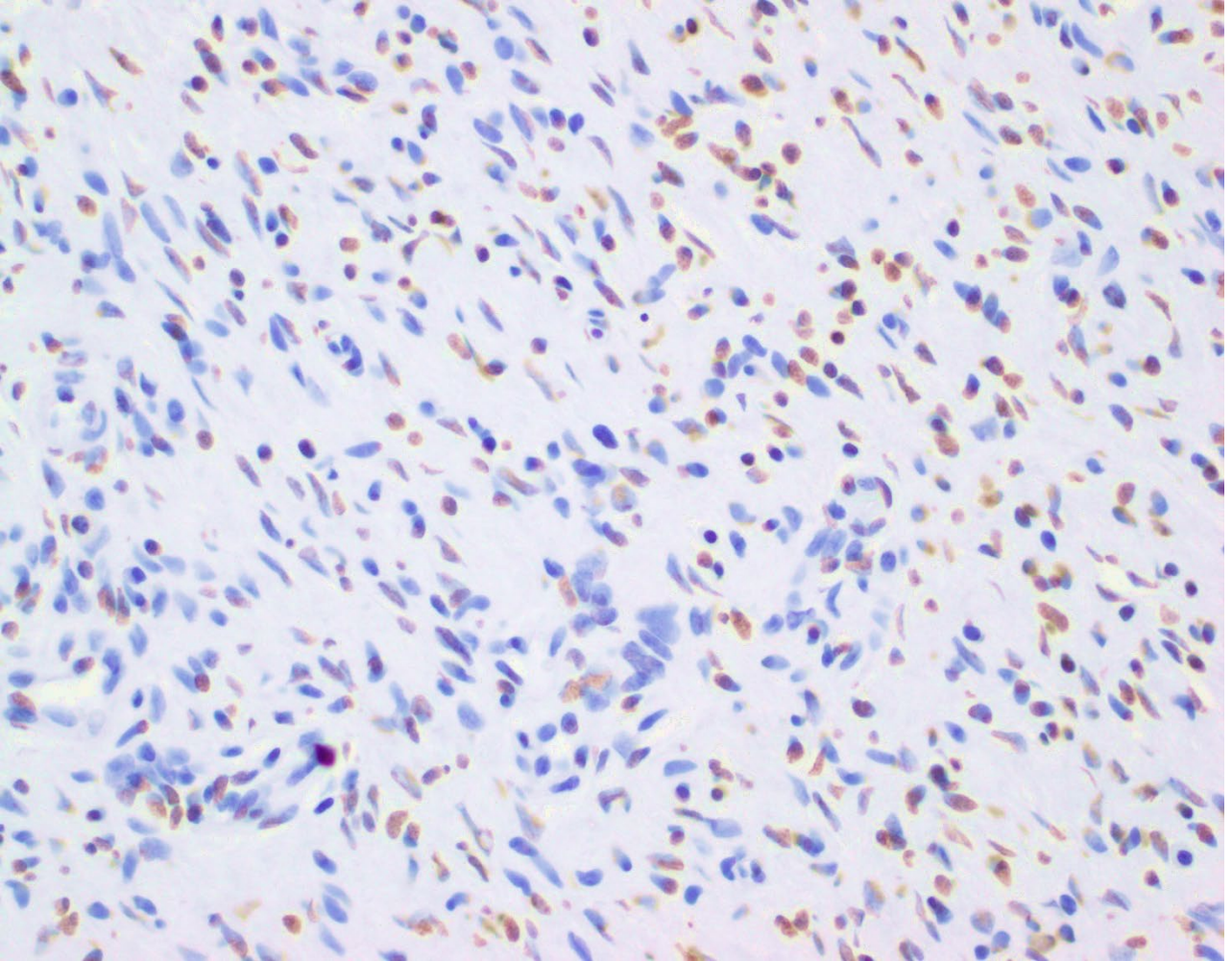
Results: Using anonymous control tissue sections provided by Dr. Yachnis, the immunostaining methodology for H3K27me3 has been optimized. (Figure 1). We are ready to stain the MPNST sections, beginning in Dec. 2021.

Figure 1 (below). 40x microphotographs of H3K27me3 immunostaining of two positive control FFPE tissue sections using rabbit monoclonal antibody from Cell Signaling Technology (#C36B11), and DAB detection protocol, thus positive nuclei are brown. Sections were counterstained with hematoxylin. (A) a human tonsil section (B cells), and (B) a human cutaneous neurofibroma.

A.



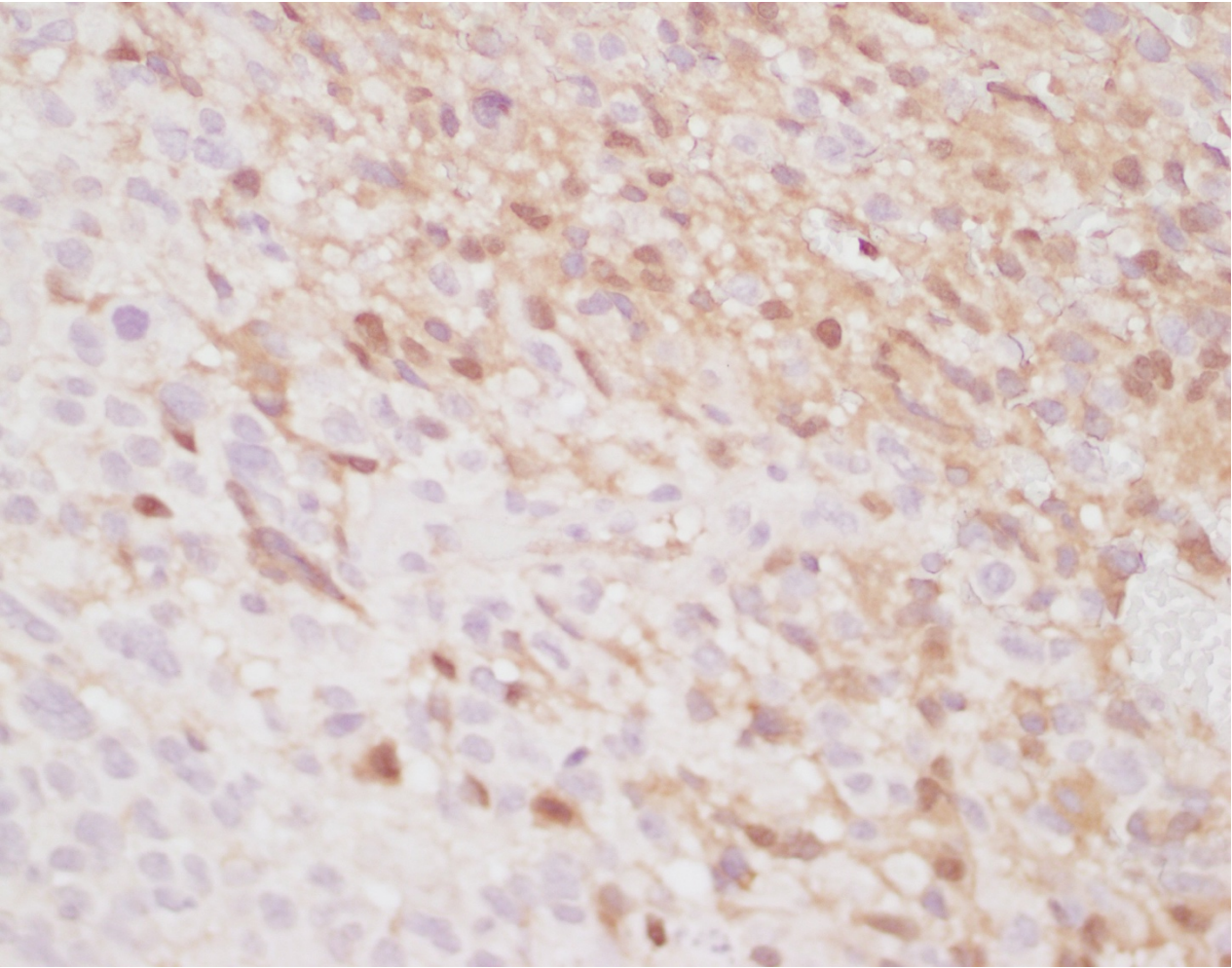
B.



Subtask 5. Optimize HMGA2 staining and stain 1 MPNST slide each. (months 4-8)

Results: Using anonymous glioblastoma multiforme (GBM) sections provided by Dr. Yachnis, the immunostaining method for HMGA2 staining was developed. Some GBMs are known to be positive for this marker. This is a relatively new antigen being studied in tumors, the staining pattern can be subtle (and nuclear and/or cytoplasmic), and there are no positive normal control tissues. We obtained some advice from a lab that published this staining as well, and feel that the staining is interpretable (example in Figure 2). Once MPNST sections are available (anticipate by Dec. 2021) we will begin immunostaining for HMGA2.

Figure 2 (below). 60x microphotographs of H3K27me3 immunostaining of a GBM FFPE tissue sections using HMGA2 rabbit monoclonal antibody (Cell Signaling Technology, #8179S), and DAB detection. Both nuclear and cytoplasmic staining is present in part of the tumor.



Subtask 6. Score slides for staining. (months 5-10)

Results: Not yet begun.

Subtask 7. Statistical analysis of the staining data relative to clinical data. (months 6-10)

Results: Not yet begun.

Subtask 8. Interpretation of data, writing and submitting manuscript for publication. (months 5-12)

Results: Not yet begun for full study, but a manuscript is now in press (*Sarcoma*, open access) reporting study of 20 cases in Orthopaedics along with NF1 gene mutation data, as described above. Data from these 20 cases will be part of this full study, including all UF MPNST cases treated prior to 2018.

4. Impact

Impact on the development of the principal discipline(s) of the project: Nothing to report yet, although if the survival rate of the full study is as high as the small study that we just published, that will likely raise interest among oncologists treating MPNSTs. They may change their treatment protocols to fit the UF experience, seeking improved survival. One notable difference is that in our small study (focusing on Orthopaedic oncology), chemotherapy was seldom used - radiation therapy of the tumor bed and/or metastases was the standard. This suggests that excellent survival may not require the use of chemotherapy in some cases, an important point given that there are no established evidence-based MPNST treatment guidelines.

Impact on other disciplines? Nothing to report.

The impact on technology transfer. Nothing to report.

The impact on society beyond science and technology. Nothing to report currently.

5. Changes/Problems

Changes in approach and reasons for change: nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them: a number of delays severely impacted the timeline on this project. It was originally scheduled to begin in May 2020, and proceed for a year (total direct budget only \$100,000). I was notified by email from help@ebrap.org on 11.22.19 that the project would be funded, and referred to the ebrap website for the reviews, etc. The approval letter indicated that a CDMRP Science Officer may contact me about further information needed, such as for human subjects, and that a Grants/Contract specialist would be in touch with my institution's business office. I did not receive any email for the next month (or know the names of these officials), so I emailed the director of the NFRP (Naba Bora) on Dec. 23, 2019, and he replied "You should have gotten an email from the Science Officer assigned to your award who can guide you through the regulatory requirements for your award. Let me touch base with her to see if she has had a chance to review your proposal to determine what is needed." On Jan. 29, 2020, having not received any emails, I emailed him again asking "can you please ask someone to email me, to help move this award forward? I haven't gotten any emails from .mil or regarding this award, other than yours." He replied that he would ask the Science Officer for NF to contact me (but did not name or cc that person). Below I have included for you a complete description of the communication problems and delays that have plagued this grant since the beginning. You will understand the confusion and frustration that I've experienced in the management of the paperwork, which ultimately has taken much more of my time than it should. These issues and covid resulted in having to submit this "interim" progress report instead of just a final report that I was anticipating for a one-year project, as a good portion of the work remains.

On Jan. 30, 2020, I received an email from Kimberly Pope saying "Dr. Colleen LaVinka is the Science Officer assigned to your award, but she is currently out of the office. She sent you an initial intro email in December, and HRPO also seems to have sent you an email last week, so I am concerned that they are not reaching you. The email we have on file is peggyw@ufl.edu, but I notice that is not the same as the email address I am using for this email. Is the @ufl.edu address accurate?" I replied that it was (that my ufl.edu email funneled into mgm.ufl.edu and was delivered to me through the department server) but changed it in ebrap to the mgm.ufl.edu in case that was the problem.

On Feb. 19, 2020, having not received any further email, I sent another message to Dr. Pope "I have not heard from Dr. LaVinka (or maybe that mysterious email black hole still exists). Can you send me her email so I can try contacting her?"

On Feb. 21, 2020 I received (cc'd) an email from Dr. Lavinka with two forwarded messages that she received but I never did:

- (1) From Dr. Lavinka to ShaDawn Mayer, cc'd me, on Jan. 18, 2020: "Hi ShaDawn, There was a problem with Dr. Wallace receiving emails and an updated email address was given (peggyw@mgm.ufl.edu). I'm forwarding your email and requests to the updated email to make sure that it was received. Dr. Wallace, if you have already received contact from ShaDawn, please just disregard this email.
- (2) Sent from Ms. Mayer to me (cc'd others) on Jan. 20, 2020: "My name is ShaDawn Mayer, Administrative Support Assistant with the USAMRDC Office of Research Protections, Human Research Protection Office (HRPO). I am responsible for conducting an initial assessment of human research proposals submitted to the HRPO to ensure all necessary documentation is received by this office. In the event that you are unfamiliar with our processes, all human subjects research funded by the Department of Defense (DoD) requires an administrative review to ensure compliance with the human subjects protection regulations and the DoD's and Army's requirements. Our office will conduct this review on behalf of the USAMRDC.

I have completed my initial triage/review of your project titled "Analysis of Clinical and Molecular Parameters in MPNST". Please send me a copy of the IRB exemption/determination letter and approved protocol application that is specific to your study and SOW. Also, please complete the attached HRPO Submission Form for use of samples/data and return it to me. I will forward your project for further review once I've received the project specific documents from you.

IMPORTANT NOTE: If the DoD is only funding a portion of the overall study (e.g. analysis of samples, but not the collection of samples as described in the protocol) the HRPO review requirements and oversight will be for the entire protocol submitted for review. Alternately, you can choose to submit

to the IRB an application or protocol that describes only the DoD funded tasks/aims described in the approved statement of work.

Please respond to this email verifying that you received the message.

Please be reminded that this research may not be implemented/initiated until you have received written approval from our office.

Thank you for your time and consideration. Please contact me with any questions or if you need any clarification. I will be your point of contact with this office until a Human Subjects Protections Scientist is assigned to review your project.”

Thus, I learned that Dr. Lavinka was my Science Officer. Ms. Mayer was an HRPO contact person but apparently there was going to be a Human Subjects Protections Scientist assigned to my project too.

On Feb. 18, 2020, Ms. Harris (UF business officer) forwarded me this email that had been sent to a Stefanie Gray at the business office but I was not cc'd, and Ms. Harris forwarded it to keep me in the loop: “My name is Asha Phillips and I am the Grant Specialist responsible for negotiating the above referenced award. You have been identified as the primary point of contact at your institution for negotiating this award. As the primary point of contact for negotiations, it is expected that all correspondence regarding this award will come through you and that all revised materials from the PI will be received, reviewed, and approved by you prior to submission. The PI should not forward any revised materials directly to me.

Please read the attached PAIR document thoroughly as guidance is provided - any item not received as detailed will be rejected and another revision required. Please also submit to me, via your email reply, the requested updated budget on the attached SF 424. Also include in your reply completed versions of the attached Organizational Data and Representations forms.

Please note that this is not an opportunity to increase the total budget amount originally proposed.

Please reference the proposal number in all correspondence and subject line of any emails that you send to me. Please submit the requested information by COB Wednesday, 26 February 2020. Please feel free to contact me with any questions or concerns that you may have regarding this message. Thank you.”

The business office then requested information from me to complete their paperwork, although in one case I informed them that I thought that the request for quotes on consumables was excessive, as I had never needed quotes for anything but equipment or similar high-cost items on previous grants. The rest of the requested information was submitted to Ms. Phillips on March 5, 2020. She then requested a precise dollar breakdown of costs for travel to one planned conference: registration, cost of lodging, per diem, airfare, ground transportation (which I think is also excessive, as that level of detail is not required by NIH). So all final details were submitted by May 1, 2020.

On March 18, 2020, Dr. Anna Tschiffely, another Science Officer, sent an email about covid-19 guidelines. I forwarded that to Ms. Harris (with this message: “I don't think this affects us since we haven't even started yet (PRO00026658, NF190086) will be finishing submitting the IRB this week), but wanted to pass it along anyway. We've been aiming for May 1, but now I'm thinking we should make it June 1 to be more certain that we will be back to normal work practices?” Ms. Harris replied “We could request the later start date. I would assume they will be touch at some point.” Which to me, suggested that the business office had not heard from the CDMRP either.

My own institution's IRB protocol for this project was approved March 28, 2020 and the business officer sent in the approval letter on March 30. A “fully executed copy of subject award document” arrived from the CDMRP on May 13, 2020 from David Adosci, Procurement Technician, which included the statement that research using human data/specimens “cannot begin until the USAMRDC's Office of Research Protections (ORP) provides authorization that the research may proceed. The USAMRDC ORP will issue written approval to begin research under separate notification.”

The notice of award came through on May 28, 2020, when my laboratory was shut down due to the covid-19 pandemic, so were unable to begin until later in the summer when my lab manager Dr. Li was back in the laboratory (she was doing computer work from home in the meantime).

I did not hear anything further until Dr. Tschiffely emailed me on August 12, 2020: “I see you are working on your HRPO approvals, please keep me cc'd on those emails as well so I can assist if there are any delays. While you were working with Dr. Lavinka, however I will be taking over as your science officer moving forward.”

Having not heard from anyone about HRPO specifics, I was confused, and queried Ms. Harris. She found out and let me know on Aug. 18, 2020 that I needed to complete a specific HRPO form. This very long form did not make much sense for my project (considered “expedited” by my IRB), and I needed to get additional information from my IRB and suggestions from Dr. Tschiffely. On Sept. 4, 2020, I followed the instructions on the HRPO form and emailed everything to the email address on the form. I then received an email from ShaDawn Mayer that day, that the procedure had changed and the documents had to be uploaded on ebrap, which I completed on Sept. 8, 2020.

I did not have any further response from CDMRP. In the meantime, while waiting for this approval, we continued with non-human subjects work on the project (planning and antibody stain troubleshooting). My lab re-opened in late August 2020.

On Sept. 30, 2020, I emailed Dr. Tschiffely asking if she had any information about the HRPO. She told me it could take up to six months and that I could request a no-cost extension if necessary.

On Nov. 22, 2020, I emailed Ms. Mayer asking for an HRPO update. I did not get a reply, so assumed that the HRPO review was not done.

On Dec. 2, 2020, I received an auto-email “Reminder: Approaching End of DOD Award.” Very confusing. Dr. Tschiffely on the same day sent a follow-up email: “If you want to request a NCE the 1st is very easy to request but documents should be submitted ~45 days prior to the end of the award. Please let me know if you’re interested in that option as we get closer to your end date and I can send you the instructions.”

On Jan. 11, 2021, Dr. Tschiffely emailed me that HRPO was requesting information, and forwarded emails that had been previously sent but never arrived, from Ms. Mayer to me on Sept. 4, Oct. 15, and in December, asking for more information (and one from Dr. Lavinka), all containing the phrase “Please respond to this email verifying that you have received this message.” Of course, I never replied because I never got them, yet there was no phone call follow-up. So I finally found out on Jan. 11 that Ms. Mayer had sent me in an email: “I have completed my initial triage/review of your project titled ‘Analysis of Clinical and Molecular Parameters in MPNST’. Please send us a copy of the consent form that is specific and limited to the activities listed in the SOW for your study. I will forward your project file for official review upon receipt of the requested documents.”

On Jan. 19, 2021, I emailed Dr. Lavinka and Dr. Tschiffely to let them know that I had never received the emails that Dr. Tschiffely had forwarded, and I stated “as indicated in the documents I uploaded, my project was approved here as Expedited with consent waived (existing specimens/data), so there is no consent form.”

Note that none of the emails ever contained a phone number, so I didn’t have the option to try to call instead of email. I also checked on ebrap to see if any notes or letters were there, but there were none.

On Jan. 26, 2021, I emailed Ms. Mayer and cc’d Dr. Tschiffely: “finally through some forwarding of emails from Dr. Tschiffely, I was informed of your HRPO question about consent form. Let me please explain this more thoroughly. This project, which was approved by the University of Florida IRB last spring as Expedited (no consent needed, as explained on the approval letter I had uploaded), has two parts: one part is gathering pertinent clinical data from patients with NF1 and a malignant MPNST tumor who were treated at our institution since 1993; the second part is immunostaining of tumor surgical tissue sections from those patients, for a couple of proteins to test if they might be useful biomarkers. We will then use statistics to test for any relationships between the NF1 clinical data and the staining pattern on the tumor slides. All data and samples were purely clinically derived from patients being seen and treated here - there was never any research consent. Our IRB makes such resources available for retrospective studies through Expedited status, because recontacting such patients is virtually impossible (some are likely deceased too). Once the study is completed, any datasets with PHI will be destroyed. Thus, there is no consent form - I have nothing else to provide.”

I let Dr. Tschiffely know on Feb. 2 that I never got a reply from Ms. Mayer. Dr. Tschiffely forwarded the email to Ms. Mayer, asking if she received it. No response, so she re-emailed Ms. Mayer on Feb. 5, who on Feb. 9 confirmed receipt of email.

On Feb. 9th, 2021, I received instructions from Dr. Tschiffely to apply for a no-cost extension (NCE), and to whom to send it. On March 16 UF's business office submitted the NCE application to Asha Phillips (she confirmed. On March 30 that she did receive it).

On Feb. 15th, I emailed Ms. Mayer asking for an update. I even provided my cell phone number as an alternative means of communication, in addition to my office phone number. I didn't receive a response, so Dr. Tschiffely emailed her on Feb. 19 asking if she had received my email of the 15th. Dr. Tschiffely received this auto-reply: "I am on extended leave until 15 March 2021. Please contact Brian Garland at brian.s.garland.ctr@mail.mil or Sarah Rogge at sarah.b.rogge.ctr@mail.mil for all questions and concerns." So Dr. Tschiffely emailed Brian Garland about this.

Mr. Garland replied to her (cc'd me, I received it) on Feb. 20th that he "moved the project forward for assignment to one of our reviewers." I surmised that no HRPO specialist had ever been assigned.

On March 3, 2021 I received an email from Dr. Zeling Cao-Harman: "I am writing to introduce myself and provide you with my contact information. I am a Human Subjects Protection Scientist (HSPS) from the United States Army Medical Research and Materials Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) located in Fort Detrick, Maryland. I have been assigned to review the aforementioned protocol and supporting documents and will serve as your primary HRPO contact for all human subjects protection issues.

In the event that you are unfamiliar with our process, a headquarters-level review is required for all research that is funded through the Department of Defense (DoD). Approval by the USAMRMC HRPO must be obtained prior to initiation of this study. Additional information and DoD specific requirements that must be included in your human use documents can be found at the following website https://mrmc.amedd.army.mil/index.cfm?pageid=Research_Protections.hrpo

Over the next couple weeks, I will conduct a detailed review of your protocol and will forward any recommendations for revision to you. In addition, please let me know if there are other individuals who should be copied on correspondence related to this project."

I replied on March 4th: "Hello Zeling, thank you for reaching out (and thank goodness this email came through, as many previous communications from your group have not).

I have cc'd the people here to be included on any future email correspondence (Dr. Tschiffely, and from my institution Ms. Harris and Mr. Howard).

Please, if at all possible, any expediting would be greatly appreciated. This is only a 1-year project, which ends in May (I am in the process of doing the NCE). I submitted the HRPO paperwork the first week in September, so have been unable to the human subjects part of the proposed work. My university's IRB approved it as expedited last March. Thank you very much."

On March 11, 2021, Dr. Tschiffely emailed "I'm sorry this has been such a mess and I've communicated these issues to others at HRPO so they can ensure these kinks are worked out in future.

I will be keeping a close eye on both the NCE and the future HRPO review to ensure this moves along as quickly as possible.

Please let me know if you have any questions along the way and thank you for your patience!" I thanked her for her extra effort, which was critical throughout this process.

On March 19th, 2021, Dr. Cao-Harman emailed me that HRPO needed more information: "Since the study will include the inclusion of minors (pg. 24 of IRB application) please provide documentation of the IRB's risk determination for children and determination waiver of parental consent/assent for minors (an email is sufficient) . This information was not cited in the approval memo."

Same day, I forwarded this request to my institution's IRB to help answer this. They responded on April 6, pointing to a part of the protocol that I had originally submitted.

On April 6th, 2021, I sent that IRB information to Dr. Cao-Harman.

On April 13th, 2021, I received an email from Dr. Jill Graygo indicating HRPO approval:

"1. The subject protocol was approved by the University of Florida Institutional Review Board (IRB) on 30 March 2020. 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 enrollment of 150 subjects with malignant peripheral nerve sheath tumors.

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. There is no yearly continuing review required for the study. 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. Zeling Cao-Harman, Human Subjects Protection Scientist, at 301-619-1118/zeling.cao-harman.ctr@mail.mil.

8. The HRPO point of contact for post-approval oversight is Ms. Katherine Devine, Human Subjects Protection Scientist, at 301-619-3179/katherine.a.devine2.ctr@mail.mil. “

My interpretation - they still didn't understand the project because of #3 above (I have no interaction with subjects, this is all retro-active). But it was approved so that was moot. And I have now been assigned an HRPO person for "post-approval oversight" as well as Dr. Cao-Harman, AND received phone numbers. It is not at clear how those two HRPO roles differ. You may have noticed that for this little grant, there has been at least 10 individuals involved on behalf of the CDMRP. In the past (I had an NFRP grant years ago), the system was not nearly as complicated, and the management functioned much more smoothly.

I then put in for and received approval for medical record access at my institution, and we submitted the MPNST manuscript based on the medical student's project as mentioned above and cited in #6.

On July 12, I received an auto-email from CDMRP: Reminder- Final Technical Report and Closeout Documents Due.

I emailed Dr. Tschiffely on July 28 asking what to do about this report, and she replied on August 2: "Indeed since you are still waiting on your NCE (I will check on that this week) please just include information regarding any work you have completed over the last year. You can certainly include a note that you just recently received your HRPO approvals and thus most of the work has just begun."

As of Sept. 22, 2021, my institution still had not received approval of the NCE.

Changes that had a significant impact on expenditures: the funds requested for a clinical research coordinator are being used to continue paying Dr. Li's salary over this extended time. Therefore, we won't be hiring a coordinator, and Dr. Li and I are gathering the medical record data on the subjects. Nothing else has changed.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents. Nothing to report.

6. Products

Publications, conference papers, and presentations:

Knewitz DK, Anderson CJ, Presley WT, Hordyski M, Scarborough MT, Wallace MR. Survival and *NF1* analysis in a cohort of orthopedics patients with malignant peripheral nerve sheath tumors. *Sarcoma*, Volume 2021, Article ID 9386823, 6 pages.

Website(s) or other Internet site(s). Nothing to report.

Technologies or techniques. Immunostaining optimized per accomplishments (#3) above.

Inventions, patent applications, and/or licenses: Nothing to report.

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Nothing to report.

7. Participants & Other Collaborating Organizations: single institution

Name	Margaret Wallace	Hua Li	Anthony Yachnis	MaryBeth Horodyski
Project Role	PI	technician	Co-investigator	Co-investigator
identifier	mwallace	HUALEE	YACHNIS	MBHATC
Nearest person month worked	1.2	1.5	0.5	1.0
Other funding support	None	None	None	None

8. Special Reporting Requirements - nothing to report.

9. Appendices - nothing to report.