Award Number: W81XWH-21-1-0487

TITLE: Overcoming Resistance to EGFR Inhibitors in Advanced Head and Neck Cancers

PRINCIPAL INVESTIGATOR: Erica Golemis, Ph.D.

CONTRACTING ORGANIZATION: Institute for Cancer Research 333 Cottman Avenue, Philadelphia, PA 19111

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PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Research Institute of Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, Pennsylvania 19111
E-Mail: osr@fccc.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Development Command
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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Head and neck squamous cell carcinomas (HNSCCs) affect more than a half million people annually worldwide. The goal of this proposal is to develop strategies to overcome HNSCC resistance to EGFR inhibitors (EGFRis). Based on extensive published and preliminary data, this proposal tests three hypotheses: 1) that upregulation of AURKA provides a major source of resistance to EGFRis in HPV- HNSCC. 2) that tumors most likely to upregulate AURKA will either have highly damaging LOF mutations in *TP53*, or upregulation of TPX2 or NEDD9, and that these tumors will have the highest level of resistance to EGFRis. 3) that targeting AURKA either with single agent kinase inhibitors, or in combination therapies that inhibit AURKA and a second protein, WEE1, that collaborates with AURKA to control mitotic progression, will be particularly effective in counteracting resistance to EGFRis. In the first year of funding, we have defined the pattern of TP53 mutations in HNSCCs. We have created HNSCC cell models resistant to EGFR-targeting inhibitors, and have been profiling response to AURKA and WEE1 inhibitors. We have accrued specimens from a clinical trial of EGFR inhibitors in HNSCC, which will support correlating therapeutic resistance with AURKA, TPX2, and NEDD9 expression. Work is ongoing.

15. SUBJECT TERMS

Head and neck cancer, head and neck squamous cell carcinoma, targeted therapy, TP53, AURKA, EGFR, WEE1, resistance, combination therapy

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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DOD Annual Report

Principal Investigator: Erica Golemis, Ph.D.
Institution: The Research Institute of Fox Chase Cancer Center
Grant Number: W81XWH-21-1-0487

INTRODUCTION:

Head and neck squamous cell carcinomas (HNSCCs) are frequently devastating cancers that affect more than a half million people annually worldwide. HNSCC is typically detected at an advanced stage, and when recurrent is treated with cytotoxic systemic therapies. The only approved targeted therapies for advanced disease are inhibitors of the epidermal growth factor receptor (EGFR), which improve disease outcomes in some patients. The goal of this proposal is to develop strategies to overcome intrinsic and acquired resistance to EGFR inhibitors (EGFRis). Aurora-A kinase (AURKA) upregulation is common in HPV- HNSCC, and activates critical downstream effectors of EGFR, including ERK1/2, AKT, and others; in addition, overexpressed AURKA causes mitotic abnormalities that promote genomic instability, leading to selection of resistant clones. Transcriptional upregulation of AURKA-binding proteins including TPX2 and NEDD9 protect AURKA from proteolytic degradation, enhancing its activity; upregulation of TPX2 and NEDD9 is common in advanced cancers, and overexpression of TPX2 has been shown to promote resistance to EGFRis. This proposal tests the hypothesis that upregulation of AURKA provides a major source of resistance to EGFRis in HPV- HNSCC. We hypothesize that tumors most likely to upregulate AURKA will either have highly damaging LOF mutations in *TP53*, or upregulation of TPX2 or NEDD9, and that these tumors will have the highest level of resistance to EGFRis. We hypothesize that targeting AURKA either with single agent kinase inhibitors, or in combination therapies that inhibit AURKA and a second protein, WEE1, that collaborates with AURKA to control mitotic progression, will be particularly effective in counteracting resistance to EGFRis.

KEYWORDS: EGFR, AURKA, WEE1, NEDD9, TPX2, TP53, alisertib, erlotinib, afatinib, adavosertib, synergy, resistance, head and neck cancer

ACCOMPLISHMENTS:

What were the major goals of the project?

The goals of the project as approved in the SOW are as follows:

Specific Aim 1: Determine how TP53 mutation class determines AURKA expression and alters sensitivity to

inhibition of AURKA and EGFR.

Specific Aim 2: Explore relative efficacy of AURKA monotherapy and an AURKA-WEE1 inhibitor combination in the setting of and in preventing or reversing adaptive resistance to EGFR inhibition.

Specific Aim 3: Define the relationship between TP53 genotype, AURKA expression, and response to EGFR inhibition using clinical trial samples for HNSCC.

What was accomplished under these goals?

Aim 1, Major task 1 (use public resources to establish relationship between TP53 mutation segregated by class, and expression of mRNA for AURKA, NEDD9, and TPX2) was completed and described at the time of the last report and published in 2022.

Aim 1, Major task 2 (Functionally testing the relation between *TP53* mutation class, AURKA mRNA and protein expression and activity, and resistance to the EGFR inhibitors afatinib and erlotinib), HNSCC cell lines were developed by growth in gradually increasing concentrations of these drugs (Burtness group, year 1, reported previously), or by overexpressing the oncogene c-MET, a common physiological cause of resistance to EGFR-

inhibiting agents (Golemis group, this report period; see Figures 1-3). We are characterizing the expression of AURKA, TPX2, NEDD9, EGFR, and sentinel effectors in these models, and characterizing their cell cycle profiles to provide context for analysis of AURKA function (Figure 4-5, and work ongoing).

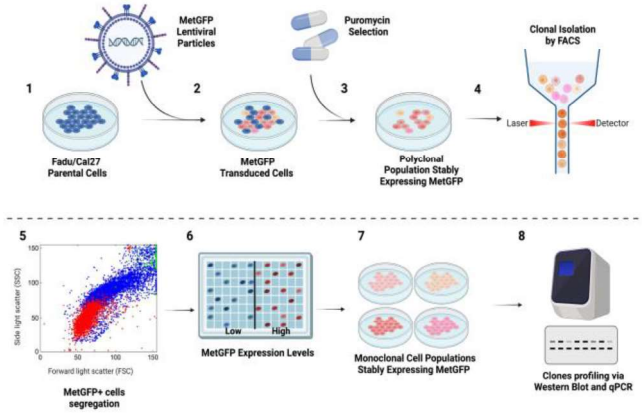

Figure 1. Generation of Fadu and Cal27 with constitutive overexpression of c-MET. Schematic of steps employed to generate cell models.

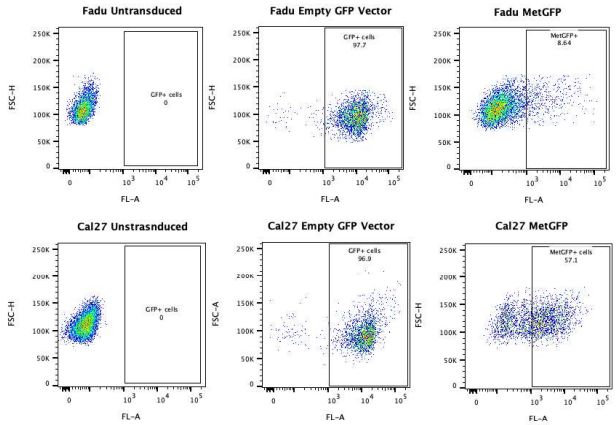

Figure 2. Clonal isolation as part of development of c-MET overexpressing models; sorting of GFP+ Cells by FACS.

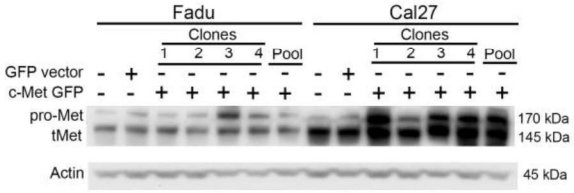

Figure 3. Western blot confirmation of clonal isolates overexpressing c-MET. Image shows examples of clonal isolates purified as specified in steps in Figure 1.

We demonstrated AURKA expression by Western blot to be elevated in *TP53* mutated and null cells, relative to WT *TP53* cells. Employing a suite of PCI-13 engineered with wild type (WT), loss of function (LOF) and gain of function (GOF) mutations, we demonstrated enhanced sensitivity to AURKA inhibition.

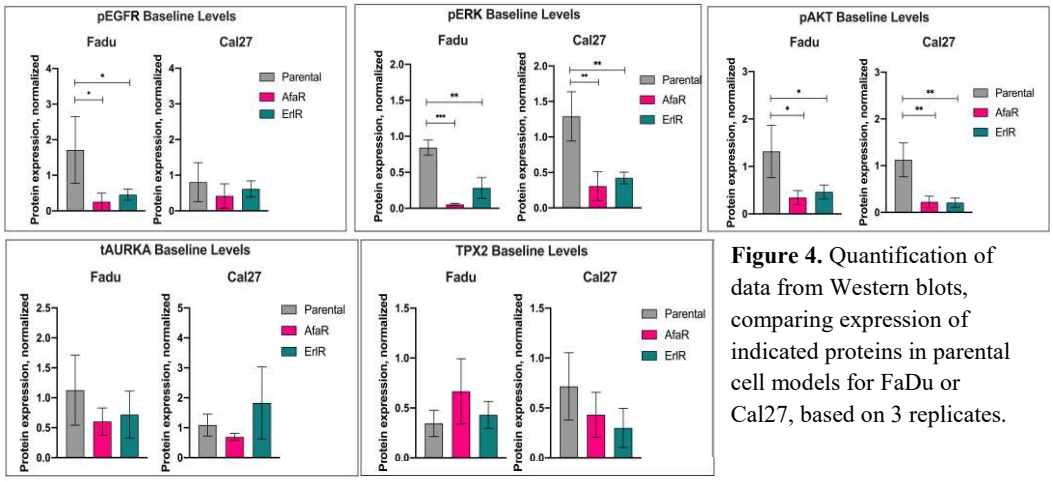

Figure 4. Quantification of data from Western blots, comparing expression of indicated proteins in parental cell models for FaDu or Cal27, based on 3 replicates.

Aim 2, Major task 3 (Using squamous cell carcinoma lines with acquired resistance to cetuximab or afatinib, conduct cell viability, clonogenic survival, and xenograft modeling to determine the cytotoxicity of AURKA inhibition alone or in combination with WEE1 inhibition in HNSCC resistant to EGFR inhibition). Also, Aim 2, Major task 4 (Determine if AURKA inhibition or AURKA plus WEE1 inhibition restores sensitivity to EGFR inhibition in resistant models). As a major component of work in the past year, the Golemis group has been systematically assessing response of afatinib- and erlotinib-resistant cell lines to the AURKA inhibitor TAS-119/VIC1911 and adavosertib, alone and in combination, as well as the combination of AURKA and EGFR inhibition, in the cell lines developed in year 1, as described in subtask 2, and while continuing to monitor the expression of AURKA, TPX2, NEDD9, EGFR, and sentinel effectors. Examples of these experiments are shown in Figures 6-13.

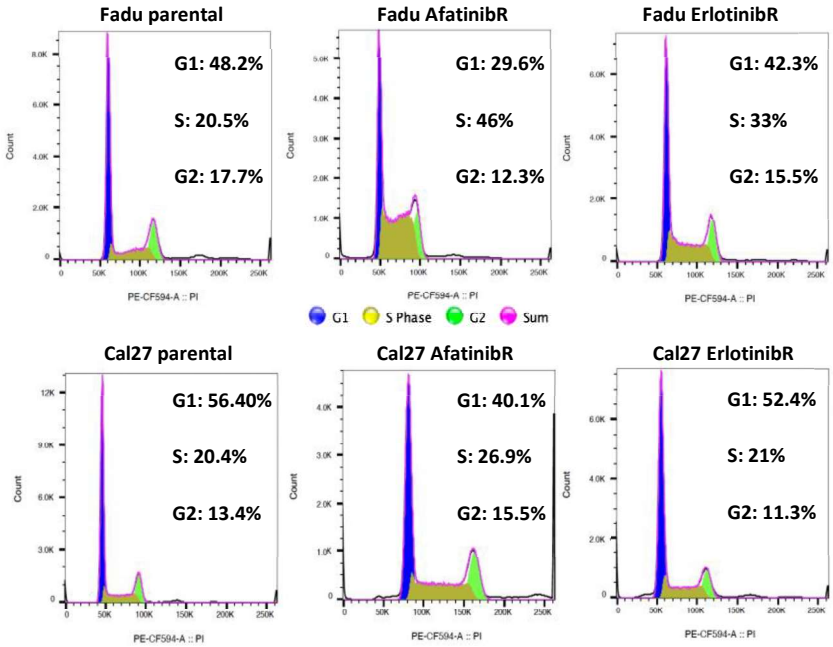

Figure 5. Representative data from FACS analysis of asynchronously growing cell populations of FaDu or Cal27 cells, or Afatinib- or Erlotinib-resistant derivative lines, typical of 3 replicates. Resistance is associated with cell cycle defects.

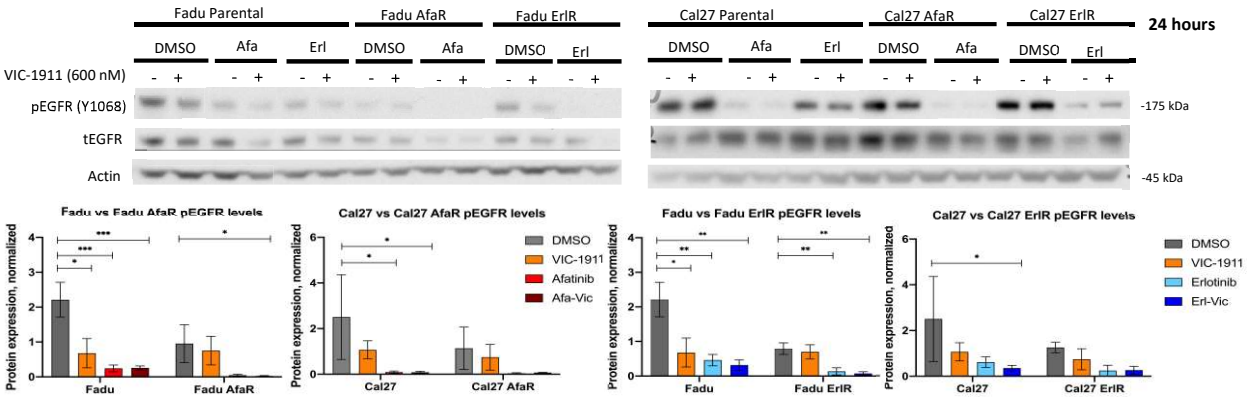

Figure 6. Top, representative Western blot data and bottom, quantification from three replicates normalized to loading control, for expression of Y1068-phosphorylated EGFR from parental, AfaR, or ErlR resistant derivatives treated with the drugs indicated. *, p<0.05; **, p<0.01, ***. P<0.001.

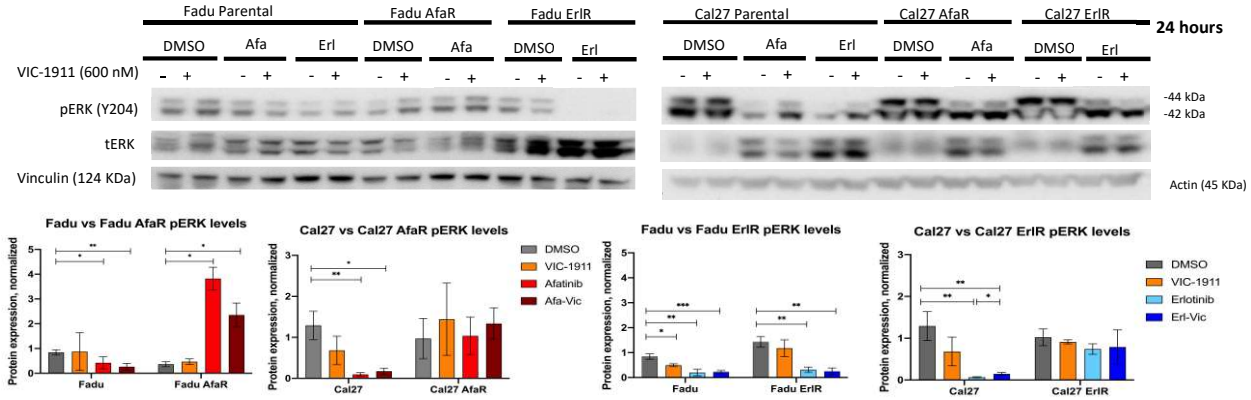

Figure 7. Top, representative Western blot data and bottom, quantification from three replicates normalized to loading control, for expression of phosphorylated ERK1/2 from parental, AfaR, or ErlR resistant derivatives treated with the drugs indicated. *, p<0.05; **, p<0.01, ***. P<0.001.

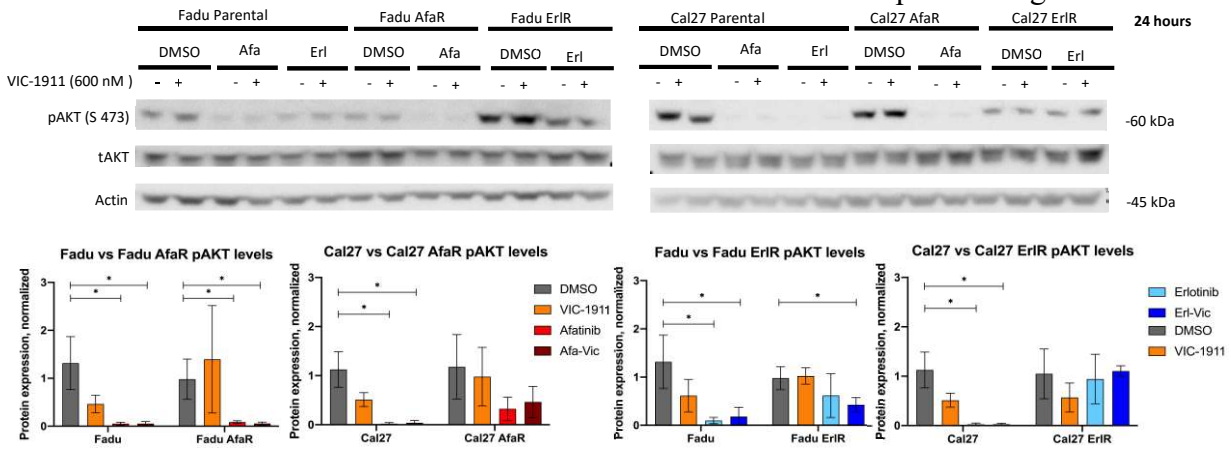

Figure 8. Top, representative Western blot data and bottom, quantification from three replicates normalized to loading control, for expression of S473-phosphorylated AKT1 from parental, AfaR, or ErlR resistant derivatives treated with the drugs indicated. *, p<0.05; **, p<0.01, ***. P<0.001.

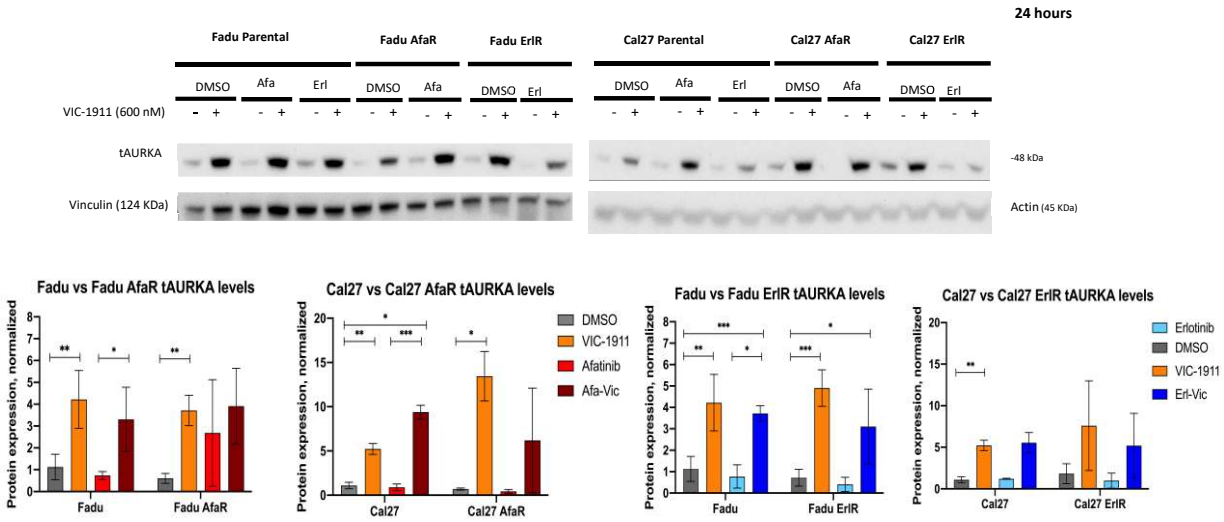

Figure 9. Top, representative Western blot data and bottom, quantification from three replicates normalized to loading control, for expression of AURKA from parental, AfaR, or ErlR resistant derivatives treated with the drugs indicated. *, p<0.05; **, p<0.01, ***. P<0.001.

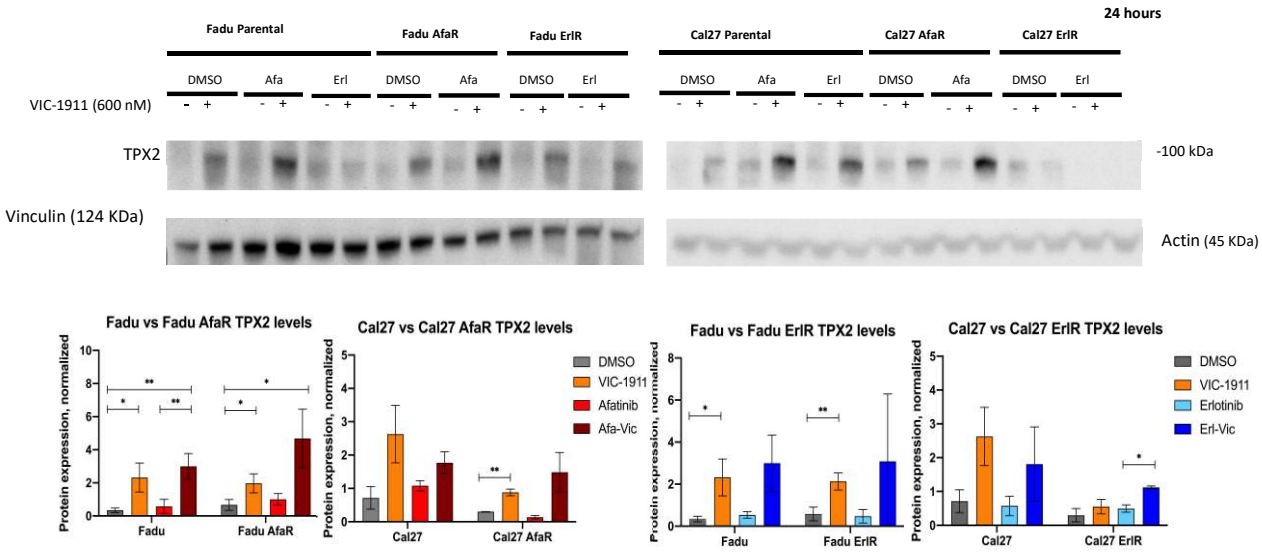

Figure 10. Top, representative Western blot data and bottom, quantification from three replicates normalized to loading control, for expression of TPX2 from parental, AfaR, or ErlR resistant derivatives treated with the drugs indicated. *, p<0.05; **, p<0.01, ***. P<0.001.

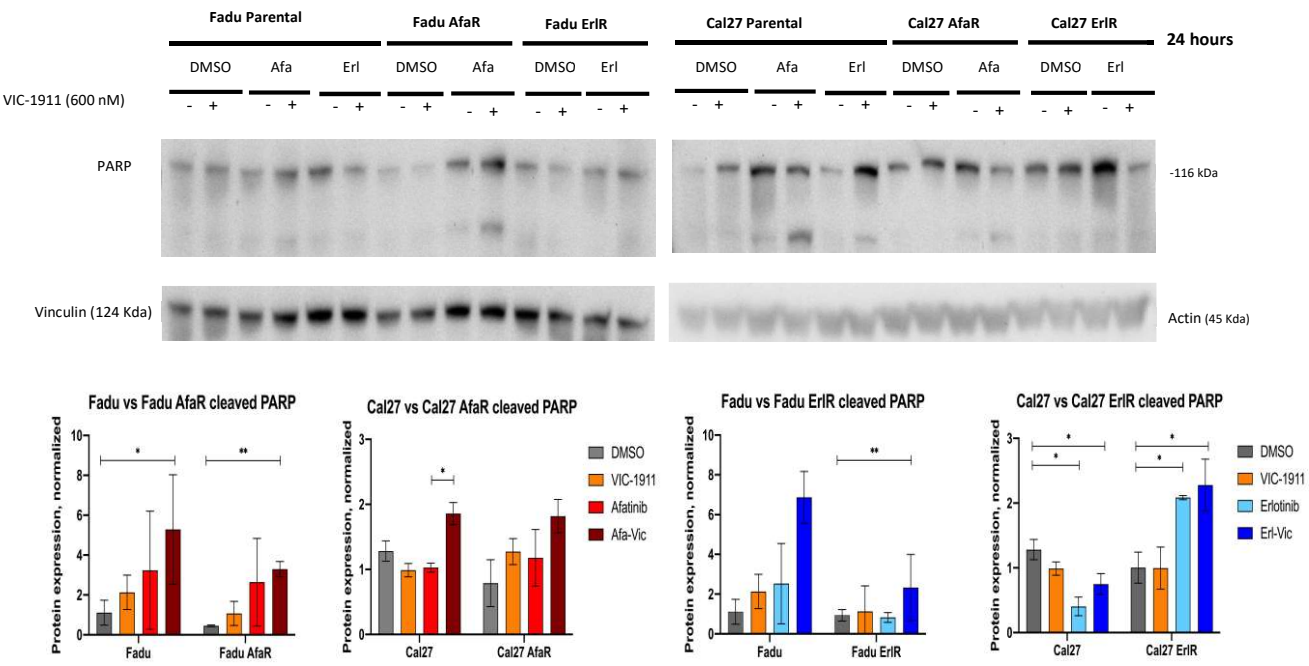

Figure 11. Top, representative Western blot data and bottom, quantification from three replicates normalized to loading control, for expression of PARP1 from parental, AfaR, or ErlR resistant derivatives treated with the drugs indicated. *, p<0.05; **, p<0.01, ***. P<0.001.

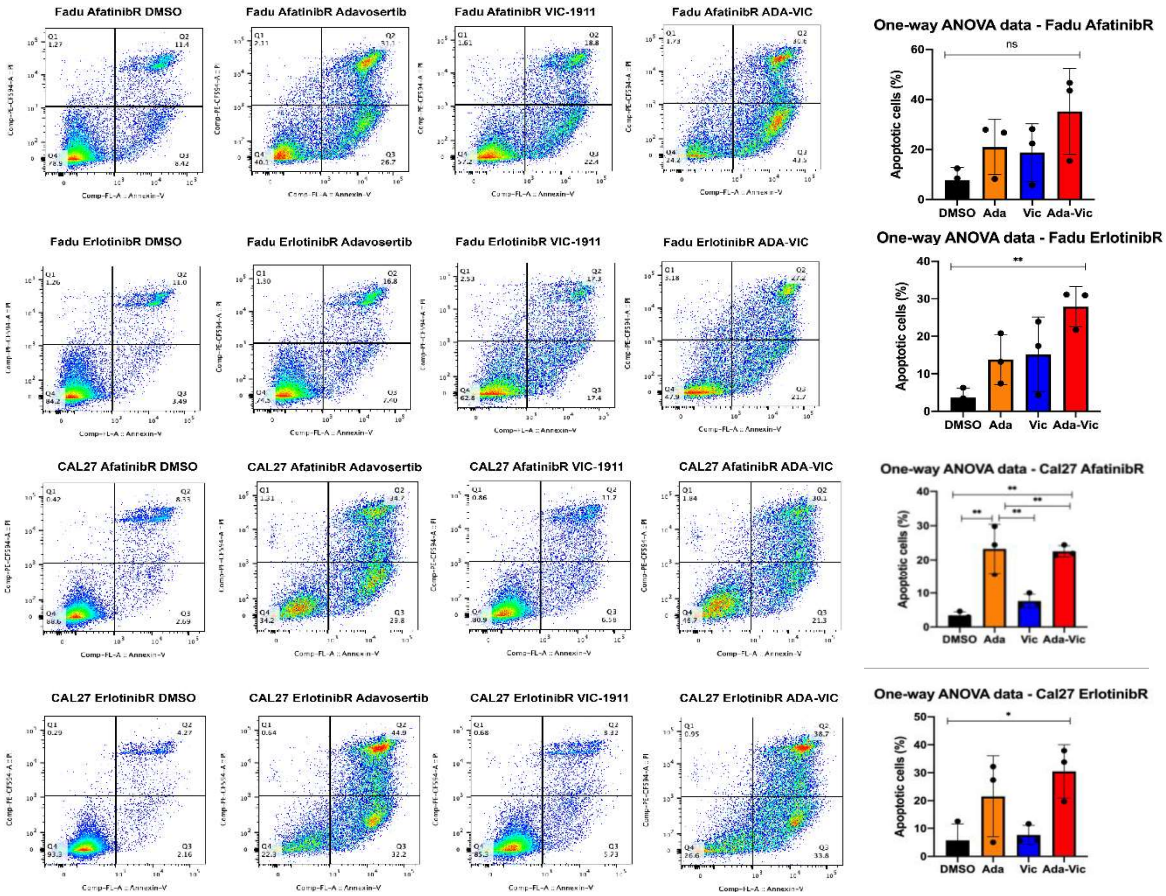

Figure 12. Left, representative FACSt data and right, quantification from three replicates, for expression of PARP1 from parental, AfaR, or ErlR resistant derivatives treated with the drugs indicated. *, p<0.05; **, p<0.01, ***. P<0.001.

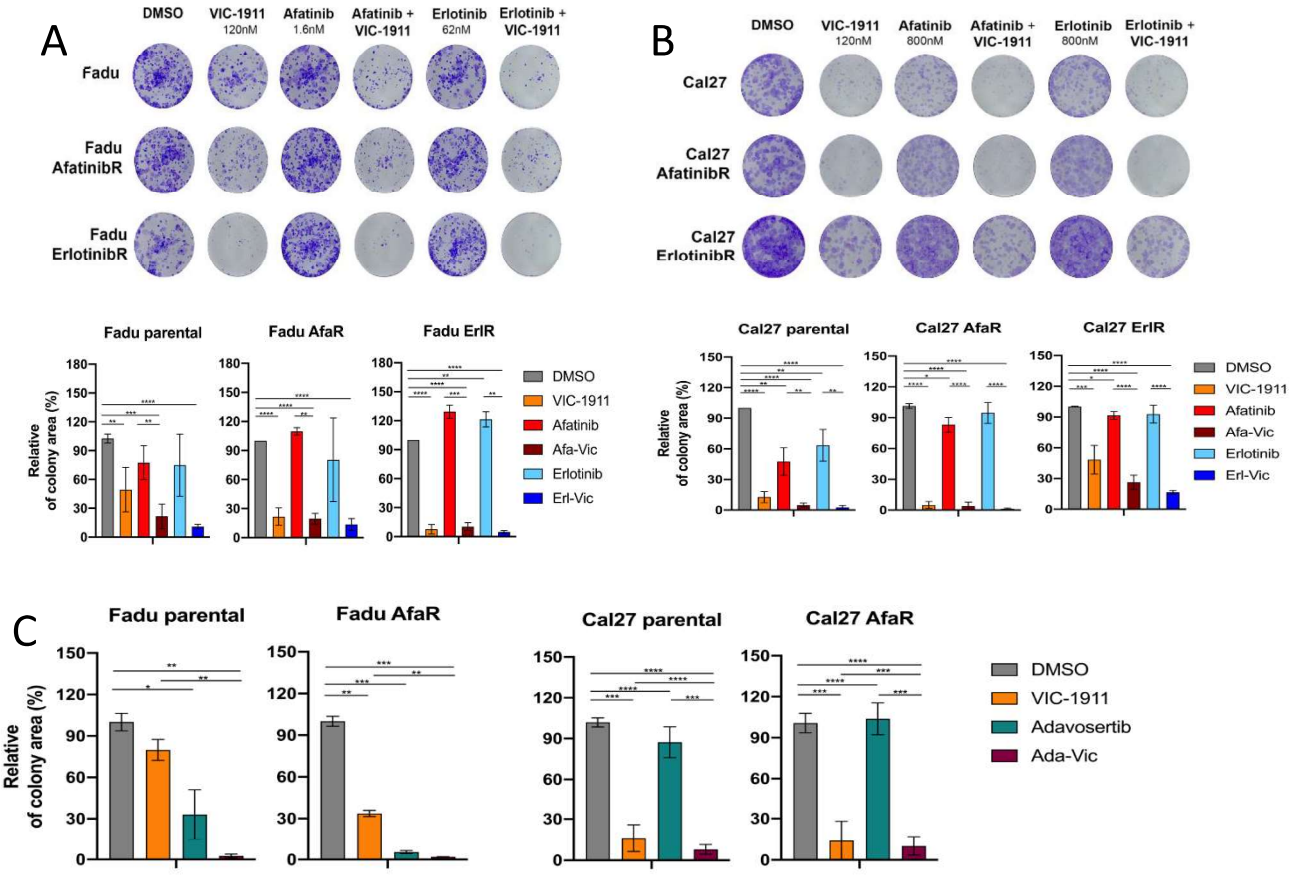

Figure 13. Clonogenic survival assays. **A, B**. Top, crystal violet staining of (**A)** Fadu and **(B)** Cal27 EGFR inhibitor -sensitive and –resistant cell lines after 12 days of treatment with DMSO or the indicated drugs. Images are representative of three biological three replicates. Cells were treated with DMSO, VIC-1911 (120nM), afatinib (1.6nM for Fadu and 800nM for Cal27), erlotinib (62nM for Fadu and 800nM for Cal27), or combination. Bottom, quantified clonogenic survival assay, n = 3. **C**. Quantified clonogenic survival assay. Cells were treated with DMSO, adavosertib (100nM for Fadu and 500nM for Cal27), VIC-1911 (50nM), or combination for 12 days. n = 2. P values are based on multiple t test comparisons. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

As a summary of specific findings from these in vitro experiments over the second reporting period, we have almost completed cell line generation suitable for profiling of the relationship between EGFR inhibitor resistance, AURKA, and WEE1. Cell lines selected for resistance to EGFR inhibition have reduced levels of active (phosphorylated) EGFR, ERK, and AKT, suggesting reduced dependence on this signaling. However, they do not upregulate AURKA and TPX2, and they have evidence of altered cell cycle. These cells retain sensitivity to AURKA inhibition, and downregulate EGFR activation further in response to treatment with inhibitors of EGFR and AURKA; however, the consequence of treatment with these inhibitors on the activation of ERK1/2 and AKT1 is variable between distinct resistant cell line models. AURKA inhibition typically leads to increased expression of AURKA, coupled with elevated expression of the AURKA-stabilizing protein TPX2. In both direct measures of apoptosis and in clonogenic assays, the adavosertib-VIC1911/TAS119 drug combination retains efficacy in synergistically promoting the death of FaDu cells that are resistant to EGFR inhibitors; CAL27-derived EGFR-resistant cells are less responsive to AURKA inhibition, although adavosertib remains effective in inducing cell death.

The Burtness lab developed EGFR-resistant models by continuous culture in increasing doses of erlotinib or afatinib. Xenografts were established from parental or afatinib-resistant FaDu cells subcutaneously injected into dorsal flanks in 7 to 8-week-old athymic female mice. Tumor-bearing mice were treated with vehicle, adavosertib (120mg/kg, q.d., p.o.), VIC-1911 (30 mg/kg, q.d., p.o.) or combination for 21 days once tumors reached ~150-250 mm^3. Compared to parental FaDu tumors, afatinib-resistant xenografted tumors demonstrated significantly greater tumor control with VIC-1911 monotherapy (Fig. 14). Furthermore, the combination of VIC-1911 and the WEE1 inhibitor adavosertib was synergistic in both parental and afatinib-resistant tumors, with greater effects in the resistant model (Fig. 15).

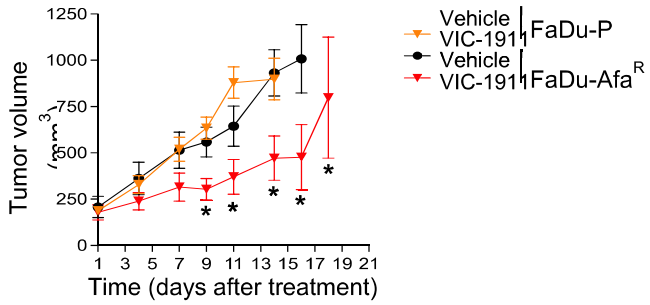

Figure 14. Afatinib-resistant HNSCC xenografted tumor is sensitive to AURKA inhibitor VIC-1911 *in vivo*. Mice harboring either FaDu parental (FaDu-P) or afatinib-resistant (FaDu-Afa^R) tumors were daily treated with vehicle (n=7) or VIC-1911 30 mg/kg (n=8) for 18 days.
*, $P < 0.05$; ** $P < 0.005$. Data are shown as mean ± SEM.

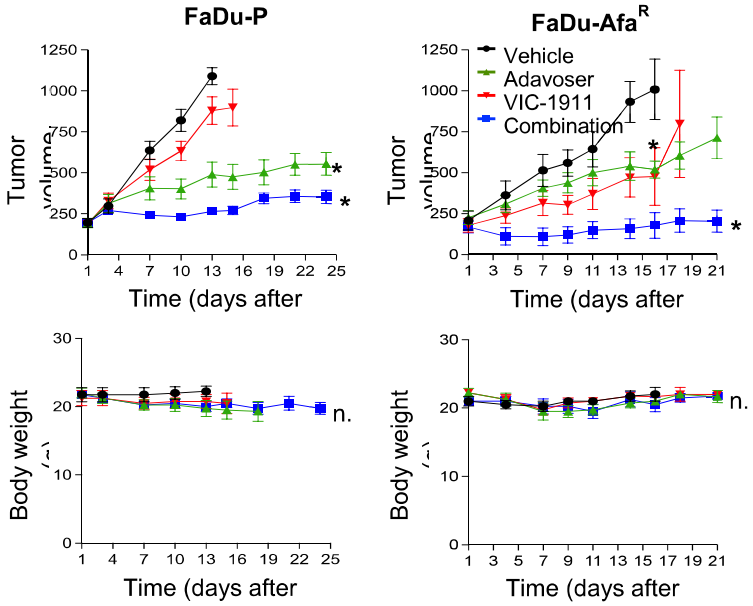

Figure 15. Combination AURKA/WEE1 inhibitor treatment is effective against acquired resistant HNSCC tumor to EGFR inhibitor *in vivo*. Mice bearing either FaDu-P or FaDu-Afa^R subcutaneous xenograft tumors were daily treated with vehicle (n=7), adavosertib 120 mg/kg (n=7), VIC-1911 30 mg/kg (n=8), or combination (n=8) for 21 days. n.s., not significant; *, $P < 0.05$; **, $P < 0.005$. Data are shown as mean ± SEM.

Specific Aim 3. The clinical trial continues to accrue well, with accrual currently at 46 of the 50 planned patients. No new or unexpected safety signals have been observed. Sample collection is proceeding as projected. One patient-derived xenograft (PDX) has been developed from a baseline biopsy. We anticipate completing accrual within the next 6 months. All regulatory approvals are up to date and have been received at DOD.

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

The faculty of the Fox Chase Cancer Center recognizes the value of periodic, scheduled reviews with graduate student and postdoctoral fellow trainees. As a Center that prides itself on excellent science and mentoring, we believe that an authentic and documented discussion helps to re-enforce trainee strengths, and to identify and remedy any limitations or concerns. Such periodic reviews are further supported by the Postdoctoral Affairs Committee who is available to provide support, training, and resources as needed to enable all trainees to be maximally competitive in the job market, and to improve or acquire specific skills identified in the IDP. In

addition, programs available to all students during the year, including the popular "How To…" series, our intensive Science Writing course, the annual Postdoc and Grad Student Research Day, mandatory ethics training, and frequent career lecturers, help to complement the laboratory experience.

Fox Chase Cancer Center does not have a proscribed Individualized Development Plan, believing that this goal can be achieved by many approaches. However, we have mandated that all trainees, regardless of their funding source, have annual (at least) planning meetings with their Principal Investigator. We also support IDPs for the graduate students that we host on Fox Chase's campus, who obtain their degrees from a number of area institutions (University of Pennsylvania, Temple University, Drexel University, etc.). In these instances, we comply with their home institution's policies and forms. Regardless, all IDPs must include: documentation of career goals and what is required to achieve those goals; a list of trainee strengths, challenges and plans for the future to address those challenges; and an opportunity for the trainee to respond and provide feedback to their mentor.

How were the results disseminated to communities of interest?

One article was published. In addition, results from the study were presented in a poster at the American Association of Cancer Research annual meeting in 2023, as well as at the annual research days at Fox Chase Cancer Center and at Drexel University School of Medicine.

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

We will continue progressing through the specific aims of the project, as specified in the SOW.

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.

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

Nothing to Report.

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

Nothing to Report.

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.

PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

This article was accepted but not published at the time of the last progress report – full citation appears here:

Nguyen, T.T., Silva, F.N., and Golemis, E.A. Aurora kinases in head and neck cancer. Cancer J. 2022 Sep-Oct 01;28(5):387-400. doi: 10.1097/PPO.0000000000000614. PMID: 36165728 PMC9836054. Federal support acknowledged.

Books or other non-periodical, one-time publications. Nothing to report.

Other publications, conference papers, and presentations.

AURKA inhibition influences glycolytic and hypoxic signaling in head and neck cancer. Nguyen, T.T., Silva, F.N., Lee, J.W., Burtness, B., and Golemis, E.A. Presented as poster at Drexel College of Medicine Discovery Day, October, 2022. Federal support acknowledged.

Synthetic lethal targeting of AURKA in Head and Neck Squamous Cell Carcinoma. Silva, F. N., Nguyen, T.T., Lee, J.W., Burtness, B., and Golemis, E.A. Presented as poster #542, AACR Annual Meeting, April 2023. Federal support acknowledged.

AURKA inhibition as a means of overcoming resistance to EGFR inhibitors in head and neck cacer. Silva, F. N., Nguyen, T.T., Lee, J.W., Burtness, B., and Golemis, E.A. Poster Presentation, Fox Chase Cancer Center Research Day, June 2023. Federal support acknowledged.

Concomitant inhibition of Aurora kinase A and WEE1 kinases results in synergistic tumor control and heightens DNA replication stress in head and neck and lung carcinomas. Lee JW, Kim S, Cruz Gomez S, Shi J, Yang C, Burtness B. Abstract 1563: *Cancer Res* (2023) 83 (7_Supplement): 1563.

Website(s) or other Internet site(s)

https://www.aacr.org/wp-content/uploads/2023/04/AACR2023_AbstractPresentations040123.pdf

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Erica Golemis, Ph.D.*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-3618-3673*
Nearest person month worked:	*1.00*
Contribution to Project:	*Provided direction.*
Funding Support:	*DOD*
Name:	*Ilya Serebriiski, Ph.D.*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6.00*
Contribution to Project:	*Provided analysis and effort on aims.*
Funding Support:	*DOD*
Name:	*Flaviane Silva*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*12*
Contribution to Project:	*Performed experiments involving drug efficacy testing, Western and other experiments to probe mechanisms.*
Funding Support:	*DOD*

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

Please see attached updated Other Support for Drs. Golemis and Serebriiski. Changes are marked with a line in the right hand margin.

What other organizations were involved as partners?

Not applicable.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Includes collaboration with Dr. Barbara Burtness, Partnering PI, Yale University. An independent annual report will be submitted by Dr. Burtness.

QUAD CHARTS: Not applicable.

APPENDICES:

None.

Other Support

Golemis, Erica A.

Remaining salary support from institutional sources.

CURRENT

P30 CA006927 (PI: Chernoff) 8/12/2016 - 7/31/2024 20.0%
NIH No Salary 2.40 calendar
Comprehensive Cancer Center Program at Fox Chase
This grant is in a no-cost extension.
The major goal of this Cancer Center Support Grant is to provide partial salary support for professional personnel, including senior and program leadership, administration, planning and evaluation, and developmental funds, as well as support for 4 established peer-reviewed Research Programs, 12 Shared Research Resources and 2 Support Elements.
Procuring Contracting/Grants Officer: Sarah Lee, 9609 Medical Center Dr., BG0609 RM 2W552, Rockville MD 20850

P50 DE030707 (PI: Burtness, Yale Univ.) 9/22/2020 - 6/30/2025 10.0%
NIH Partial Salary 1.20 calendar
Yale Head and Neck Cancer SPORE: Overcoming
Treatment Resistance in Head and Neck Cancer
This project is a subcontract from Yale University. Fox Chase Cancer Center will participate on this SPORE as a primary site. Investigators at FCCC will co-Lead Project 2, entitled, "Synthetic Lethal Therapy in TP53 Mutated Head and Neck Cancer." Fox Chase Cancer Center investigators will also support the Biostatistics and Bioinformatics Core, Biospecimen Core and the Career Enhancement Program.
Procuring Contracting/Grants Officer: Makawa Kourouma, OSP, 25 Science Park, 34d Floor, 150 Munson St., New Haven, CT 06520

R25 CA259244 (PI: Golemis) 3/15/2022 - 2/28/2027 10.0%
NIH 1.20 calendar
Empowering the Next Generation of Cancer Professionals: The Fox Chase Cancer Center-University of Delaware Partnership for Undergraduate Research and Career Development
The major goals of this project are to: 1) Expose 60 students per year to cancer research careers; 2) Provide immersive mentored research opportunities in laboratories at an NCI-designated Comprehensive Cancer Center; and 3) Mentor research fellows to effectively communicate and establish strong professional networks.
Procuring Contracting/Grants Officer: Long Nguyen, 9609 Medical Center Dr., Rm. 2W532, Rockville, MD 20850

N/A (PI: Swayam/Golemis) 1/1/2022 - 12/31/2023 5.0%
TEMPLE No Salary 0.60 calendar
Exploiting Radiotherapy-Induced MSC Tumor Homing
to Deliver Immunomodulators to Lung Cancers (Multi-PI)
The major goal of this pilot project is to explore innovative strategies to increase the therapeutic impact of radiation therapy for lung cancer. In addition to providing advice and guidance, Fox Chase Cancer Center will assist with mouse model experiments.
Procuring Contracting/Grants Officer: Rosemary Dillon, 1801 N. Broad St., Phila., PA 19122, 215-204-7551

U54 CA272686 (PI: Clapper) 9/1/2022 - 8/31/2027 5.0%
NIH Salary only 0.60 calendar
Cancer Prevention-Interception Targeted Agent Discovery Program at Fox Chase Cancer Center
The major goals of this project are: 1) To use the existing resources of the FCCC RAP and public databases, engineered cell lines and archived biosamples from high-risk subjects to validate the critical function of

candidate molecular pathways/targets in the transition from precancer to early cancer, and confirm their utility for precision prevention/early interception; 2) To identify agents that modulate the lead targets and inhibit tumor initiation and/or progression using customized in vitro screening assays and cell lines from high-risk subjects, followed by prioritization and selection of the optimal target and agents; 3) To perform pilot efficacy studies in clinically-relevant mouse models that recapitulate the cancer continuum (precancer to cancer) to assess the on-target effects of lead agents and evaluate potential toxicities at doses efficacious for tumor inhibition; and 4) To collaborate with other CAP-IT Centers and the NCI through the Data and Resource Coordination Center to foster productivity and integration, and share data and resources across the CAP-IT Network.
Procuring Contracting/Grants Officer: Rebecca Brightful, 8490 Progress Dr., Rm. 4083, Frederick, MD 21701

R21 CA280446 (PI: Golemis/ Ward, Temple Univ.) 4/1/2023 - 3/31/2025 10.0%
NIH 1.20 calendar Interaction
of Cannabidiol (CBD) with Targeted Inhibitors of Essential Cancer Signaling Pathways (Multi-PI) The major goals of this project are to: 1) Define interactions between CBD and targeted inhibitors relevant to cancer therapy; and 2) Study in vivo analysis of CBD-drug interactions.
Procuring Contracting/Grants Officer: Mallory Shramek, 9609 Medical Center Dr., Rockville, MD 20850,

P50 DE030707 Supp (PI: Burtness, Yale) 9/1/2022 - 6/30/2024 NA
NIH No Salary
Yale Head and Neck Cancer SPORE: Overcoming Treatment Resistance in Head and Neck Cancer
The major goals of the diversity supplement are: 1) To evaluate the relationship between rs3136717 genotype and sub-cellular localization of POLB under normal and stressed conditions; and 2) To investigate the influence of endogenous variation in POLB expression on cell growth and survival in response to DNA damage and oxidative stress.
Procuring Contracting/Grants Officer: Beth Kingsley, osp, 25 Science Pk, 3rd Flor, 150 Munson St., New Haven, CT 06520

W81XWH-21-1-0487 (PI: Golemis) 7/1/2021 - 6/30/2025 10.0%
DOD (Partial Salary) 1.20 calendar
Overcoming Resistance to EGFR Inhibitors in Advanced Head and Neck Cancers
The major goals of this project are to: 1) Determine how TP53 mutation class determines AURKA expression and alters sensitivity to inhibition of AURKA and EGFR; 2) Explore relative efficacy of AURKA monotherapy and an AURKA-WEE1 inhibitor combination in the setting of, and in preventing or reversing adaptive resistance to, EGFR inhibition; and 3) Define the relationship between TP53 genotype, AURKA expression, and response to EGFR inhibition using clinical trial samples for HNSCC.
Procuring Contracting/Grants Officer: Amanda Carrera, 820 Chandler St., Fort Detrick, MD 21702,

OVERLAP

None

Other Support

Serebriiskii, Ilya G.

CURRENT

R21 CA280446 (PI: Golemis/ Ward, Temple Univ.) 4/1/2023 - 3/31/2025 15.0%
NIH Salary only 1.80 calendar
Interaction of Cannabidiol (CBD) with Targeted Inhibitors of Essential Cancer Signaling Pathways (Multi-PI)
The major goals of this project are to: 1) Define interactions between CBD and targeted inhibitors relevant to cancer therapy; and 2) Study in vivo analysis of CBD-drug interactions.
Procuring Contracting/Grants Officer: Mallory Shramek, 9609 Medical Center Dr., Rockville, MD 20850,

W81XWH-21-1-0487 (PI: Golemis) 7/1/2021 - 6/30/2025 30.8%
DOD Salary only 3.70 calendar
3.70 cal mths yrs 1-3
4.60 cal mths yr 4
Overcoming Resistance to EGFR Inhibitors in Advanced Head and Neck Cancers
The major goals of this project are to: 1) Determine how TP53 mutation class determines AURKA expression and alters sensitivity to inhibition of AURKA and EGFR; 2) Explore relative efficacy of AURKA monotherapy and an AURKA-WEE1 inhibitor combination in the setting of, and in preventing or reversing adaptive resistance to, EGFR inhibition; and 3) Define the relationship between TP53 genotype, AURKA expression, and response to EGFR inhibition using clinical trial samples for HNSCC.
Procuring Contracting/Grants Officer: Amanda Carrera, 820 Chandler St., Fort Detrick, MD 21702,

R03 CA256234 (PI: Serebriiskii) 12/14/2020 - 11/30/2023 25.0%
NIH 3.00 calendar
Comprehensive Identification of RAS Mutations and Allelic Co-Segregation Patterns in Colorectal Cancer This grant is in a one year extension.
The major goals of this project are to: 1) Comprehensively characterize the landscape of RAS mutations in CRC; and 2) Elucidate gene, codon and variant level analysis of co-occurrence of RAS mutations with other driver genes commonly mutated in CRC.
Procuring Contracting/Grants Officer: Sarah Lee, 9609 Medical Center Dr., BG0609 RM 2W552, Rockville MD 20850

OVERLAP

None