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TITLE:

Functional Characterization and Modeling of Acquired Resisance to Immune Modulation in Lung Cancer

PRINCIPAL INVESTIGATOR: Katerina Politi

CONTRACTING ORGANIZATION: Yale University

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14. ABSTRACT

Immune checkpoint inhibitors are increasingly being used in the clinic to treat patients with advanced lung cancer. Even when these agents are effective, acquired resistance to immune checkpoint inhibitors can occur and very little is known about the mechanisms of resistance to these agents. Through this grant, we investigated genomic and transcriptional mechanisms of resistance in patient specimens and identified new potential mechanisms affecting antigen presentation, interferon signaling and other pathways that can affect innate immune cells and exclude immune cells from tumors. We also optimized immunocompetent mouse models to study resistance and to validate mechanisms in vivo including loss of b2-microglobulin and the tumor suppressor gene Pten. Finally, we investigated mechanisms to overcome resistance using these models.

15. SUBJECT TERMS

lung cancer, immune checkpoint inhibitors, resistance, mouse models, antigen presentation

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1. INTRODUCTION:

Lung cancer is the leading cause of cancer death worldwide. Immune checkpoint inhibitors (ICIs) that interfere with signals like PD-1, PD-L1 and CTLA4 that negatively regulate the activity of T-cells are now standard-of-care for the treatment of lung cancer. Response rates to these immune checkpoint inhibitors are modest (objective response rates are ~15-20% in unselected patients) but the *durability of the responses* is remarkable. Despite such prolonged responses, most of these patients with lung cancer are not cured and develop acquired resistance to the agents. *At present, we lack a comprehensive understanding of the cellular and molecular mechanisms that underlie acquired resistance to immune checkpoint inhibitors.* The overarching goal of this grant was to fill this knowledge gap and to identify mechanisms of acquired resistance to immune modulation and begin to establish strategies to overcome this resistance in lung cancer by: 1) Establishing the genomic landscape of lung cancers with acquired resistance to ICIs and 2) Functionally characterizing mechanisms of acquired resistance to ICIs. As a result of this award we have identified new mechanisms of resistance to these agents, established and optimized models to functionally study resistance *in vivo* and are also beginning to develop potential strategies to therapeutically target resistant tumors.

2. KEYWORDS:

- Lung cancer
- Immune checkpoint inhibitors
- Resistance
- Mouse models
- Antigen presentation

3. ACCOMPLISHMENTS:

a. What were the major goals of the project?

The major goals of the project were to establish the genomic landscape of lung cancers with acquired resistance to ICIs and to functionally characterize the mechanisms of acquired resistance to ICIs.

Major goals/tasks
Major Tasks 1&2: Perform and analyze whole exome/RNA sequencing/QIF of 40 cases
Major Task 3: Test candidate resistance genes *in vivo*
Major Task 4: Study the immune system in resistant mouse tumors
Major Task 5: Test therapeutic strategies to overcome resistance

b. What was accomplished under these goals?

For each of the goals proposed, the following progress has been made during the period of the award:

Specific Aim 1: Establish the genomic landscape of lung cancers with acquired resistance to ICIs.

Major Goals 1 and 2. Perform and analyze whole exome, RNA sequencing and QIF of 40 cases.

As proposed, we have been collecting tumor samples and processing them for DNA and RNA sequencing. We have performed whole exome sequencing of 27 cases and RNA sequencing of 19 cases over the course of this award (4 additional cases are pending for both DNA and RNA seq) (**Figure 1**). These numbers are slightly lower than our target of 40 cases to be analyzed overall mostly due to strict QC measures that we have implemented to ensure that the data collected are of high quality and the lower than expected number of cases where biopsies are resistance were performed. Importantly, however, this still represents a large collection of cases of lung cancers resistant to immune checkpoint inhibitors that will provide very useful data for the community. Once we have obtained the sequencing data from the 4 cases that are pending we will perform an analysis of all of the data obtained to date and plan on preparing a manuscript to describe the findings. We have performed an interim analysis of the data and made some very interesting findings: 1) analysis of whole exome sequencing data from 17 cases revealed recurrent mutations in 3 genes at acquired resistance (in 2 cases each). These genes are SERPINA3, C8orf46 and PHLDA1. In particular, SERPINA3 is of interest because its overexpression has been implicated in protecting cells from immune mediated apoptosis and the residue that is mutated in the samples we studied is involved in regulating degradation of the protein. We also identified numerous genes that were recurrently mutated in >2 cases (but at different residues). One of these genes, *PREX2* was mutated at acquired resistance in 4 different cases. PREX2 is a guanine nucleotide exchange factor for RAC. It also can interact with and inactivate the tumor suppressor gene *PTEN* which is very interesting given that we have shown (see below) that *PTEN* loss mediates resistance to immune checkpoint inhibitors. We also identified additional genes with recurrent mutations, including genes in the antigen processing and presentation machinery pathway (e.g. *PSME2*) and interferon signaling (e.g. *TYK2* and *IFIT3*). Having identified these promising candidates, we will functionally validate them *in vivo* using the approaches developed below and we will determine whether they are mutated in additional cases in the cohort. Through analysis of the RNA sequencing data we have: 1) Identified the presence of an inflammatory tumor microenvironment with significant upregulation of the inhibitory receptor LAG-3 at immune checkpoint inhibitor resistance. 2) An increase in expression of inhibitory receptors and ligands for NK cells at acquired resistance including KIR2DL3, NKG2A and SIGLEC7. This is especially interesting because it provides insight into why NK cells may not be exerting their anti-tumor effects even when tumors potentially

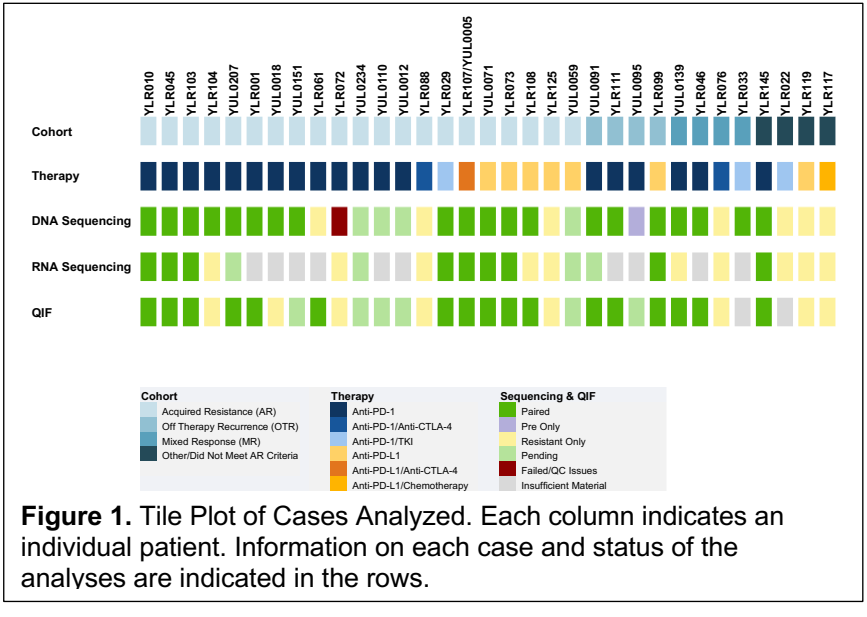

Figure 1. Tile Plot of Cases Analyzed. Each column indicates an individual patient. Information on each case and status of the analyses are indicated in the rows.

downregulated MHC I and should be recognized by these cells. 3) Found a dramatic increase in FGB, the fibrinogen beta chain, in samples at acquired resistance compared to pre-treatment. High levels of fibrinogen could potentially impede entry of immune cells into the tumors thus conferring resistance to immune checkpoint inhibitors. Thus, we have identified several novel potential mechanisms of resistance from analysis of the RNA sequencing data. We have also performed histological analysis of immune cell profiles in tumors with acquired resistance to immune checkpoint blockade using multiplexed quantitative immunofluorescence for localized measurements of the immune inhibitor receptors PD-1, LAG-3, TIM-3 and the T cell activation markers Ki-67 and GZMB in CD3+ T lymphocytes. Overall analysis of these data to date support the presence of a more inflammatory microenvironment in tissues following treatment with immune checkpoint inhibitors compared to pre-treatment specimens including through upregulation of LAG-3 and PD-1. In summary, our comprehensive study of tissue from lung tumors resistant to immune checkpoint inhibitors has uncovered new potential genomic and transcriptional mechanisms of resistance to these agents that can be validated mechanistically.

Specific Aim 2: Functionally characterize mechanisms of acquired resistance to ICIs.
Major Goal 3. Test candidate resistance genes *in vivo*.
We have taken two approaches to study/validate mechanisms of acquired resistance *in vivo*. The first approach is to use a Kras mutant, immune checkpoint inhibitor sensitive, murine lung cancer cell line (UN-SCC680AJ). Using this line, we have used CRISPR/*Cas9* mediated genome editing to knock-out candidate drivers of resistance to immune checkpoint inhibitors. These include the essential component of the MHC I antigen presentation machinery *B2m*, the tumor suppressor gene *Pten*, and the proteasome components *Psme2* and *Psmd5*. *B2m* and *Pten* inactivation were both confirmed to confer resistance to immune checkpoint inhibitors when they were knocked out and the cells were transplanted into a syngeneic, immunocompetent mouse. The establishment of this platform has provided a system that can now be readily used to further investigate the functional role of genomic alterations found in immunotherapy resistant tumors, such as mutations in antigen presentation machinery and interferon pathway genes. Currently we are in the process of functionally validating *Psme2* and *Psmd5*. We have established 54 and 39 clones for *Psme2* and *Psmd5*, respectively and have begun to screen them to identify knock-out clones for either of these genes by analyzing protein extracts from the clones using western blotting. We also attempted to obtain a knock-out clone for Smarca4 but were not successful and are currently trying an alternative approach to do this. Once we have clones deficient for these different genes, we will measure the levels of cell surface MHC I and test whether this alteration affects sensitivity to ICIs *in vivo*. In summary, we now have two models of resistance to immune checkpoint inhibitors arising as a result of different resistance mechanisms that can be used as platforms to test new therapies and are currently investigating others. We also have used genetically engineered mouse *Kras* mutant lung adenocarcinoma model-derived cell lines with a mutation in the mismatch repair gene *Msh2*. These cell lines have more mutations than the parental cell lines and, as a result of the increased mutation burden, are sensitive to immune checkpoint inhibitors. Importantly, these lines also develop acquired resistance when treated long-term with the drugs and can be used to study the mechanisms that underlie this resistance. Importantly, this model will allow us to validate our findings in the squamous model in another relevant lung cancer model system (adenocarcinoma).

Major Goal 4. Study the immune system in resistant mouse tumors
Our knowledge of changes in the immune system in tumors resistant to immune checkpoint inhibitors is very limited to date in part due to the lack of robust *in vivo* models to study drug resistance. In our studies we have developed new models of lung cancer resistant to immune

checkpoint inhibitors and have studied the phenotypes of these tumors and of the immune cell infiltrates. Specifically, we modeled resistance to anti-PD1 therapy in the immunocompetent UNSCC680AJ squamous lung cancer syngeneic model by deleting either *B2m* or *Pten*. In major goal 3, we demonstrated that these were resistant to therapy. Here we characterized immune cells present in the *B2m*- and *Pten*- deficient settings. Not surprisingly, the *B2m*-deficient tumors lacked cell surface MHC I. However, MHC I was present on the surface of *Pten*-deficient tumors indicating that these must have a different defect that is leading to resistance to therapy (Fig XA). Therefore, we have established models of resistance that are MHC I -deficient and MHC I-proficient. We have most extensively characterized the immunophenotype of the B2m-deficient model and found that these tumors harbor fewer tumor infiltrating CD8 T cells and myeloid cells as compared to UN-SCC680AJ wild-type tumors. We also observed that the CD8 T cells in the immunotherapy resistant tumors (UN-SCC680AJ B2m knockout) were less proliferative and produced less IFNγ, TNFα, and Granzyme B. Moreover, while we observed no change in the total number of NK cells in tumors with *B2m* loss, we did notice that B2m null, tumor-infiltrating NK cells had lower TIGIT and TNFα expression, indicative of reduced activation. The numbers of CD4 T cells were unchanged in *Pten*-deficient tumors compared to wild-type, while CD8 T cell numbers were quite variable between tumors and did not exhibit any differences in proliferation (**Figure 2**). These results suggest that the tumors do not have defects in the recruitment and proliferation of the T cells but that specific signals must be restricting the function of the CD8 T cells in these tumors. Having uncovered this result we have begun to perform mRNA profiling of the tumors to identify the mechanisms that are suppressing T cell function in these *Pten*-/- tumors. Initial data indicate that there are significant changes in immunosuppressive molecules and will further pursue this interesting research direction going forward.

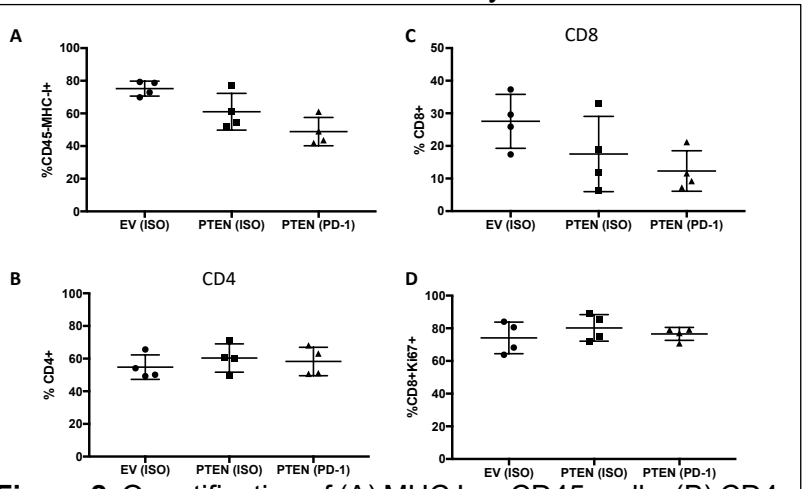

Figure 2. Quantification of (A) MHC I on CD45- cells, (B) CD4 T cells, (C) CD8 T cells and (D) Ki-67+ CD8 T Cells in UNSCC680AJ wild-type (EV) or *Pten* -/- (PTEN) tumors treated with isotype or anti-PD1.

Major Goal 5. Test therapeutic strategies to overcome resistance

One of the challenges of treating tumors that have developed acquired resistance to immunotherapies especially if they have become resistant due to defects in MHC I antigen presentation is that CD8 T-cell directed therapies can no longer be used to treat these tumors. NK cells, however, recognize cells with low/no cell surface MHC I (as per the "missing self" hypothesis) and, in theory, should exert a cytotoxic effect on these cells. Since MHC I tumors do growth out, it is likely that NK cell activity is somehow suppressed in the tumors. We hypothesized that one approach to overcome resistance due to defects in MHC I was to test therapies that could activate NK cells. In this regard, we have evaluated the efficacy of using a pro-inflammatory cytokine DRIL-18 to overcome resistance due to B2m loss. To our surprise we found that the combination of anti-PD1 plus DR-IL18 could overcome resistance in ~40% of *B2m*-/- tumors. This is especially interesting because neither drug alone has an effect and one would predict that anti-PD1 would act on CD8 T cells which are non-functional in the *B2m*-deficient context. Analysis of

immune cells in these mice upon treatment revealed that NK cells are activated (e.g express high levels of Klrg1, **Figure 3**) and that DRIL-18 increases the level of PD1 on NK cells probably rendering them sensitive to anti-PD1 therapy. As final confirmation that NK cells functionally mediate tumor regression, we will perform an NK depletion experiment to see whether this abrogates the response. We are planning to complete a manuscript on this topic in the first part of 2020. Since targeting NK cells is a promising approach from these studies we are expanding our efforts in this research area using additional therapies that act on these cells.

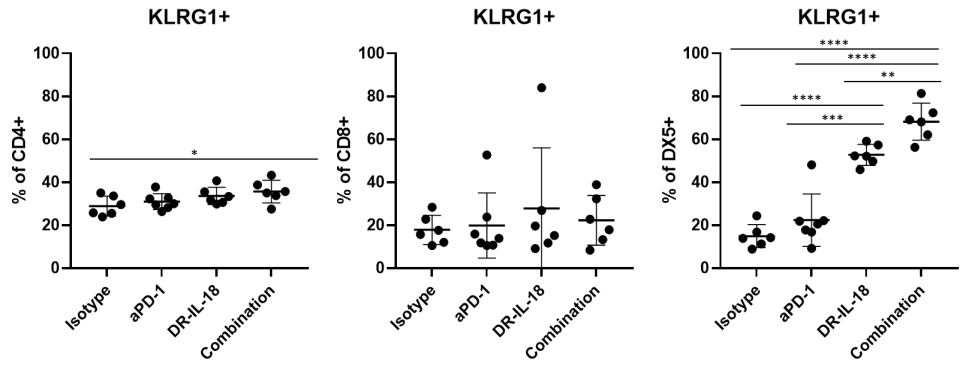

Figure 3. Increased expression of the activation marker Klrg1 on DX5+ NK cells following treatment with DR-IL18 and anti-PD1 but not on CD4 or CD8 T cells.

Collectively, through this 2-year project we have: 1) identified new potential drivers of resistance, 2) established models of resistance to immunotherapy and new models to validate and study resistance and 3) begun to investigate strategies to overcome resistance. This work lays the groundwork for further studies that we are building on now in the lab stemming from this grant.

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

The project has provided opportunities for trainees in the PIs lab and collaborators to learn and work on Cancer Immunology over the course of the award. Dr. Hastings, for example, who is trained as a cancer biologist, has gained significant expertise in Cancer Immunology by studying problems tackled in this grant. She has also attended the AACR Tumor Immunology and Immunotherapy meeting in Boston in 2017. Camila Robles-Oteiza, a graduate student, attended a CSHL Mechanisms and Models of Cancer meeting and a CSHL course on analysis of genomic data which was valuable for her professional development. Moreover, she was recently awarded a prestigious F99/K00 predoctoral to post-doctoral transition award that will allow her to continue her cancer immunology studies in my lab and as a post-doc when she graduates. Jordan Cardenas, a Yale NIH PREP student who worked on the project attended a Keystone symposia last year on innate and non-classical immune cells in cancer immunotherapy and he is now a graduate student in Immunobiology at Yale. Perhaps most importantly this grant has provided everyone on the team the opportunity to work collaboratively on an important scientific question and capitalize on the value of multidisciplinary team research.

d. **How were the results disseminated to communities of interest?**

The results were disseminated to audiences mainly through presentation of the results at National and International Conferences as described below in section 6.

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

Not applicable. We have used the data and models obtained through these studies to apply for additional funding to extend the studies and have successfully competed for an NCI R01.

4. IMPACT:

Nothing to Report

5. CHANGES/PROBLEMS:

a. Changes in approach and reasons for change

None

b. Actual or anticipated problems or delays and actions or plans to resolve them

We did have a delay in collecting and analyzing samples from patients for Goals 1&2. This meant that the analysis of the data are somewhat delayed and we will have a more limited number of specimens to study than anticipated. However, this is still a large (if not the largest) cohort of cases at acquired resistant to immune checkpoint inhibitors in lung cancer. Moreover, the data analyzed to date have already revealed a number of interesting findings and candidates for further investigation.

c. Changes that had a significant impact on expenditures

None

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

Nothing to report

e. Significant changes in use or care of human subjects

Nothing to report

f. Significant changes in use or care of vertebrate animals.

Nothing to report

g. Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

a. Publications, conference papers, and presentations

i. **Journal publications.**

Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer. **Gettinger** S, Choi J, Hastings K, Truini A, Datar I, Sowell R, Wurtz A, Dong W, Cai G, Melnick MA, Du VY, Schlessinger J, Goldberg SB, Chiang A, Sanmamed MF, Melero I, Agorreta J, Montuenga LM, Lifton, R, Ferrone S, Kavathas P, Rimm DL, **Kaech** SM, **Schalper** K, **Herbst** RS, **Politi** K. Cancer Discov. 2017 Dec;7(12):1420-1435. doi: 10.1158/2159-8290.CD-17-0593. Epub 2017 Oct 12. PMID:29025772. Published. This manuscript is directly relevant to the work in this grant but was accepted shortly after the grant was initiated therefore support from this grant is not acknowledged.

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

Nothing to Report

iii. **Other publications, conference papers, and presentations.**

List of Speaking Engagements, Presentations, Symposia and Workshops:

2018

30th EORTC NCI AACR Symposium. Dublin, Ireland. "Mechanisms of Acquired Resistance to Immune Checkpoint Inhibitors." *Invited Speaker*

The 23rd Annual Scientific Symposium of the Hong Kong Cancer Institute, Hong Kong. "Mechanisms of Acquired Resistance to Immune Checkpoint Inhibitors", *Invited Speaker*

World Conference on Lung Cancer, Toronto, CA. "Leveraging Mouse Models to Study Cancer Immunology", *Invited Speaker*

27th Annual Short Course on Experimental Models of Human Cancer, The Jackson Labs, Bar Harbor, ME. "Unraveling the Complexity of Drug resistance in Lung Cancer", *Invited Speaker*

CHI Biomarker World Congress, Boston, MA. "Acquired Resistance to Immune Modulation in Lung Cancer". *Invited Speaker*

Society for the Immunotherapy of Cancer, Cancer Immune Responsiveness Workshop, San Francisco, CA. "Leveraging Mouse Models to Study Sensitivity and Resistance to Cancer Therapies", *Invited Speaker*

British Columbia Cancer Agency Seminar Series, Vancouver, Canada. "Unraveling the Complexity of Drug resistance in Lung Cancer", *Invited Speaker*

AACR-SNMMI meeting, San Diego, CA. "Modeling Drug Resistance in Lung Cancer." *Invited Speaker*

Fifth AACR-IASLC International Joint Conference on Lung Cancer, San Diego, CA. "Mechanisms of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer". *Invited Speaker*

2017

New York Cancer Genome Network Meeting, New York, NY. "Unraveling the Complexity of Drug resistance in Lung Cancer", *Invited Speaker*

Society for the Immunotherapy of Cancer, National Harbor, MD. "Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer". *Plenary Session Co-Chair and Speaker*

AACR Advances in Modeling Cancer in Mice: Technology, Biology, and Beyond, Orlando, FL, "Tackling Drug Resistance Lessons from Mouse Models", *Co-organizer and Speaker*

b. **Website(s) or other Internet site(s)**

Nothing to Report

c. **Technologies or techniques**

Nothing to Report

d. **Inventions, patent applications, and/or licenses**

Nothing to Report

7. Other Products

Nothing to Report

8. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	***Katherine Hastings,*** *no change*
Name:	***Susan Kaech,*** *no change*
Name:	***Scott Gettinger,*** *no change*
Name:	***Roy Herbst,*** *no change*
Name:	***Kurt Schalper,*** *no change*
Name:	***Hongyu Zhao,*** *no change*

Name	*Katerina Politi*
Project Role	*No change*
Researcher Identifier	
Nearest person month worked	*2*
Contribution to Project	*No change*
Funding Support	*Refer to funding changes in tables below*

Name	*Stellar Levy*
Project Role	*Post-graduate Research Associate*
Researcher Identifier	
Nearest person month worked	*4*
Contribution to Project	*Ms. Levy managed the animal colony including the mice allocated to this research project.*
Funding Support	*NIH/NCI* *AstraZeneca*

Name	*Nicholas Rashleigh*
Project Role	*Post-graduate Research Associate*
Researcher Identifier	
Nearest person month worked	*6*
Contribution to Project	*No change*
Funding Support	*No change*

Name	*Camila Robles-Oteiza*
Project Role	*Graduate Student*
Researcher Identifier	
Nearest person month worked	*6*
Contribution to Project	*Ms. Robles-Oteiza performed follow-up experiments and is developing the LKR13 and 368T1-TGL cell lines and their knockout derivatives as outlined in Specific Aim 2.*
Funding Support	*NIH/NCI*

Name	*Jordan Cardenas*
Project Role	*PREP Student*
Researcher Identifier	
Nearest person month worked	*6*
Contribution to Project	*Mr. Cardenas worked with Ms. Robles-Oteiza and conducted the DRIL-18 studies outlined in major goal 5.*
Funding Support	*NIH*

Name	*Victor Du*
Project Role	*No change*
Researcher Identifier	
Nearest person month worked	
Contribution to Project	*No change*
Funding Support	*NIH* *SITC Holbrook*

Name	*Robert Homer*
Project Role	*No change*

Researcher Identifier	
Nearest person month worked	*No change*
Contribution to Project	*No change*
Funding Support	*Refer to funding changes in tables below*

Name	*Francisco Exposito-Rincon*
Project Role	*Visiting Graduate Student (SPAIN)*
Researcher Identifier	
Nearest person month worked	*3*
Contribution to Project	*Mr. Exposito-Rincon performed follow-up studies using the murine lung cancer cell lines and developed new tumor suppressor deficient derivatives of these lines.*
Funding Support	*Home institutional support (University of Navarra)*

Name	*Mary Ann Melnick*
Project Role	*No change*
Researcher Identifier	
Nearest person month worked	*1*
Contribution to Project	*No change*
Funding Support	*NIH/NCI*

Name	*Anna Wurtz*
Project Role	*No change*
Researcher Identifier	
Nearest person month worked	*3*
Contribution to Project	*No change*
Funding Support	*No change*

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

Listed below are updates to the active other support of the PI, Katerina Politi and Robert Homer (Pathologist) since the last reporting period (September 2018 Annual Technical Report). Table 1 provides a status update of the active awards that were reported at the time of the 2018 Annual Technical Report. Table 2 provides information on awards that were activated since the 2018 Annual Technical Report.

Table 1: Updates to funding support status reported on the September 2018 Annual Technical Report

Investigator	*Funding Agency*	*Award Number*	*Project Title*	*Status at time of 2018 Annual*	*Current status*

				Technical Report	
Politi	*SWOG*	*Not Applicable*	*A Randomized Phase II/III Trial of Afatinib Plus Cetuximab Versus Afatinib Alone in Treatment Naïve Patients with Advanced, EGFR Mutation Positive Non Small Cell Lung Cancer*	*Active*	*Completed – 04/13/2019*
Politi	*Symphogen*	*Not Applicable*	*Pre-clinical Assessment of the Efficacy of Sym004 in EGFR Mutant Lung Cancer*	*Active*	*Early termination by Funding Agency – 03/28/2019*
Politi	*American Lung Association*	*Not Applicable*	*Targeting Cancer Metabolism in Therapy Resistant EGFR Mutant Lung Cancer*	*Active*	*Completed – 09/12/2019*
Homer	*NIH/NHLBI*	*R01HL126094*	*Host-Pneumococcal Interaction in the Lung*	*Active*	*Completed – 11/30/2019*
Homer	*NIH/NHLBI/DHHS*	*R01HL127349-01*	*Genomic Analysis of Tissue and Cellular Heterogeneity in IPF*	*Active*	*Completed – 05/31/2019*
Homer	*Department of the Army*	*PR151124*	*Large Non-Coding RNAs as Therapeutic Targetsin IPF*	*Active*	*Completed – 09/30/2019*

Table 2: Additional funding support for key personnel activated since the 2018 Annual Technical Report

Investigator	*Funding Agency*	*Award Number*	*Project Title*	*Award Activation Date*	*Current Status*
Politi & Homer	*Roche Genentech*	*Not Applicable*	*Transforming the Immune Desert into an Immunostimulatory Microenvironment in Lung Cancer*	*08/28/2018*	*Active*
Politi	*NIH/NCI*	*R01CA230275*	*Understanding and Overcoming Resistance to Cancer Immunotherapy Due to Defective Antigen Presenation*	*02/06/2019*	*Active*

Politi & Homer	*NIH/NCI*	*U01CA235747*	*Uncovering the Biology of Resistance to Tyrosine Kinase Inhibitors in EGFR Mutant Lung Cancer Patient-Derived Models*	*04/23/2019*	*Active*
Homer	*NIH/NHLBI*	*R01HL141852-01A1*	*Epithelial Protective Effects of Thyroid Hormone Signaling in Fibrosis*	*12/01/2018*	*Active*
Homer	*Department of the Army*	*PR170078P1*	*Cell Type-Specific KLF4 Regulation of Lung Fibrosis*	*08/01/2018*	*Active*

What other organizations were involved as partners?

Organization Name: Fundacion para la Investigacion Medica Aplicada (FIMA)
Location of Organization: Avda. Pio XII 55, 31008, Pamplona, SPAIN
Partner's contribution to the project: In-kind support – provided UN-SCC680AJ cell line

Organization Name: The Salk Institute
Location of Organization: 10010 North Torrey Pines, La Jolla, CA
Partner's contribution to the project: Collaboration with Dr. Susan Kaech

Organization Name: Massachusetts Institute of Technology
Location of Organization: 77 Massachusetts Avenue, Cambridge, MA
Partner's contribution to the project: In-kind support – provided LKR13, LKR13 1c16, and LKR13 3c6 cell lines

Organization Name: University of Navarra
Location of Organization: Calle Irunlarrea 1, Pamplona, SPAIN
Partner's contribution to the project: Collaboration with Dr. Alfonso Calvo (follow-up studies)

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:**

Not applicable

- **QUAD CHARTS:**

Not applicable

9. APPENDICES:

No appendices