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TITLE: Targeting a Stress-Derived Immunosuppressive Adenosine Pathway in Tumors Resistant to Checkpoint Inhibitors

PRINCIPAL INVESTIGATOR: Yong Qin

CONTRACTING ORGANIZATION: The University of Texas at El Paso

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Immunotherapies largely ineffective in uveal melanoma (UM) and pancreatic ductal adenocarcinoma (PDAC). The mechanisms underlying poor response to immunotherapy in UM and PDAC are unclear. Our preliminary analysis showed that A2AR and CD73 were overexpressed in UM and PDAC and associated with poor survival. CD73 and A2AR are crucial factors in the immunosuppressive adenosine pathway. A major gap lies in our knowledge of the role of the adenosine pathway driving immune suppression in UM and PDAC. In this proposal, we hypothesize that the CD73-Adenosine-A2AR axis represents a stress-induced immunosuppressive mechanism in UM and PDAC. The overall goal of this proposal is to analyze the functional roles of CD73 and A2AR in the immunosuppressive microenvironment of UM and PDAC. Furthermore, we will develop a new strategy combining CD73/A2AR inhibitors with checkpoint inhibitors to inhibit UM and PDAC tumor growths. This preclinical translational research will help to establish CD73 and A2AR as novel biomarkers and immunotherapy targets for metastatic UM and PDAC.

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Immunotherapies are largely ineffective in uveal melanoma (UM) and pancreatic ductal adenocarcinoma (PDAC). The mechanisms underlying poor response to immunotherapy in UM and PDAC are unclear. Our preliminary analysis showed that A2AR and CD73 were overexpressed in UM and PDAC and associated with poor survival. CD73 and A2AR are crucial factors in the immunosuppressive adenosine pathway. A major gap lies in our knowledge of the role of the adenosine pathway in driving immune suppression in UM and PDAC. In this proposal, we hypothesize that the CD73-Adenosine-A2AR axis represents a stress-induced immunosuppressive mechanism in UM and PDAC. We will conduct a series of studies to systematically characterize CD73 and A2AR related immune signatures in UM and PDAC tumors and release adenosine-driven immunosuppression by targeting CD73 and A2AR. The overall goal of this proposal is to analyze the functional roles of CD73 and A2AR in the immunosuppressive microenvironment of UM and PDAC. Furthermore, we will develop a new strategy combining CD73/A2AR inhibitors with checkpoint inhibitors to inhibit UM and PDAC tumor growths. This preclinical translational research will help to establish CD73 and A2AR as novel biomarkers and immunotherapy targets for metastatic UM and PDAC.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Uveal melanoma (UM), Pancreatic ductal adenocarcinoma (PDAC), Immunotherapy, Immunosuppression, Adenosine pathway, CD73, A2AR, Checkpoint inhibitor.

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

The major goals for years 1-2 of this project are outlined below.

Specific Aim 1: To Quantify and evaluate CD73 and A2AR expressions and their clinical relevance in uveal melanoma (UM) and pancreatic ductal adenocarcinoma (PDAC) tumors.

Major Task 1: To characterize profiles of CD73 and A2AR in UM and PDAC tumors.

Major Task 2: To characterize the immune infiltrates and their correlations with CD73 and A2AR in UM and PDAC tumors.

Specific Aim 2: To enhance immune response in UM and PDAC tumors by small inhibitors targeting CD73 and A2AR, and further examine their anti-tumor effects in combination with CPIs.

Major Task 1: To examine the effects of CD73 and A2AR inhibitors on the growths of UM and PDAC cells *in vitro*.

Major Task 2: To examine the efficacy of checkpoint inhibitors (CPIs, anti-PD-1 or anti-CTLA4 drug) with CD73/A2AR inhibitors on antitumor immune cell response, especially for cytotoxic T lymphocytes, *in vitro*.

Major Task 3: To test the efficacy of combining CPIs (anti- PD-1 or anti-CTLA4 drug) with blockade of adenosine signaling (co-inhibition of CD73 and A2AR) on antitumor immune response in humanized mouse models of UM and PDAC.

What was accomplished under these goals?

In **Year 1**, we planned to quantify and evaluate CD73 and A2AR expressions and their clinical relevance in UM and PDAC tumors by immunohistochemistry (IHC) (**Aim 1, Major Task 2**). These studies will allow us to evaluate the expression levels and locations of CD73 and A2AR in UM and PDAC tumors. From the 5th month of Year 1, we planned to perform quantitative multiplex immunofluorescence (qMIF) staining to characterize various immune infiltrates in UM and PDAC tumors and further analyze correlations among various immune markers CD73 and A2AR (**Aim 1, Major Task 2**). The qMIF study was originally designed to extend into **Year 2**. We also planned to initiate a study to investigate the antitumor effects of small inhibitors targeting CD73 and A2AR on UM and PDAC cells. The basic *in vitro* pharmacological study will be conducted to examine the effects of CD73 and A2AR inhibitors on the growths of UM and PDAC cells (**Aim 2, Major Task 1**). From the second half of Year 1, we planned to establish an *in vitro* cytotoxic T cell assay platform to examine the efficacy of CPIs (anti-PD-1 or anti-CTLA4 drug) combined with CD73/A2AR inhibitors on antitumor immune cell response for UM and PDAC cells (**Aim 2, Major Task 2**). The study of *in vitro* cytotoxic T cell assay was designed to extend into **Year 2**. Due to my Faculty appointment at the University of Texas at El Paso (UTEP) and the grant transfer, we also planned to establish institution-approved IRB and IACUC protocols for this project at UTEP in **Year 1**.

For **Year 2**, we proposed to complete the qMIF analysis and *in vitro* cytotoxic T assay to determine the antitumor immune cell response of CD73/A2AR inhibitors in combination with CPIs. In addition, we proposed to test the efficacy of combining CPIs (anti- PD-1 or anti-CTLA4 drug) with blockade of adenosine signaling (co-inhibition of CD73 and A2AR) on antitumor immune response in humanized mouse models of UM and PDAC (**Aim 2, Major Task 3**).

It should be noted that our studies were slower than planned due to the Covid-19 Pandemic, which affected us to order and obtain some research supplies on time, especially for several CD73 and A2AR drugs/inhibitors. The initial planned IHC and qMIF studies in different academic or commercial histology labs were proved to be overly expensive and slow. Moreover, it's challenging to recruit a postdoc with suitable research background for this project. We missed a couple of early identified candidates due to delayed graduation or the travel/visa restriction during the Pandemic. We finally recruited Dr. Mariana Grigoruta as the postdoc, and she formally joined us at UTEP on 6/7/2021. While this put us a little behind in our proposed timeline, we are now in a position to move forward with the project, and the approach will not change. We should be on track to complete most, if not all, of the proposed Year 1tasks and milestones in the first half of Year 2. We hoped to complete the Major Task of Aim 2 by the end of Year 2 or by the extension into Year 3.

As detailed below, we secured a research contract with the commercial histology lab of prismCDX (Gyeonggi-do, Korea) to conduct both IHC and Multiplex for this project, which provided the much-needed services and support and significantly advanced the marker studies in Aim 1 under our requested budget. The progress to date is summarized below, and we detailed where we are behind in the timeline and when we plan to complete tasks.

Aim 1. To Quantify and evaluate CD73 and A2AR expressions and their clinical relevance in uveal melanoma (UM) and pancreatic ductal adenocarcinoma (PDAC) tumors.

We have established a new IRB protocol (1677978-1) and a new IACUC protocol (A-202007-2) for this project, which were approved by UTEP, HRPO (E00922.1b), and ACURO.

Major Task 1: To characterize profiles of CD73 and A2AR in UM and PDAC tumors (IHC).

The IHC staining of CD73 and A2AR have not been tested in UM and PDAC tumor samples. We conducted experiments to optimize the IHC staining of CD73 and A2AR in UM tumors. The initial antibodies validation was conducted at the Clinical Pathological Laboratory through our co-researchers and sub-contract serves at MD Anderson Cancer Center (MDACC). We identified the CD73 antibody (CST, 13160), the A2AR antibodies (Abcam, ab3461), and primary antibodies for IHC staining of UM and PDAC. As shown in Figure 1A, we successfully detected CD73 and A2AR expressions in formalin-fixed paraffin-embedded (FFPE) melanoma tissues at a 1:100 dilution. This work also laid a foundation for us to further optimize experimental conditions for the qMIF of CD73 and A2AR along with other immune markers.

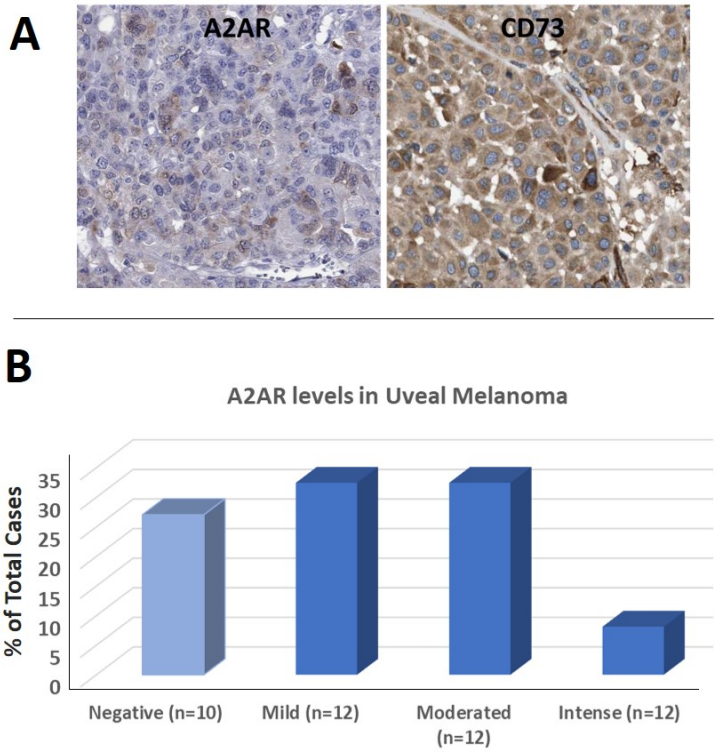

Figure 1. (A) Representative IHC staining of A2AR and CD73 in UM tumors. Positive staining in UM tumor cells was presented in brow chromogen. Magnification 20X. (B) Quantification of A2AR in UM tumors as negative, mild, moderated, and intense staining.

After antibody optimization, we conducted IHC staining of A2AR in the FFPE UM tissue microarray (TMA). Two sets of UM TMAs from the Uveal Melanoma Project at MD Anderson Cancer Center were used in our study, which contained 72 UM tumor cores. We were able to quantify the IHC staining of A2AR for patients' tumors from these two UM TMAs. There were 27 UM patients' tumors that showed positive staining for A2AR (83%), and 10 UM patients' tumors were negative for A2AR staining (23%) (Figure 1B). Moreover, 24 UM patients' tumors showed moderated or intensive staining of A2AR (64.8%). These data further confirmed that the majority of UM tumors expressed high levels of A2AR.

The IHC staining of A2AR on PDAC TMAs and IHC staining of CD73 on UM and PDAC TMAs are currently ongoing with the qMIF analysis, which should be complete in 3 months. The antibody optimization for IHC could be time-consuming and expensive. The successful antibody optimization for CD73 and A2AR IHC staining would accelerate our remaining studies of IHC and qMIF. Upon completion of IHC staining, we will be able to analyze further the clinical relevance of CD73 and A2AR in UM and PDAC tumors and determine if there is a correlation between expression of CD73 and A2AR and prognosis. We hope these works will be completed in 4 months.

Major Task 2: To characterize the immune infiltrates and their correlations with CD73 and A2AR in UM and PDAC tumors (qMIF).

Due to the correlation of immune infiltrate with tumor response to anti-CD73 or anti-A2AR therapy in several tumor models, we proposed to quantitatively analyze the immune infiltrate in patients' tumor samples by phenotype and function. The same FFPE tumor tissue arrays of UM and PDAC in Aim 1 Major Task 1 would be utilized to analyze CD73, A2AR, and multiple immune markers by qMIF. QMIF uses a serial IHC approach that allows for staining and visualization of multiple antigens within the same tissue specimen resulting in more sophisticated computational analysis of immune cell phenotypes within the tumor tissues. Moreover, qMIF is capable of analyzing cells based on tissue segmentation to determine the proximity of individual immune cell subsets to each other and tumor cells.

We worked with the commercial histology lab, prismCDX, to conduct the qMIF analysis on UM and PDAC TMAs. We had been able to identify several important immune markers, CD4, CD8, FOXP3, CD56, CD11, CD68, PD-1, and IDO, to be analyzed in our qMIF panels with CD73 and A2AR. Additionally, Ki-67 will be used as the cancer cell marker, and Glut1will be applied as the hypoxic marker in our qMIF panels. The experimental conditions for qMIF staining of CD73 and A2AR were optimized in human melanoma tissues. The CD73 antibody with 1:400 titration and the A2AR antibody with 1:100 titration showed good staining intensity for qMIF (Figure 2).

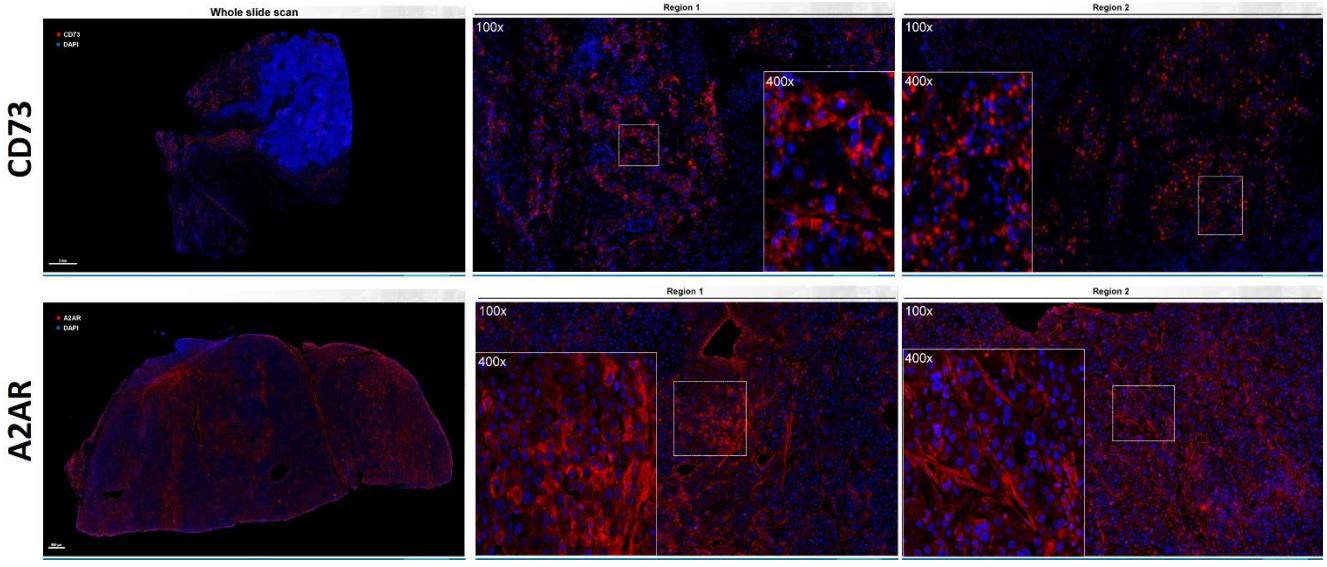

Figure 2. The validation of multiplex immunofluorescence staining for CD73 + DAPI (top panel) and A2AR + DAPI (bottom panel) in FFEP melanoma tissues.

We further optimized experimental conditions for qMIF staining of the above two 7-plex panels of makers in human melanoma tissues. **Panel 1** included CD8, CD73, A2AR, FOXP3, CD4, CD56, DAPI, and **Panel 2** included CD68, CD11b, Ki67, PD-1, Glut-1, IDO, and DAPI. Figure 3 showed the successful qMIF staining of all 7 makers in **Panel 1** on human tonsil tissue.

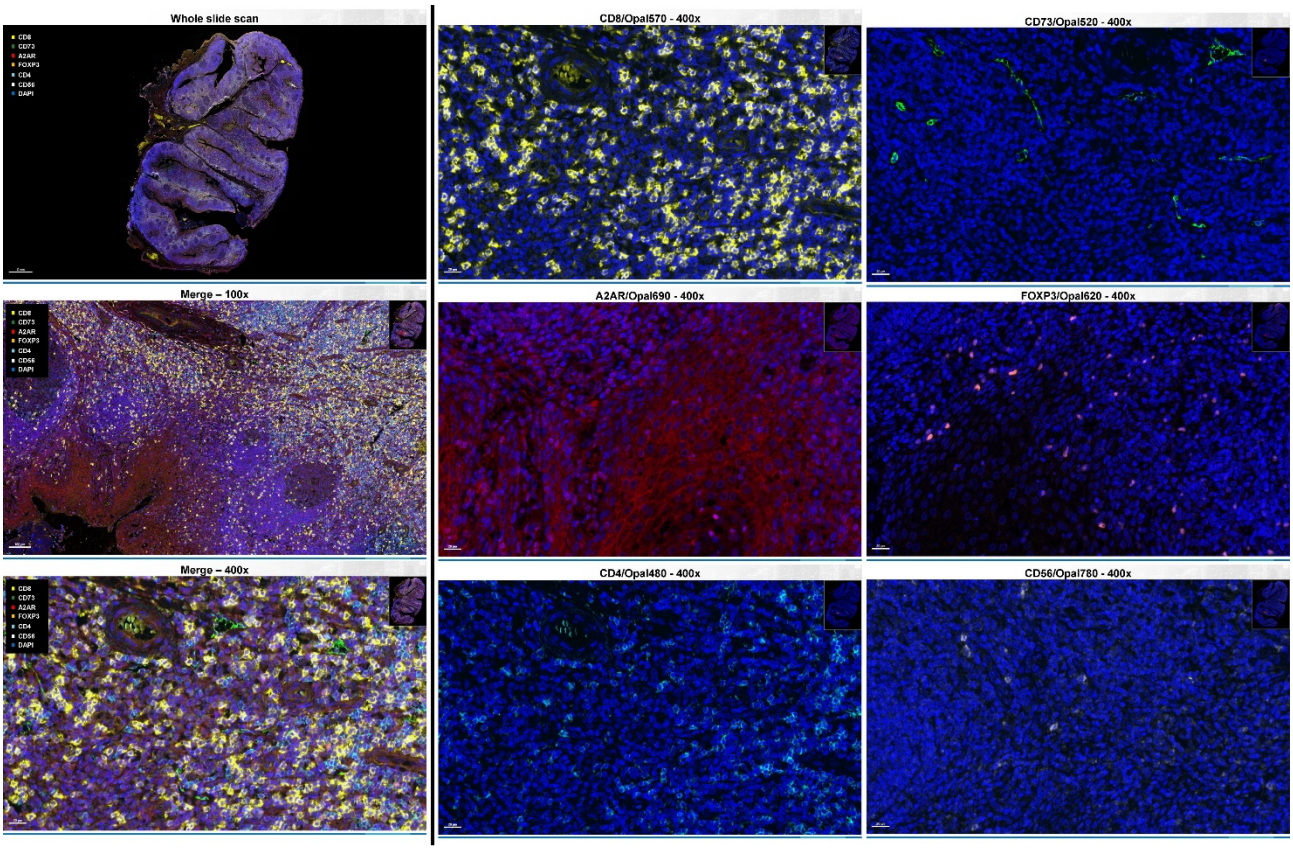

Figure 3. The optimization of multiplex immunofluorescence staining for CD8, CD73, A2AR, FOXP3, CD4, CD56, and DAPI in FFEP tonsil tissue. The whole slide/tissue scans were shown in the left panel. The individual immunofluorescence staining of each maker was shown in the right panel along with DAPI. The color for each maker was indicated on the right top of the whole slide scan.

The same, we also are able to optimize experimental conditions and obtain good quality qMIF staining for all 7 makers in **Panel 2** on human tonsil tissue (Figure 4). To date, we have successfully customized the qMIF staining conditions for two panels of 14 markers, which could be directly applied to the qMIF staining of UM and PDAC TMAs.

We expect the qMIF staining UM and PDAC TMAs for the above two makers to be complete in the following three months. Following that, it may take up to 2-3 months to scan, analyze, and quantify all the staining tissue cores. The Statistical analyses will be conducted to identify different immunophenotypes present in UM and PDAC tumors and to further determine the clinical relevance of different immune subsets, which should be finished in the first half of Year 2. One of the tumors we planned to study is uveal melanoma (UM), which is rare cancer. The limited uveal melanoma TMAs from our collaborators at MD Anderson (Dr. Patel) might not be sufficient for our ongoing study. I am trying to acquire additional UM tissues and TMA from other commercial tissue biorepositories and our collaborators in Spain and Italy.

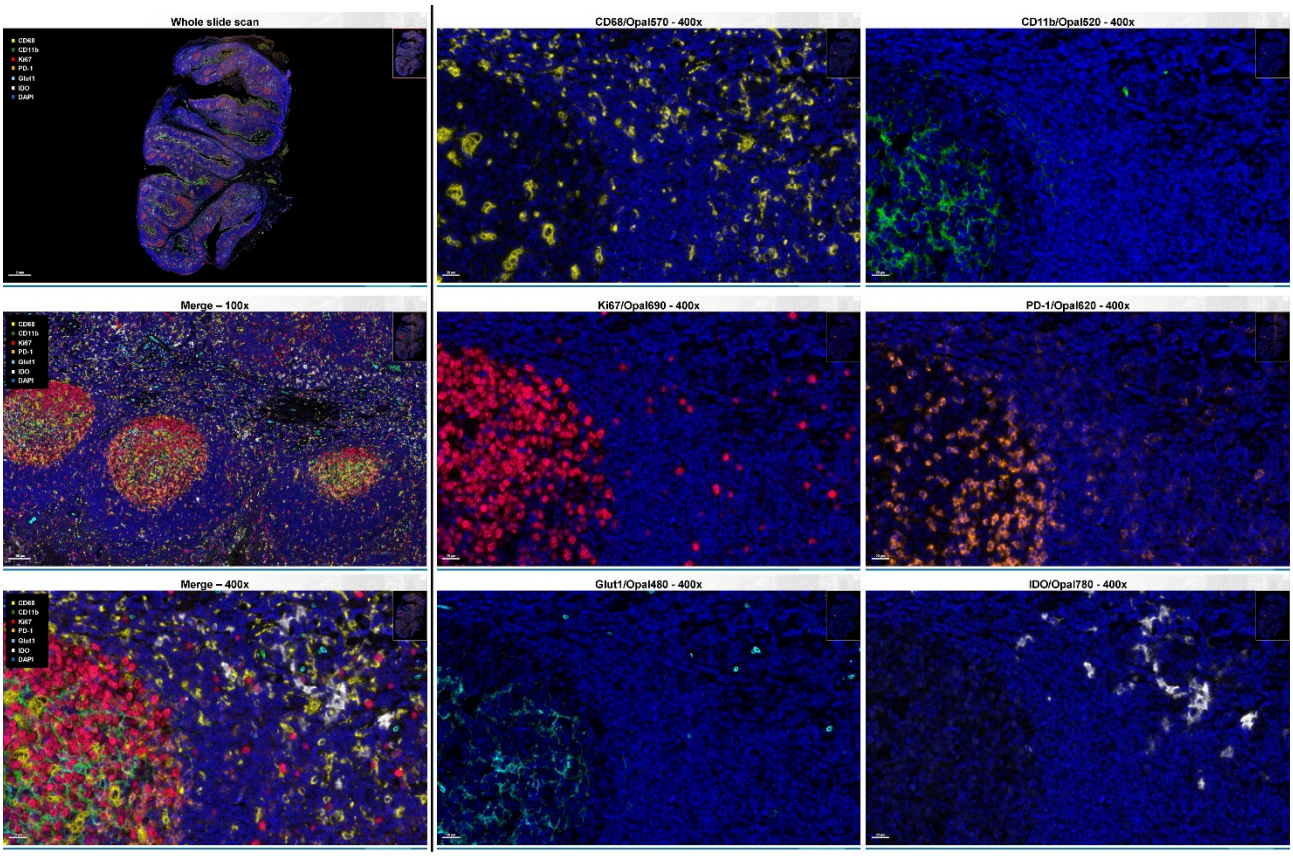

Figure 4. The optimization of multiplex immunofluorescence staining for CD68, CD11b, Ki67, PD-1, Glut-1, IDO, and DAPI in FFEP tonsil tissue. The whole slide/tissue scans were shown in the left panel. The individual immunofluorescence staining of each maker was shown in the right panel along with DAPI. The color for each maker was indicated on the right top of the whole slide scan.

Aim 2: To enhance the immune response in UM and PDAC tumors by small inhibitors targeting CD73 and A2AR, and further examine their anti-tumor effects in combination with CPIs.

As discussed above, our studies for Major Tasks 1 & 2 in Aim 2 were a bit slower than anticipated. The supplies of some A2AR and CD73 inhibitors from the commercial vendors were delayed. The Pandemic also impeded the recruitment of the postdoctoral fellow for this project. Dr. Mariana Grigoruta joined our team after 7 months of this project's starting date (11/1/2020). She is currently the main researcher to conduct the experiments of Aim 2.

Major Task 1: To examine the effects of CD73 and A2AR inhibitors on the growths of UM and PDAC cells in vitro.

We were able to obtain istradefylline (A2AR antagonist) and α,β-methylene ADP (APCP, CD73 inhibitor). The MTT assay was applied to examine the effects of these two drugs on the growth of UM or PDAC cell lines. Four UM cell lines (MEL202, 92.1, OCM8, and MEL270) and a PDAC cell line (Mia Paca-2) were treated with istradefylline for 72 hours. The MTT assay showed that 10 μM istradefylline could substantially inhibit the cell viability of all above 5 cancer cell lines, which led to more than 60% of downregulation of cell viability (Figure 5). Among the tested cell lines,

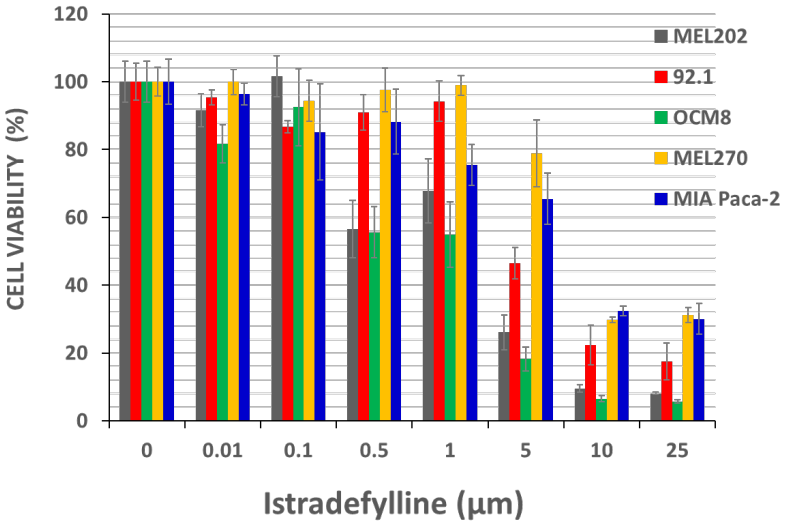

Figure 5. Dose-dependent inhibition of UM and PDAC cells growth by istradefylline under normoxia. MEL202, 92.1, OCM8, MEL270, and Mia Paca-2 cells were treated with istradefylline at the indicated doses. After 72 h of culture, cell survival was determined via MTT assay. The percent cell survival in each treatment group was calculated relative to cells treated with medium only under the same conditions. Each experiment was carried out three times, and the means were presented here.

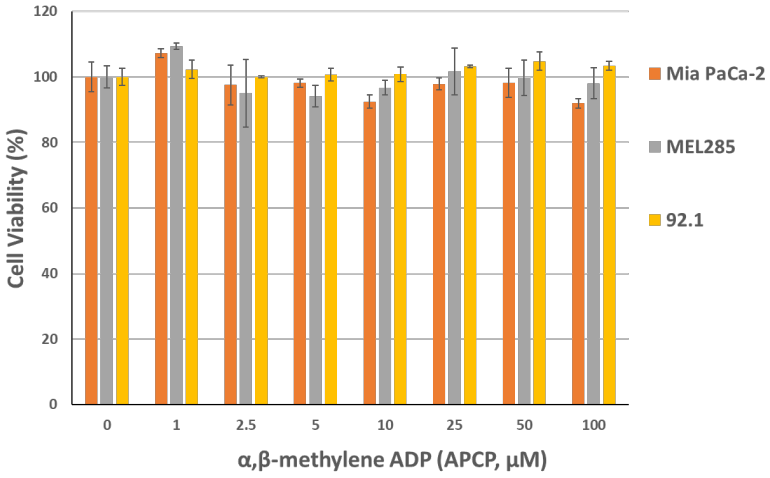

Figure 6. UM and PDAC cells (MEL285, 92.1, and Mia Paca-2) were treated with APCP at the indicated doses. After 72 h of culture, cell survival was determined via MTT assay. The percent cell survival in each treatment group was calculated relative to cells treated with medium only under the same conditions. Each experiment was carried out three times, and the means were presented here.

MEL202 and OCM8 were more sensitive to the inhibitory effects of istradefylline. We also treated two UM cell lines (MEL285 and 92.1) and one PDAC cell line (Mia Paca-2) with APCP for 72 hours. As detailed in the MTT assay of Figure 6, APCP did not show any significant inhibitory effects on the growth of MEL 285, 92.1, and Mia Paca-2 cells.

Besides istradefylline, we will continue to examine the effects of other A2AR inhibitors, SCH 58261, CPI-444, and AZD4635, on the growths of UM and PDAC cells *in vitro*. Also, additional PDAC cell lines (BxPC-3, AsPC-1, and Capan-1) and UM cell lines (OMM1, OMM2.3, OMM2.5, 39, 70, 196, and Mel202) will be applied in the same *in vitro* growth assay to access the effects of A2AR or CD73 inhibitors. We expect these works will be complete in the next 3-4 months upon the availability of different drugs.

The expression levels (mRNA and protein) of CD73 and A2AR in listed PDAC and UM cell lines will be examined under hypoxic and normoxic conditions in various UM and PDAC cell lines by western blot and real-time PCR. We hope to complete these works in the following 2-3 months. The data derived from this Major Task will guide us to select suitable UM and PDAC cell lines for the studies in Major Tasks 2 & 3 of Aim 2

Task 2: To examine the efficacy of checkpoint inhibitors (CPIs, anti-PD-1 or anti-CTLA4 drug) with CD73/A2AR inhibitors on antitumor immune cell response, especially for cytotoxic T lymphocytes, in vitro.

Unlike the traditional anticancer drugs screen, the screen and evaluation of small agents as potent enhancers of specific cytotoxic T-cells to kill tumor cells will require a functional multiplex system

to access the immune cells and tumor cells simultaneously. This immune-oncology drug screen system will comprise the equipment to detect and monitor T-cell cytotoxic assays. Supported by the School of Pharmacy start fund, I had built a T cell cytotoxicity assay platform at UTEP. The Lionheart FX Automated Microscopes System (BioTek) was set up in my laboratory (Figure 7). We will apply this platform to conduct the cytotoxic T cell assay proposed in this Major Task. We are currently optimizing the experimental protocol for cytotoxic T cell assay on this platform. The construction of GFP-expressing UM cell lines is ongoing, and the GFP-expressing PDAC cell line will be obtained from commercial vendors. We expect to complete the studies of this Major Task in next following 6 – 7 months.

Figure 6. The establishment of Lionheart FX Automated Microscopes System (BioTek) in Dr. Qin's laboratory at UTEP.

What opportunities for training and professional development has the project provided?

Dr. Mariana Grigoruta was recruited as a postdoctoral fellow to join us at UTEP on 6/7/2021. She is one of the main researchers for this project. Also, this project provides a great platform to train Dr. Grigoruta in cancer pharmacology, cell and molecular biology, and translation research.

How were the results disseminated to communities of interest?

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

University of Texas at El Paso Site (Dr. Yong Qin, PI):

Early in Year 2, we will continue to work with prismCDX to complete IHC and qMIF studies. We will analyze the staining date with the pathologist Dr. Phyu Aung and biostatistician Dr. Jason Roszik

at MDACC. In addition, we anticipate submitting a scientific manuscript of biomarker studies from this project. During this time, Dr. Qin's group will work towards examining the antitumor effects of small inhibitors targeting CD73 and A2AR in UM and PDAC tumors by *in vitro* and *in vivo* studies. Moreover, we will investigate whether the drugs targeting adenosine pathways could enhance the immune response in UM and PDAC tumors combined with CPIs based on proposed in vitro and in vivo models.

MD Anderson Cancer Center (Dr. Sapna Patel, Dr. Phyu Aung, and Dr. Jason Roszik):
In Year 2, Dr. Patel will identify and provide UM TMAs for the studies of Aim 1.
Dr. Phyu Aung and biostatistician Dr. Jason Roszik will facilitate the analyses of IHC and qMIF staining data. Dr. Roszik will also participate in the statistical analyses of the results generated in the studies of Aim 2.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

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

As detailed above, we got about 6 months behind in our timeline given the delay of postdoc recruitment. The studies were slowed by the need to order molecules from a wide variety of obscure international vendors and the cost of qMIF staining. For the qMIF study, the problem was solved by the sponsored research contract with prismCDX. Thus, this delay does not change our approach.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Nothing to report

  Journal publications.

  Nothing to report

  Books or other non-periodical, one-time publications.

  Nothing to report

  Other publications, conference papers and presentations.

  Nothing to report

- **Website(s) or other Internet site(s)**
  Nothing to report

- **Technologies or techniques**

  Nothing to report

- **Inventions, patent applications, and/or licenses**

  Nothing to report

- **Other Products**

  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

University of Texas at El Paso (Dr. Qin, PI):

Name:	Yong Qin
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0003-4743-938x
Nearest person month worked:	2 months
Contribution to Project:	Dr. Qin provided oversight of the project, provided guidance and consultation to Mariana Grigoruta, and assisted with the analysis and interpretation of data.
Funding Support:	This project only

Name:	Mariana Grigoruta
Project Role:	Postdoc
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12 months
Contribution to Project:	Dr. Grigoruta will perform biomarker analyses of UM and PDAC tumor samples and pharmacological studies of CD73/A2AR inhibitors and immune checkpoint inhibitors in UM and PDAC. She will oversee tissue acquisition and storage and data management, conduct experimentation, and participate in data analysis and manuscript preparation.
Funding Support:	This project only

MD Anderson Cancer Center (Co-investigators):

Name:	Sapna Patel
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.48 months
Contribution to Project:	Dr. Patel will identify and acquire UM tumor tissues from appropriate patients via biopsy or surgical resection from the Melanoma Tissue Bank at MD Anderson Cancer Center and facilitate the transfer of samples from institutional banks to the research lab. She works directly with the laboratory investigators for all needed problem solving, review of plans, and data analysis.
Funding Support:	This project only

Name:	Jason Roszik
Project Role:	Co-investigator (Biostatistician)
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.36 months
Contribution to Project:	Dr. Roszik will assist with the integration, visualization, and analysis of data, especially in statistical analyses.
Funding Support:	This project only

Name:	Phyu Aung
Project Role:	Co-investigator (Pathologist)
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.36 months
Contribution to Project:	Dr. Aung will perform quality control for acquired tissues and will facilitate the transfer of specimens to the research lab. She will also provide support for IHC experimentation, digital capture, and tissue processing and analysis of in vivo studies.
Funding Support:	This project only

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

University of Texas at El Paso (Dr. Qin, PI): Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

This report is a single PI (Dr. Qin) project and was prepared by Dr. Qin.

COLLABORATIVE AWARDS:

Nothing to report

QUAD CHARTS:

Nothing to report

9. APPENDICES:

None