AWARD NUMBER: W81XWH-18-1-0439

TITLE: Targeting Glucose Reliance in Lung Squamous Cell Carcinoma

PRINCIPAL INVESTIGATOR: Dr. Tae Hoon Kim

CONTRACTING ORGANIZATION: University of Texas at Dallas
Richardson, TX 75080

REPORT DATE: Sept-2020

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Sept 2020	Annual Report Year 2	01 Sep 2019 – 31-Aug-2020

4. TITLE AND SUBTITLE

Targeting Glucose Reliance of Lung Squamous Cell Carcinoma

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0439

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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Richardson, TX 75080

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall goal of this proposal is to evaluate elevated blood glucose levels as a metabolic biomarker with prognostic feasibilities for lung squamous cell carcinoma (LSCC) patients (Aim 1) and to investigate whether dietary (Aim 2) and pharmacological (Aim 3) glucose restriction can suppress tumor progression of LSCC. Toward this end, we successfully demonstrated that high blood glucose levels are strongly associated with poor overall survival in LSCC patients. We also performed comprehensive in vivo tumor xenograft experiments, in which LSCC tumor bearing mice were fed with ketogenic diet (KD, dietary glucose restriction) or treated with small molecule inhibitor of sodium-glucose co-transporter 2 (SGLT2, pharmacological glucose restriction). We have shown that KD or SGLT 2 inhibition specifically inhibited tumor growth of LSCC but not lung adenocarcinoma (LADC) supporting our central hypothesis that targeting glucose reliance of LSCC can be a novel targeted therapeutic strategy for LSCC patients. These results have been presented at the Keystone Symposia – Tumor Metabolism (Colorado, USA, Feb 2428, 2019) and recently published at Cell Reports (Hsieh et. al. 2019;28(7):1860-78.e9).

15. SUBJECT TERMS
GLUT1, Squamous cell carcinoma, glucose restriction, ketogenic diet, SGLT2, Vitamin C

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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INTRODUCTION:

Lung squamous cell carcinoma (LSCC) is a major class of pulmonary malignancy, which accounts for 25-30% of all lung cancers. LSCC patients have benefited very little from the application of targeted therapeutic options. As a result, decades-old platinum-based chemotherapy or radiation regimens with limited efficacy and specificity remain the first-line treatment options. Therefore, identification and elucidation of targetable vulnerabilities in LSCC is urgently needed to improve therapeutic outcomes in LSCC patients. Our efforts to identify targetable pathways crucial for LSqCC growth and survival led to the discovery of exceptional overexpression of glucose transporter 1 (GLUT1, encoded by the SLC2A1 gene) and exceptional glucose reliance for tumor growth and survival (1, 2). This metabolic signature phenotypically embedded in the squamous lineage subtype of lung cancer provides rationale to target glucose reliance for a novel targeted therapeutic strategy for LSCC patients. The central goal of this proposal is to evaluate higher blood glucose levels as a metabolic biomarker with prognostic feasibilities for LSCC patients and to investigate whether dietary and pharmacological glucose restriction can suppress LSCC tumor progression. If successful, this study will possibly lead to novel diagnostic as well as therapeutic strategies for a cure of LSCC.

KEYWORDS:
GLUT1, Squamous Cell Carcinoma, Glucose Restriction, SGLT2, Vitamin C

ACCOMPLISHMENTS:

1. Major goals of current ongoing studies

Goal 1: Pharmacological glucose restriction by SGLT2 inhibitor Canagliflozin in SCC PDXs.
Subtask 1: Evaluate anti-tumor efficacy of Canagliflozin in LSCC and LADC cell lines and PDX models by measuring tumor growth, blood glucose and insulin levels as well as IHC analysis of tumor cell proliferation, viability, and PI3K signaling pathway.

Goal 2: Determine if combinatorial targeting of anti-oxidative capacity of SCC can achieve superior therapeutic outcomes.
Subtask 1: Evaluate pro-oxidant effect of Vitamin C in LSCC and LADC by measuring cell proliferation, viability and oxidative stress
Subtask 2: To evaluate if a combination of GLUT1 inhibitors or SGLT2 inhibitors with Vitamin C could achieve more potent therapeutic outcomes in LSCC by measuring tumor growth, as well as immunohistochemical (IHC) analysis of tumor

2. Accomplishments under goals

i) Goal 1: Identification of a GLUT1/SGLT2 glucose transport switch upon GLUT1 inhibition

Our recent work has demonstrated that GLUT1 inhibition exerts significant tumor growth inhibition in LSqCC. However, resistance to GLUT1 inhibition has emerged as a challenge to the efficacy of GLUT1 inhibitors in SCC. Mechanistically, LSqCC adapts to GLUT1 inhibition by compensatory induction of the SLGT2 glucose transport system suggesting a novel mechanism of glucose transport to preserve glucose availability. Although our recent studies show that SGLT2 is not expressed in LSqCC cell lines and TCGA LSqCC patient tumors, we observed that shGLUT1 knockdown dramatically induced SGLT2 expression in LSqCC xenograft tumors (Figure. 2B). Notably, SGLT2 induction was more prominent in larger tumors that regained proliferative capacity (Fig. 1A, blue arrow), suggesting that GLUT1 knockdown in LSqCC may induce SGLT2 to overcome glucose restriction. These critical observations identify SGLT2 as an important therapeutic target in SCCs.

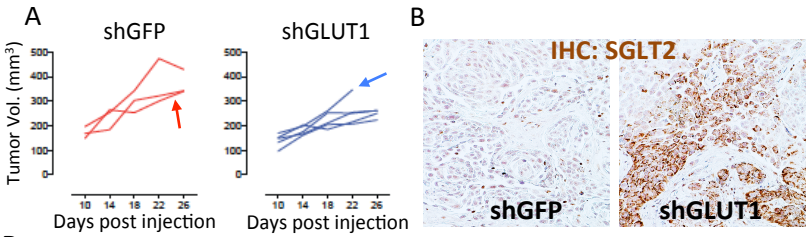

Figure 1. (A) Individual growth curve of shScr (n=3) and shGLUT1 (n=5) of HCC95 LSqCC xenografts. (B) IHC staining for SGLT2 expression in indicated (arrows) xenograft tumors.

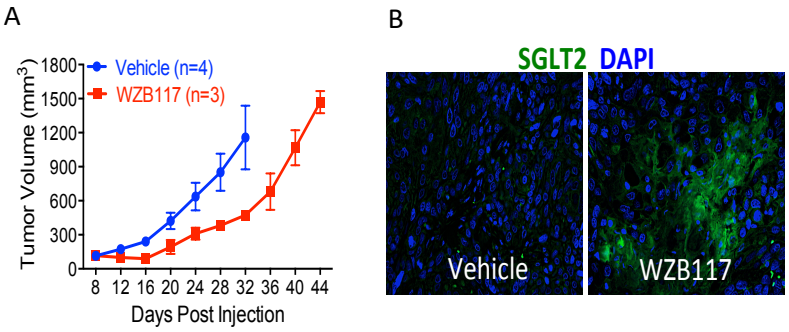

Figure 2. Tumor growth (A) and IF staining for SGLT2 (B) of vehicle (n=4) and WZB117-treated (n=3) HCC2814 LSqCC xenograft tumors.

To pharmacologically inhibit GLUT1, we treated LSqCC tumor bearing mice with GLUT1 inhibitor, WZB117 (10 mg/kg/day, i.p.). WZB117 treatment significantly inhibited LSqCC tumor growth. However, consistent with genetic GLUT1 inhibition, most of WZB117-treated LSqCC tumors regained their tumorigenic capacity and proliferated (Fig. 2A) and robustly express SGLT2 (Fig. 2B). Notably, intratumoral oxidative stress in WZB117-resistant tumors (6 weeks post treatment) was reduced to the levels comparable to the vehicle control tumors (Fig. 3). Collectively, these results provide evidence for the adaptive glucose transport switch to SGLT2 when the predominant glucose transporter for LSqCC, GLUT1 is inhibited.

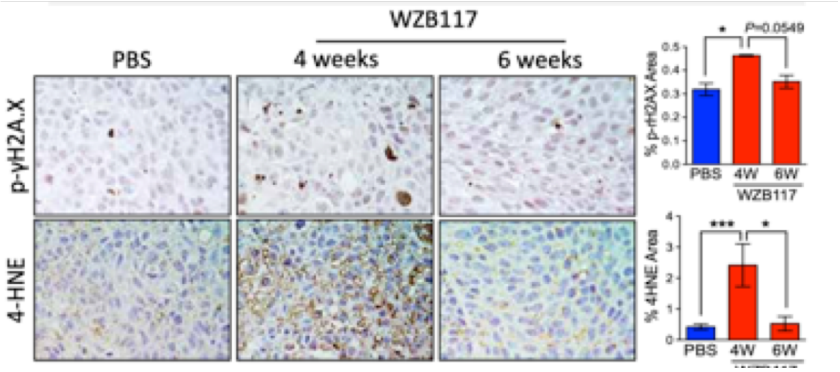

Figure 3. IHC staining and quantification for ROS markers, p-H2A.X and 4-HNE in vehicle (n=4) and WZB117-treated (n=3) HCC2814 LSqCC xenograft tumors. Mean ± SEM ***P<0.001, *P<0.05.

ii) Goal 2: Combinatorial targeting of anti-oxidative capacity of SCCs

Glucose influx via glycolysis in cancer cells provides essential energetic power as well as anabolic building blocks for cellular proliferation. [U-13 C] glucose tracing indicates that GLUT1-mediated glucose influx feeds PPP to promote antioxidative capacity and contribute to the survival of LSqCC. The glucose fueled generation of NADPH from the oxidative pentose phosphate pathway (PPP) and glutathione (GSH) from de novo serine biosynthesis provides sustaining anti-oxidative capacity in cancer cells. Given that oxidative stress is closely linked to squamous cancer initiation and progression (e.g. cigarette smoking as a major etiological causative factor in human LSqCC), LSqCC essentially requires a heightened anti-oxidative capacity for survival and proliferation.

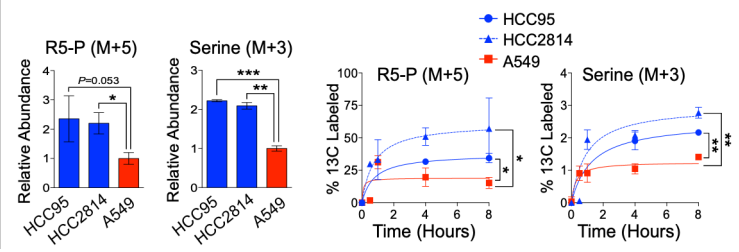

Figure 4. Glucose contribution to ribose 5-phosphate (R5-P) and serine in LSqCC (HCC95 & HCC2814) and LADC (A549) cells. Relative 13 C abundance (A) or percent 13 C incorporation (B) of R5P and serine from [U 13 C] glucose was determined by GC-MS. Values represent the average of triplicates ± SEM. Data represent a minimum of two independent experiments. ****P<0.0001, **P<0.01, *P<0.05. t-test (A), Two-way ANOVA (B).

Pre-clinical as well as clinical studies have demonstrated that high dose vitamin C exhibits significant anti-cancer effects by perturbing cellular redox homeostasis and glycolytic metabolism especially when combined with standard cancer therapies. Vitamin C is a reducing agent that is readily oxidized to dehydroascorbate (DHA) and is taken up into cells through sodium-ascorbate cotransporter (SVCT1/2) and GLUTs. Once inside the cells, DHA is reduced back to ascorbate consuming GSH, thereby causing oxidative stress as a pro-oxidant.

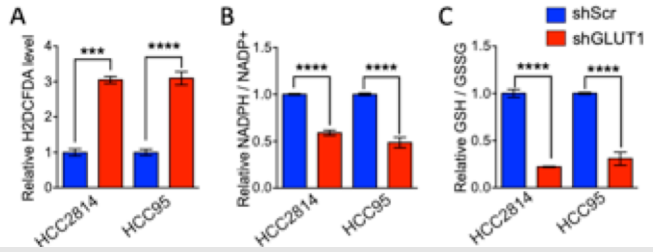

Figure 5. Intracellular ROS (A), NADPH/NADP+ ratio (B), and GSH/GSSG ratio (C) in shScr and shGLUT1 LSqCC cell lines. n=3-5. Mean ± SEM. ****P<0.0001, ***P<0.001. t-test.

Despite considerable controversy with the utilization of vitamin C for cancer treatment and prevention over several decades, overwhelming evidence from recent pre-clinical and clinical studies as well as numerous clinical trials argues for promising anti-cancer properties and rapid clinical translatability of vitamin C in certain contexts. Conflicting reported data are clear basis for an urgent need for a more comprehensive evaluation of the efficacy of Vitamin C as a pro-oxidant adjuvant cancer therapy. Our recent discoveries of GLUT1 overexpression and strict glucose reliance of LSqCC on sustaining anti-oxidative capacity provide compelling rationale to employ high-dose vitamin C as a therapeutic pro-oxidant concurrently to target GLUT1 inhibited LSqCC. We hypothesize that combinatorial targeting of GLUT1-mediated glucose influx with a therapeutic pro-oxidant, high-dose vitamin C can induce potent cytotoxicity and prevent resistance to GLUT1 inhibition by synergistically exerting profound oxidative stress specifically in squamous cancer.

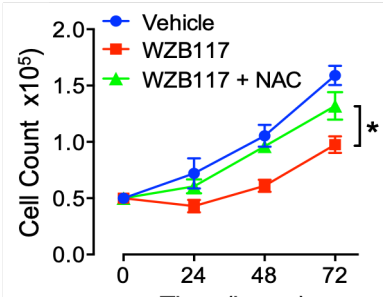

Figure 6. in vitro proliferation of LSqCC HCC2814 cells treated with WZB117 (25 μM) and NAC (5 mM). n=4. Mean ± SEM. *P<0.05. Two-way ANOVA

For our studies we employed the well-characterized irreversible GLUT1 inhibitors WZB117 and BAY-876 to target GLUT1-mediated glucose influx and redox homeostasis, in combination with pro-oxidant high-dose vitamin C to potently disable cellular oxidative defense machinery in SCC. We and other groups have extensively characterized the specificity and anticancer activities of these GLUT1 inhibitors. Metabolic tracing analysis using [U13 C] glucose showed that LSqCC exhibits augmented anabolic build up from glucose into PPP and de novo serine biosynthesis indicated by markedly enhanced glucose influx into 13 C-labeled Ribose 5-P and serine (Fig 4). These results suggest that GLUT1-mediated high glucose influx is directed to anabolic pathways to provide NADPH and GSH pools for heightened oxidative defense in LSqCC.

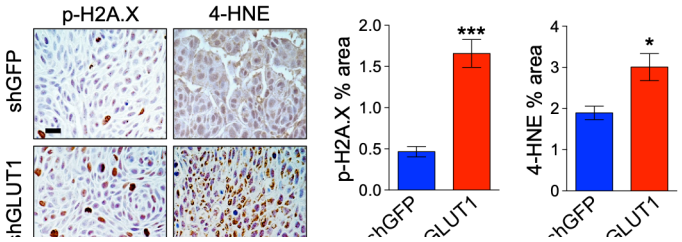

Figure 7. Representative IHC images (left) and quantification (right) of p-H2AX and 4-HNE in shGFP (n=4) and shGLUT1 (n=5) LSqCC HCC95 xenograft tumors. Scale bars, 100 μm. Mean ± SEM. ***P<0.001, *P<0.05. t-test.

We next sought to test whether inhibition of GLUT1-mediated glucose influx disrupts cellular anti-oxidative capacity by depleting NADPH and GSH pools in LSqCC. Inhibition of glucose influx by shRNA-mediated GLUT1 knockdown resulted in a significant increase in cellular oxidative stress (Fig. 5A), which is associated with a reduction in intracellular NADPH/NADP+ (Fig. 5B) and GSH/GSSG (Fig. 5C) ratios. Importantly, restoring the cellular oxidative capacity by supplementing with an antioxidant, N-acetylcysteine (NAC) considerably rescued the cellular viability of GLUT1-inhibited LSqCC cells (Fig. 6). We further demonstrated that GLUT1 inhibition by shGLUT1 or GLUT1 inhibitor, WZB-117 resulted in significant tumor growth inhibition as well as increase in intratumoral oxidative stress in LSqCC xenograft tumors indicated by p-2HAX (oxidative DNA damage) and 4HNE (lipid peroxidation) staining (Fig. 7). These results are in line with metabolic data of elevated PPP and de novo serine biosynthesis (Fig. 4) supporting our hypothesis that GLUT1mediated glucose influx accounts for the enhanced anti-oxidative capacity in LSqCC.

Next, to characterize oxidative perturbation and associated cytotoxicity induced upon inhibition of GLUT1-mediated glucose influx combined with a pro-oxidant, vitamin C, we sought to evaluate the pre-clinical efficacy of GLUT1 inhibitor and vitamin C combination in SCC cell lines and xenograft models. Indeed, combining WZB117 with vitamin C resulted in a dramatic reduction of proliferation and viability of human LSqCC cell line, HCC2814 (Fig.8).

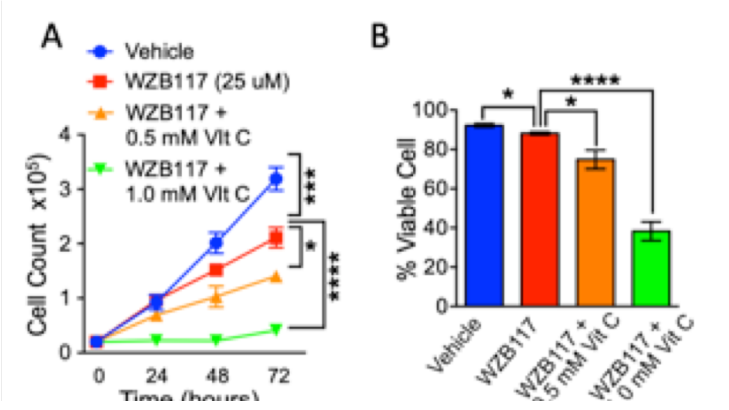

Figure 8. In vitro proliferation (A) and viability (B) of LSqCC HCC2814 cells treated with WZB117 (25 μM) and vitamin C (0.5 – 1 mM). n=4. Mean ± SEM. ****P<0.0001, ***P<0.001, *P<0.05. Two-way ANOVA (A), t-test (B).

To evaluate the feasibility of this combination treatment across squamous cancers we expanded our experiments to include Human Head & Neck SqCC (HNSCC) cell lines. Preliminary experiments using Human HNSCC cell line (FaDu) show that vitamin C greatly reduced the proliferation (Fig. 9A) and viability of HNSCC cells. Furthermore combination treatment resulted in significantly decreased xenograft growth in Human HNSCC cell line (FaDu) xenograft tumors (Fig.9B, C). As expected, and in support of our hypotheses, preliminary immunohistochemical analyses of these tumors show increased oxidative stress and DNA damage markers (4-HNE and p-H2A.X) in combination treatment group compared to control group (Fig. 9D)

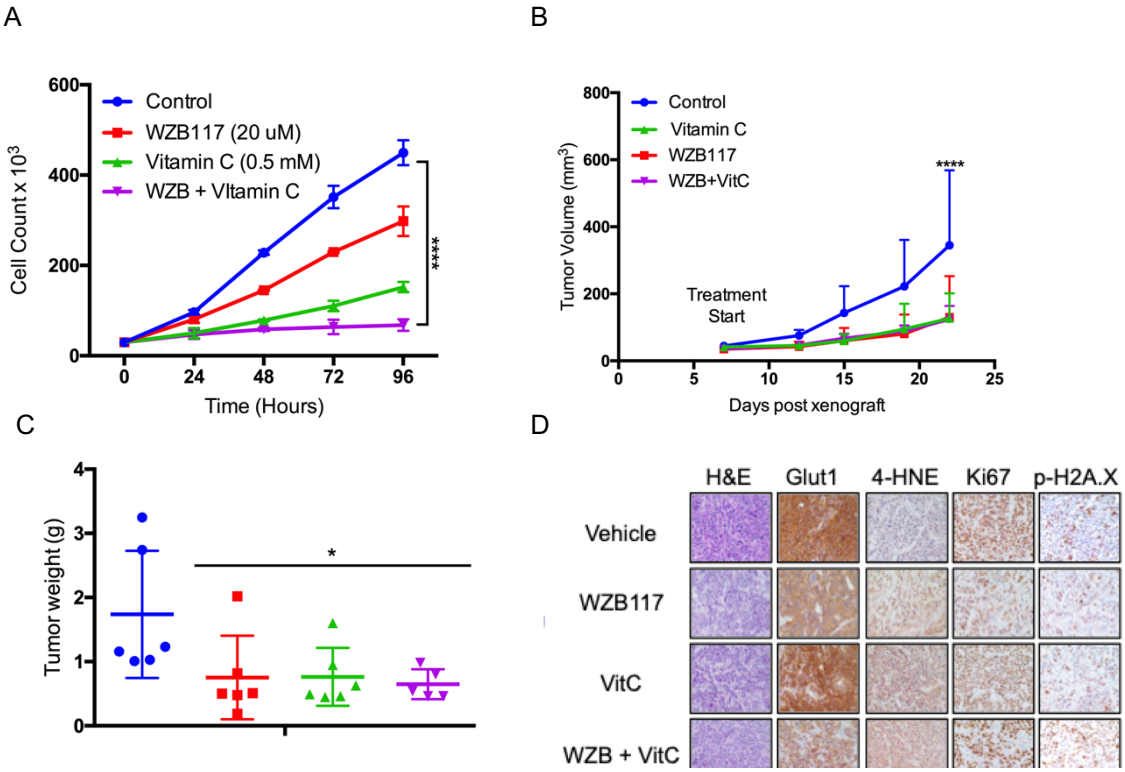

Figure 9. In vitro proliferation (A) of HNSCC FaDu cells treated with WZB117 (20 μM) and vitamin C (0.5 mM) n=3. Tumor volume (B) and weight (C) of HNSCC FaDu xenograft tumors (n=6). Representative immunohistochemical analysis of GLUT1, 4-HNE, Ki67 and p-H2A.X in HNSCC FaDu xenograft tumors (D).
Mean ± SEM. ****P<0.0001, ***P<0.001, *P<0.05. Two-way ANOVA (A,B), One-way ANOVA (C).

Summary of Achievements
i) Goal 1: Demonstration of SGLT2 induction in GLUT1-inhibited LSqCC tumors
ii) Goal 2: Evaluation of high-dose vitamin C as a pro-oxidant cancer therapeutic

3. Opportunities for training and professional development this project has provided
i) AACR-IASLC International Joint Conference Jan 2020, San Diego, California, USA

4. How were result disseminated to communities of interest?
i) Key findings produced during the reporting period have been presented as a poster at the Sixth AACR-IASLC International Joint Conference – Lung Cancer Translational Science From the Bench to the Clinic, Jan 11 – 14, 2020, San Diego, California, USA.

5. What do you plan to do during the next reporting period to accomplish the goals?
ii) Goal 2: We will further validate if GLUT1 inhibition and vitamin C can potentiate oxidative stress and cytotoxicity in LSqCC PDS lines. LSqCC PDS lines will be treated with WZB117 (10–50 μM) or BAY-876 (10–100 nM) with vitamin C (0.11 mM) and cellular oxidative stress will be examined by measuring intracellular H_2O_2 (H_2DCFDA staining and PeroxyTrace, InVivoSwiss), superoxide radicals (dihydroethidium, DHE), lipid peroxidation (C11-BODIPY). In addition, NADPH/NADP+ ratio (Promega) and GSH/GSSG ratio (Promega) will be also measured. In vitro proliferation and viability of treated LSqCC PDSs will be characterized by flow cytometry of Ki67, BrdU, and Annexin-V staining and by immunoblotting of Ki67 and cleaved-caspase 3 (CC3). To confirm that oxidative stress accounts for GLUT1 inhibition/vitamin C-mediated cytotoxicity in LSqCC, we will treat LSqCC PDSs with an antioxidant, NAC (10 mM) to determine if NAC can rescue the cytotoxic effects of GLUT1

inhibition/vitamin C. To validate the specificity of pharmacological GLUT1 inhibition, we will utilize two independent lentiviral shRNA targeting the 3'UTR of GLUT1 and shScramble as a control in our established PDSs. GLUT1 knockdown in LSqCC cell lines as well as in LSqCC PDS has been validated (7, 8). Throughout the proposed study, we will authenticate the specificity of shGLUT1 and potential off-target effects by rescuing shRNA-resistant ORF overexpression.

IMPACT:

1. Impact on development of the principle of the project

There is increasing evidence that keeping blood glucose levels in check can help individuals manage certain cancer types, yet there is a lack of clinical evidence and molecular mechanisms underlying glucose restriction-mediated anti cancer effects remain poorly understood. Our key findings of evident anti-cancer effects of glucose restriction in a specific type of cancer, lung squamous cell carcinoma provide compelling evidence that lung squamous cell carcinoma is highly vulnerable to glucose restriction (1, 2), thereby can be the most suitable cancer type to be rationally targeted by glucose restriction. Importantly, our studies found a robust correlation between higher blood glucose concentration and worse survival among patients with lung squamous cell carcinoma highlighting clinical relevance.

2. What was the impact on other disciplines?

Nothing to report.

3. What was the impact on technology transfer?

Nothing to report.

4. What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS:

1. Changes in approach and reason for change

No significant changes were made during this reporting period.

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

The original PI (Jung-Whan Kim) of the project has taken a position at the pharmaceutical industry and transferred the management and oversight of the project to Tae Hoon Kim in the beginning of 2020. The new PI has collaborated extensively on the project and was a coauthor on the major manuscript resulting from the current project, Hsieh et al, Cell Reports 28:1860 (2019). Due to the premature departure and transfer of PI, an no cost extension of current project was requested during the PI transfer application, and NCE request was approved February 15, 2020. The project is on schedule to complete by the end of the extension at August 31, 2021 with another major publication as a deliverable product, as well as conference presentation of the results.

3. Changes that had a significant impact on expenditures.

Nothing to report.

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

Nothing to report.

PRODUCTS:

1. Publications, conference papers, and presentations

i) Journal publications

ii) Books or other non-periodical, one-time publications

Nothing to report

iii) Other publications, conference papers, and presentations

Targeting Glucose Reliance in Lung Squamous Cell Carcinomas. Mazambani S, Hsieh MH, Choe JH, Knighton JK, Scafoglio C, Shackelford DB, Minna JD, Singh PK, Kim J, Inoue M, DeBeradinis RJ, Kim TH, Kim JW. Sixth AACR-IASLC International Joint Conference, Jan 11-14, 2020, San Diego, CA, USA

2. Website(s) or other Internet site(s)

Nothing to report.

3. Technologies or techniques

Nothing to report.

4. Inventions, patent application, and/or licenses

Nothing to report

5. Other products

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

1. Participants

Name:	Jung-whan Kim
Project Role:	Collaborator
Research Identifier (ORCID ID):	0000-0002-7829-1480
Nearest Person Month Worked:	N/A
Contribution to Project:	Continue to provide input and advise on the proposed study.
Funding Support:	

Name:	Simbarashe Mazambani
Project Role:	Graduate Research Assistant
Research Identifier (ORCID ID):	
Nearest Person Month Worked:	12.0
Contribution to Project:	Execution of all in vitro as well as in vivo experiments, analysis and interpretation of experimental results
Funding Support:	

Name:	Ji Yun Jeong
Project Role:	Subcontract Co-Investigator
Research Identifier (ORCID ID):	
Nearest Person Month Worked:	1.0

Contribution to Project:	Performing detailed pathological diagnosis on lung cancer tissue samples.
Funding Support:	Full salary support by Kyungpook National University

Name:	Mi Jeong Hong
Project Role:	Subcontract Postdoctoral Researcher
Research Identifier (ORCID ID):	0000-0002-9504-334X
Nearest Person Month Worked:	3.0
Contribution to Project:	Assisting Drs. Shin Yup Lee and Ji Yun Jeong to manage and analyze human lung cancer samples
Funding Support:	

2. Changes in active support for PI and key personnel

i) Tae Hoon Kim, PI

Current

W81XWH-18-1-0439 (Kim, PI) 09/01/2018 – 08/31/2021
DOD
Targeting Glucose Reliance of Lung Squamous Cell Carcinoma
Role: PI

R01HL131652 (Srinivasan, PI) 06/01/2016 – 05/31/2020
NIH/NIHLB
Defining the mechanisms of lymphatic and lymphovenous valve development
Role: Co-I

Completed

R21MH109945 (Ploski, PI) 07/01/2016 – 06/30/2018
NIH/NIMH
Generation of viral based inducible and cre dependent genome editing tools for neuroscience
Role: Co-I

13-SCB-Yale-06 (Kim, PI) 11/01/2013 – 08/31/2017
Connecticut Department of Public Health
Pluripotency and Heterochromatin Topology
Role: PI

R01CA140485 (Kim, PI) 07/15/2010 – 05/31/2017
NIH/NCI
Analysis of higher order chromatin structures in normal and cancer epigenomes
Role: PI

R21AI107067 (Kim, PI) 07/01/2013 – 06/30/2017
NIH/NIAID
Nuclear, Genomic and Molecular Regulation of Type I Interferon Transcription
Role: PI

3. Other organizations as partners

i) Kyungpook National University, Deagu, Korea

Location: 807 Hoguko, Bukgu, Deagu, KOREA

Contribution: This is a subcontract partnering organization (Subcontract PI, Dr. Shin Yup Lee). Dr. Lee's group has expertise in biomarker and clinical correlation studies in lung cancer. Dr. Ship Yup Lee and his group contribute to the collection of clinical information and clinical correlation analysis.

SPECIAL REPORTING REQUIREMENTS:
Not applicable.

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