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TITLE: Deconstruction of Oncogenic K-RAS Signaling Reveals Focal Adhesion Kinase as a Novel Therapeutic Target in NSCLC

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

About 25% of lung adenocarcinomas express mutant KRAS (KM) often is association with co-occurring mutations that inactivate the the CDKN2A locus, which comprises $p16^{INK4A}$ and $p14^{ARF}$, or the p53 tumor suppressors. These mutations contribute to disease progression. There are no therapies that target cancers that express mutant KRAS. Thus, it is notable that inhibition of FAK causes cell death specifically in KM lung cancer cells (KMLC) that are either CDKN2A mutant or p53 mutant. Furthermore, we found that pharmacologic inhibition of FAK causes the regression specifically of high-grade mutant Kras;Cdkn2a null lung cancers in genetically engineered mice. These findings provided the rationale for a multi-institutional Phase II clinical trial using the FAK inhibitor (FAKi) VS-6063 in KMLC patients (PI Dr. Gerber at UT Southwestern Medical Center). This trial has completed accrual and was presented at the 2015 World Lung Conference in Denver. Ongoing work aims at establishing whether: 1. FAK is a therapeutic target in KMLC using genetically engineered mice; 2. determining the underpinnings of the dependency on FAK both in cultured lung cancer cells and in vivo. In this regards, we found that FAK inhibition impairs the DNA damage response, potentiating the effects of radiotherapy specifically in KMLC cells in vitro and in vivo. This finding provides the rationale to combine radiation therapy to FAKi.

15. SUBJECT TERMS

Nothing listed

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1. Introduction:

This application rests on the hypothesis that the genotype of cancer cells determines specific vulnerabilities that can be exploited in cancer therapy. The KRAS proto-oncogene is a small guanosine triphosphatase that is constitutively activated (mutant KRAS, KM thereafter) in 25% of non-small cell lung cancers (KM lung cancer, KMLC thereafter). At present, there are no drugs that effectively target KMLC. We identified focal adhesion kinase (FAK) as an essential requirement for the survival of KMLC that are deficient for either the CDKN2A or the p53 tumor suppressors. We proposed to test the hypothesis that FAK is a critical druggable vulnerability in KMLC using an approach that integrates the use of lung cancer cell lines, engineered mouse models of KMLC, RNA interference (RNAi) and targeted pharmacologic inhibitors of FAK. We have made significant progress as demonstrated by the fact that our work provided the rationale for a Phase II multicenter clinical trial using defactinib a FAK small molecule inhibitor, to treat KMLC in patients. This trial, which is not directly funded by this award, has completed its target accrual of 55 patients (ClinicalTrials.gov Identifier: NCT01951690). The results of this trial are maturing. This work is presently supported with a no cost extension to complete the remaining major goals of this award: 1. The characterization of the radiosensitizing effect of FAK inhibition in KMLC both in vitro and in vivo because this is the best strategy we have found that maximizes the therapeutic effect of FAK inhibition; 2. To test genetically in mouse models of lung cancer whether FAK is required for the development of high grade KLMC; 3. To publish our data in high quality peer-reviewed journals to share with the research community and the public our research.

2. Keywords

KRAS, lung cancer, mouse lung cancer models, FAK, targeted kinase inhibitors, RNAi, preclinical studies, radiotherapy, radiosensitization.

3. Accomplishments for grant W81XWH-12-1-0210.

3.1 What were the major goals of the project?

Goal 1. Determination of the anti-cancer effects of FAK inhibition in NSCLC cells.   We propose to use genetic and pharmacologic approaches to establish whether FAK is required for the survival of lung cancer (LC) expressing mutant KRAS (KM) and deficient for either CDKN2A or for p53. We propose to: 1. Characterize the anti-tumor effects of FAK inhibition in LC; 2 Determine the effect of genetic inactivation of FAK in KMLC using a conditional knock-out allele of FAK.

Goal 2. Identification of strategies that synergize with inhibition of FAK to induce the death of NSCLC expressing oncogenic KRAS. Here we will use a genetic and pharmacologic approach in LC cells and in mouse lung models to identify strategies to maximize cancer cell death upon pharmacologic inhibition of FAK. We propose to: 1. Determine whether FAK inhibition synergizes with inhibition of PI3K/mTOR signaling or of other druggable oncogenic signaling pathways in LC cells; 2. Complete the validation of a whole genome siRNA screening to identify KM synthetic lethal interactions in LC cells.

For the purpose of this progress report we will follow the format mandated by the "technical reporting requirements" applied to the approved statement of work.

3.1 What was accomplished under these goals?

Goal #1. Determination of the anti-cancer effects of FAK inhibition in NSCLC cells.

  Our preliminary data suggest that FAK is required for the viability of KMLC cells deficient for either CDKN2A or p53 (1). We proposed : 1. To establish whether NSCLC cells are dependent on FAK; 2. To identify the mechanisms responsible for this dependency; 3. To identify additional KM vulnerabilities.
  Our preclinical data led to a phase II clinical trial with the FAK inhibitor VS-6063 (ClinicalTrials.gov Identifier: NCT01951690) in KMLC patients. This trial is not directly funded by this grant and has completed its targeted accrual of 55 patients. Our goal is to provide the framework for the development of FAK inhibitors in KMLC.

Subtask 1a. Pharmacologic inhibition of FAK in human NSCLC cells in vitro.
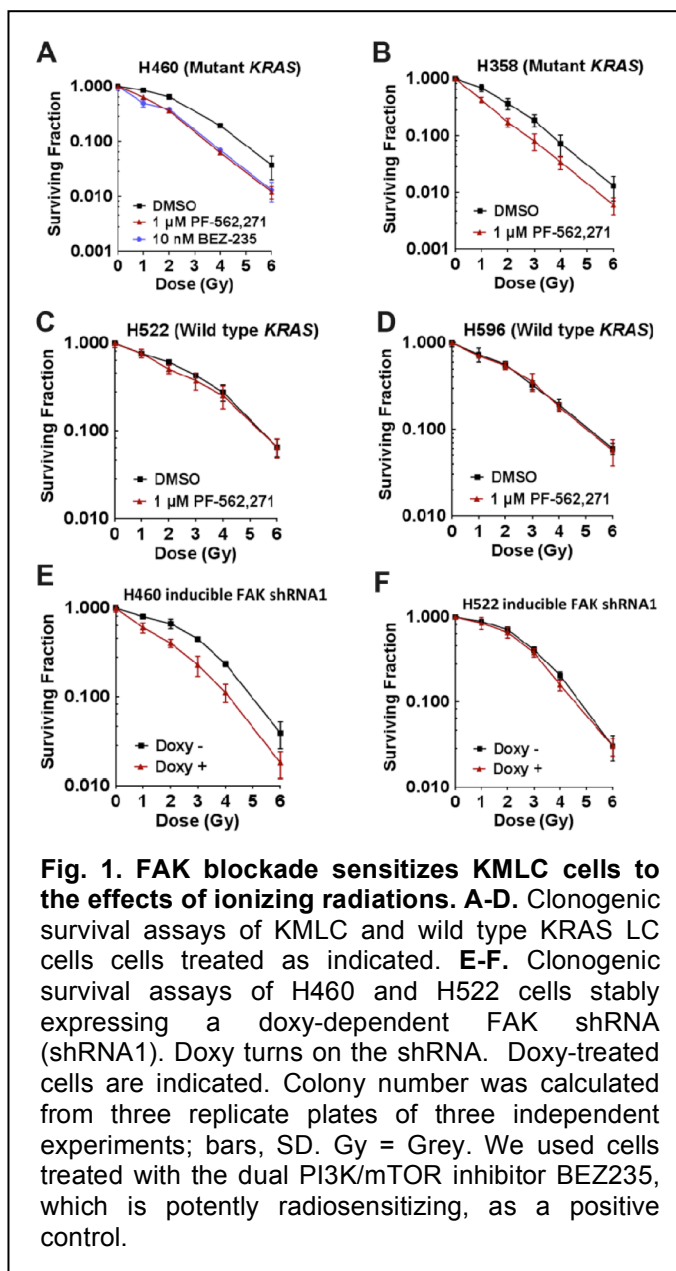**Major activity:** As proposed in the statement of work, we tested the sensitivity of a panel of lung cancer cells (21 cell lines), which include the major mutations that occur in lung cancer, to FAK inhibitors (FAKi) PF-562271 (now renamed VS-6063) VS-4718, previously known as PND- 1186 (2, 3).
We reported last year that this task was completed.

  In aggregate our experiments demonstrated that FAKis lead to significant cytopathic effects in KMLC cells deficient for either CDKN2A or p53. We did not find that other oncogenic mutations that commonly occur in LC are dependent on FAK.

Subtask 1b: Determination of the functional consequences of FAK inhibition in NSCLC cells.

Major activity: as proposed in the statement of work, we performed experiments in cultured LC cells.
Specific Objectives: The goal of subtask 1b is to identify the cellular networks that mediate the antitumor effects of FAK suppression in KMLC.

Fig. 1. FAK blockade sensitizes KMLC cells to the effects of ionizing radiations. A-D. Clonogenic survival assays of KMLC and wild type KRAS LC cells cells treated as indicated. **E-F.** Clonogenic survival assays of H460 and H522 cells stably expressing a doxy-dependent FAK shRNA (shRNA1). Doxy turns on the shRNA. Doxy-treated cells are indicated. Colony number was calculated from three replicate plates of three independent experiments; bars, SD. Gy = Grey. We used cells treated with the dual PI3K/mTOR inhibitor BEZ235, which is potently radiosensitizing, as a positive control.

Significant results: We reported last year that in LC cells, FAK inhibition does not affect canonical FAK-dependent signaling pathways (i.e. AKT, ERK or JNK). Instead, we found that FAK silencing or pharmacologic inhibition induces DNA damage. In the previous years we also reported that FAK physically interacts with the SUMO E3 ligase Protein inhibitor of activated STAT1 (PIAS1). This finding is coherent with the observation of others that: 1. A fraction of FAK is SUMOylated and interacts with PIAS1 in the nucleus (4); 2. PIAS1 positively regulates DNA double stand break repair (5).

Over the last year of funding we determined that FAK silencing or pharmacologic inhibition sensitizes KMLC cells to the cytopathic effects of ionizing radiations.

We performed clonogenic survival assays with H460 and H358 (KMLC) and H522 and H596 cells (wild type KRAS) as representative examples of LC cells we used in task 1a, exposed to increasing doses of IR (1-6 Gy) (Fig. 1A-D). We administered 1 µM of FAKi PF-562,271 four hours before exposure to ionizing radiations (IR). We chose this concentration because it inhibits the activated form of FAK (phospho-FAK, P-FAK thereafter) in a comparable manner in all the LC cells used for this study (data not shown). We limited the incubation time to 48 hours not to affect cell plating efficiency. We scored colonies of >50 normal appearing cells 15-30 days after treatment and graphed the survival fraction (SF) versus dose of IR (expressed in Greys, Gy) used. We calculated Do (relative dose of IR required for 37% lethality on a log-phase kill curve), Dq (inherent DNA repair capacity: dose (Gy) required to eliminate the survival curve shoulder) and dose enhancement ratios (DERs at LD_{50} and

LD_{20}) as described (6).

We found that pharmacologic inhibition of FAK resulted in profound changes in Dq as well as significant, but less dramatic, decreases in Do in KMLC cells ((Fig. 1A-B). Thus, we concluded that FAKi reduces inherent DNA repair capacity (Dq). In contrast, exposure of wild-type LC cells to FAKi had no significant effect on IR-induced lethality as noted by the survival curve and estimations of Dq and Do (Fig. 1C-D). Most importantly, the presence of FAKi increased dose enhancement ratios (DERs) with values ranging between 2.1 and 1.9 at LD_{50} levels, and between 1.7 and 1.4 at LD_{20} levels, respectively in KMLC cells (Table 1).

Notably, the effect of FAKi treatment was comparable to the dual PI3K/mTOR inhibitor BEZ-235, which is a known radiosensitizing agent (Fig. 1A) (7, 8).

We confirmed these findings with an independent approach. We used the GEPIR retrovirus to express FAK shRNA1, which we validated in preliminary experiments, in a doxycycline-regulated manner at the time of IR exposure (Fig. 1E-F). These findings suggest that **FAK blockade sensitizes KMLC cells to the effects of ionizing radiations.**

Next, we determined that treatment with FAKi PF-562,271 in combination with IR (2 Gy) leads to a striking persistence of γ-H2AX foci, a well-known marker of DNA double-strand breaks damage, at 24 hours post-IR administration compared with exposure with IR alone. The effect of PF-562,271 was comparable to the effects of the dual PI3K/mTOR inhibitor BEZ-235, a known radiosensitizer (Fig. 2A) (7, 8). Inhibition of FAK in the absence of IR induces γ-H2AX foci slightly above background level in this assay (Fig. 2A).

| | Dq (Gy) | Do (Gy) | DER Values | |
			LD50	LD20
H460 (Mutant *KRAS*)				
DMSO	2.0	2.0		
PF-562,271	1.0	1.7	1.9	1.6
BEZ-235	1.0	1.7	2.0	1.6
H358 (Mutant *KRAS*)				
DMSO	1.1	1.4		
PF-562,271	0.2	1.1	1.9	1.7
H522 (wild-type *KRAS*)				
DMSO	1.4	1.7		
PF-562,271	1.4	1.7		
H596 (wild-type *KRAS*)				
DMSO	1.7	1.0		
PF-562,271	1.7	1.0		
H460 inducible FAK shFAK1				
Doxy -	2.0	2.1		
Doxy +	1.3	1.0	2.1	1.4
H522 inducible FAK shFAK1				
Doxy -	1.8	2.0		
Doxy +	1.8	1.9		

Table 1. Dq, Do and DER of lung cancer cells treated as indicated. DER at LD_{50} and LD_{20} levels were calculated by direct examination of survival curves. Survival parameters (i.e., Dq and Do) were also derived from survival curves shown in Fig. 1 using the relationship, $\log_e n = Dq/Do$. **Note that the effects occur specifically in KMLC cells.**

We obtained equivalent results when we determined the induction and resolution of γ-H2AX and TP53BP1 foci, as readout of DNA damage, in H460 (derived from KMLC) cells where we ablated FAK by CRISPR/CAS9 editing (data not shown).

Next, we confirmed the effects on γ-H2AX by flow cytometry (data not shown). In addition, we found that KMLC cells treated with FAKi in association with IR display a significant increase of the percentage of cells in the G_2 phase of the cell as compared to H460 cells treated with IR only (data not shown).

Taken together these data suggest that inhibition/suppression of FAK results in persistent DNA damage in KMLC cells because of inhibition of DNA repair or augmentation of damage by cell cycle checkpoint abrogation, which occur without affecting the activation and recruitment to sites of DNA damage of the DNA damage sensing machinery. These observations also suggest that IR therapy could be exploited to sensitize KMLC to therapy with FAKis.

Other achievements:

Last year we mentioned in the progress report that: 1. *PIAS1* and *FAK* genes are co-amplified in LC cell lines; 2. FAK and PIAS1 proteins are upregulated in metastatic LC; 3. PIAS1 and FAK colocalize in the perinuclear region ; 4. FAK knockdown leads to significant reduction of PIAS1 protein. This year we have found that PIAS1 is required for the prosurvival function exerted by FAK in KMLC cells.

What do you plan to do during the next reporting period to accomplish the goals? During the no cost extension, we will finalize manuscripts detailing our findings and satisfy editors and reviewers.

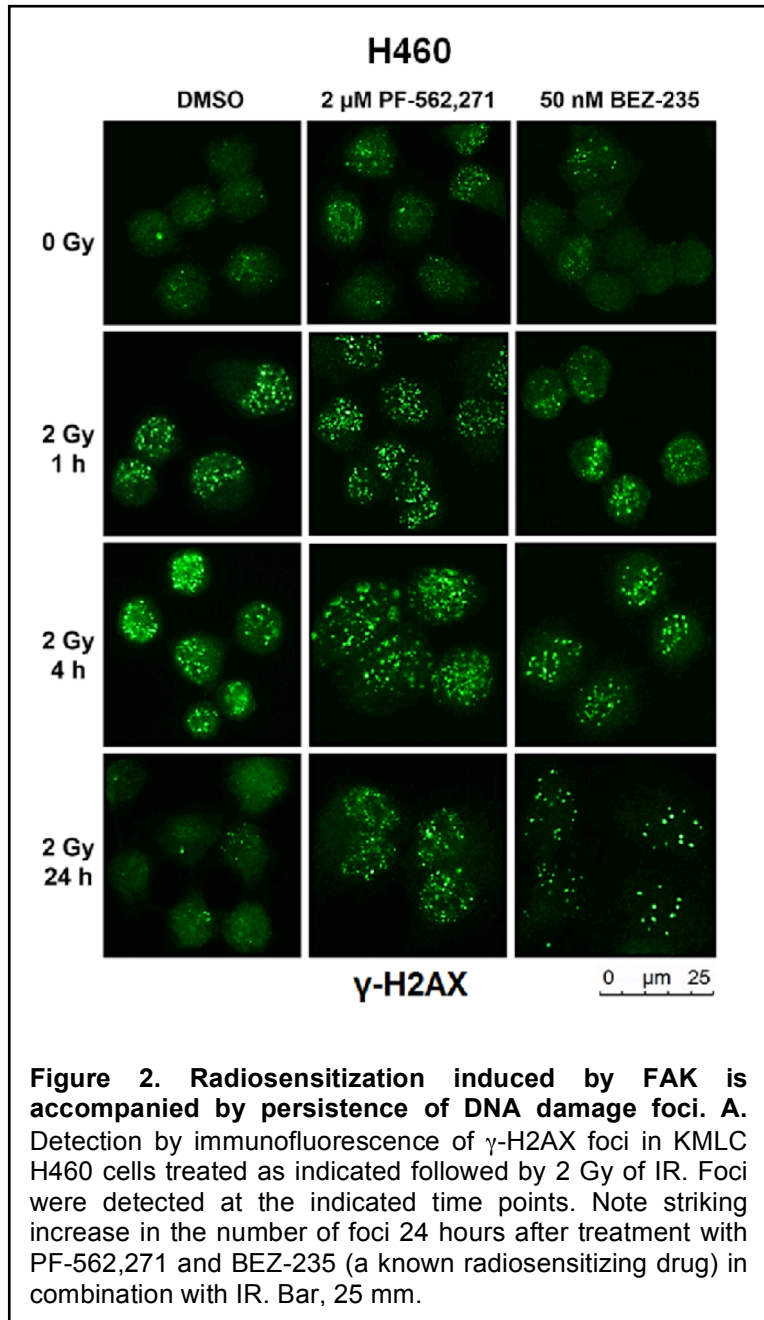**Subtask 1c:** Pharmacologic inhibition of FAK in human NSCLC cells in vivo.

Major activity: Treatment with FAKi mice carrying xenografts of lung cancer cell lines.
Specific Objectives: Testing the antitumor effect of pharmacologic inhibition of FAK in human lung cancer cells grown as xenografts in mice.

   Significant results: We tested the anti-tumor effects of FAK inactivation mediated by CRISP/CAS9 editing, which was not available at the time the initial grant was submitted. In agreement with the data shown in Figure 1, we found that genetic inactivation of FAK decreased the growth or H460 and H358 cells significantly, increasing also the survival of mice carrying FAK null xenografts (Fig. 3A-B and data not shown). Even though the results were statistical significant, we did not detect tumor regression, a desirable effect in cancer therapy. We obtained equivalent results in xenografts of KLMC cells treated with FAKi (data not shown). These findings indicate that FAKi may have limited efficacy as single agents in cancer therapy.

   Next we tested whether FAK ablation results in meaningful radiosensitization in KMLC vivo. To this end, we generated cohorts of athymic nude mice bearing xenografts of H460 *T2.2 FAK+* and H460 *T2.2 FAK-* cells. When xenografts reached 300 mm^3 in size, we delivered five 4 Gy fractions every other day for 10 days specifically to the tumor xenograft using lead-shielded mice. We used a fractionated dose to limit overall tissue toxicity and mimic the administration modality used in the clinic (9). Notably, this xenograft volume and IR dose is comparable with previous studies involving H460 xenografts (7, 10).

   IR treatment of H460 *T2.2 FAK-* cells resulted in a greater than 75% reduction in xenograft volume as compared to H460 *T2.2 FAK+* cells 30 days after the first dose of IR (*P* < 0.001) (Fig. 3C-D). All irradiated mice carrying xenografts of H460 *T2.2 FAK-* cells were alive 40 days after the initiation of IR treatment, in

Figure 2. Radiosensitization induced by FAK is accompanied by persistence of DNA damage foci. A. Detection by immunofluorescence of γ-H2AX foci in KMLC H460 cells treated as indicated followed by 2 Gy of IR. Foci were detected at the indicated time points. Note striking increase in the number of foci 24 hours after treatment with PF-562,271 and BEZ-235 (a known radiosensitizing drug) in combination with IR. Bar, 25 mm.
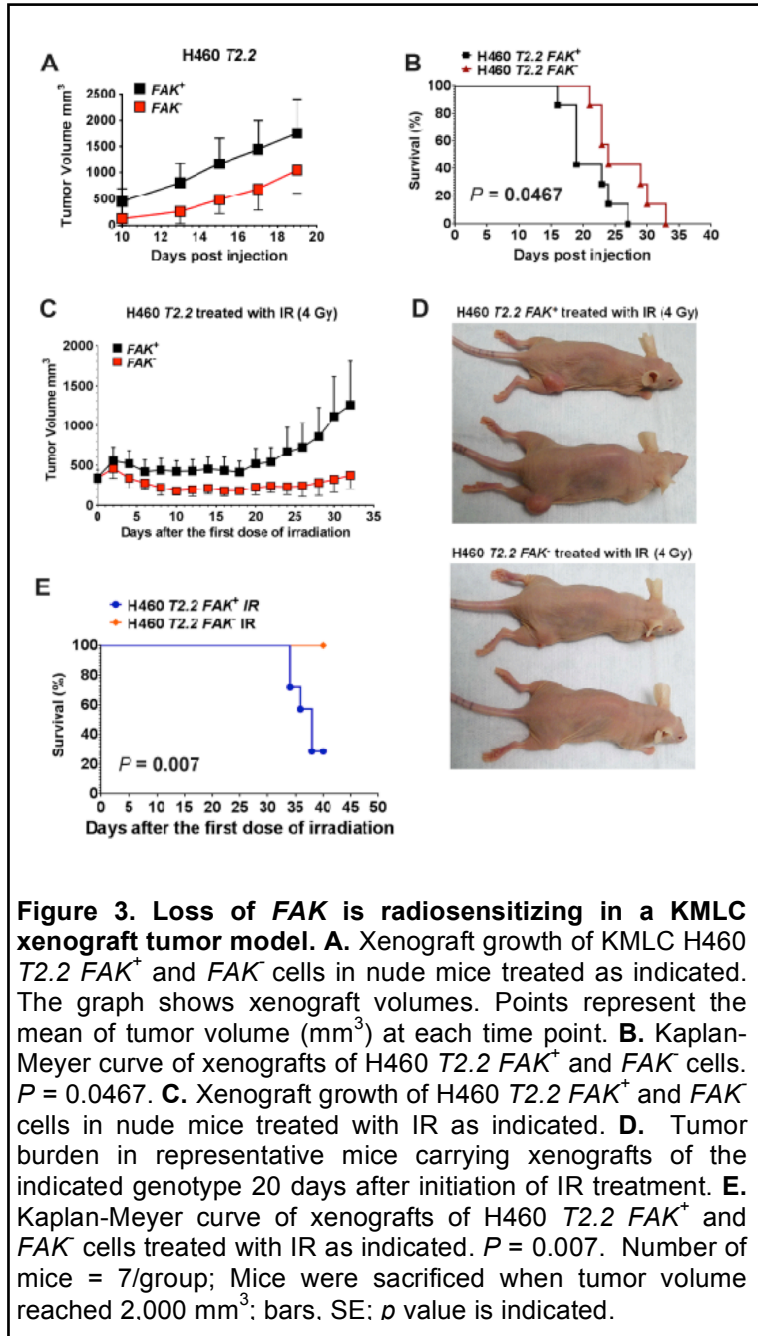
contrast five out of seven mice carrying of H460 *T2.2 FAK⁺* cells were sacrificed between days 34 and 38 post-radiation due to excessive tumor burden (Fig. 3E).

IR treatment was well tolerated in xenograft bearing nude mice and we didn't observe any drop in body weight or other signs of toxicity in both groups (data not shown).

These results indicate that the ablation of FAK leads to significant radiosensitizing effects, which in turn led to significant anti-tumor effects *in vivo*.

Figure 3. Loss of *FAK* is radiosensitizing in a KMLC xenograft tumor model. A. Xenograft growth of KMLC H460 *T2.2 FAK⁺* and *FAK⁻* cells in nude mice treated as indicated. The graph shows xenograft volumes. Points represent the mean of tumor volume (mm³) at each time point. **B.** Kaplan-Meyer curve of xenografts of H460 *T2.2 FAK⁺* and *FAK⁻* cells. *P* = 0.0467. **C.** Xenograft growth of H460 *T2.2 FAK⁺* and *FAK⁻* cells in nude mice treated with IR as indicated. **D.** Tumor burden in representative mice carrying xenografts of the indicated genotype 20 days after initiation of IR treatment. **E.** Kaplan-Meyer curve of xenografts of H460 *T2.2 FAK⁺* and *FAK⁻* cells treated with IR as indicated. *P* = 0.007. Number of mice = 7/group; Mice were sacrificed when tumor volume reached 2.000 mm³: bars. SE: *p* value is indicated.

Other achievements: NA

What do you plan to do during the next reporting period to accomplish the goals? During the no cost extension, we will finalize manuscripts detailing our findings and satisfy editors and reviewers.

Subtask 1d. Determination of anti-tumor effects due to pharmacologic inhibition of FAK in transgenic mice with NSCLC induced by oncogenic KRAS.

Major activity: Treatment with FAKi of genetically engineered mice with KMLC.
Specific Objectives: Testing the antitumor effect of FAKi in vivo in mouse models of KMLC.
Significant results: Since the submission of the grant, we have determined that FAK inhibition causes striking inhibition of lung adenocarcinomas but not of lung adenomas of mutant *KRAS/Cdkn2a⁻/⁻* mice (1). Thus, we proposed to determine whether treatment with FAK inhibition increases overall survival. However, the results of task 1c, reduce the enthusiasm for these experiments because they suggest that human KMLC cells have mechanisms that allow the bypass of FAK loss. Indeed, lung cancers invariably develop resistance to treatment with targeted cancer drugs. Exactly to counteract this concern, we proposed to test FAKi in combination with other agents.

Furthermore, subtask 1e will also be determine the role of Fak in KM lung tumorigenesis. For this reason, we plan to prioritize the experiments of subtask 1e.

What do you plan to do during the next reporting period to accomplish the goals? We are considering testing the effects of pharmacologic inhibition of FAK in LsL-*Kras*, LsL-*Kras/p53⁻/⁻* and LsL-*Kras/Cdkn2a⁻/⁻* mice (11). Given the result s of the experiments described in subtask 1c and the fact that the task 1e has not been completed, it is possible that the experiments described in subtask 1d are redundant and not informative. According we will execute these experiments after the completion of subtask 1e.
Other achievements: NA

Subtask 1e. Determination of the impact of FAK deficiency in transgenic mice with NSCLC induced by oncogenic KRAS.

Major activity: Study the impact of Fak deficiency on KMLC in genetically engineered mice.
Specific Objectives: determination of the impact of Fak deficiency on mutant Kras tumorigenesis in vivo in genetically engineered mice.
Significant results: We proposed to test the requirement of Fak for the progression from lung adenoma to adenocarcinoma. For this purpose, we are using mice carrying a floxed allele of *Fak* to generate cohorts of LsL-*Kras*/*Cdkn2a*$^{-/-}$ and LsL-*Kras/Cdkn2a*$^{-/-}$*/Fak*$^{f/f}$ mice (12). We have recently developed conditions to deliver the cre recombinase to the respiratory epithelium with lentiviruses that allow the generation of primary tumors and also of their metastatic spread. Thus, we will study the effect of FAK deficiency in primary and metastatic tumors.
Other achievements: Should these experiments demonstrate that Fak is required for lung tumorigenesis, we will perform experiments with mice carrying a knocked-in allele encoding an inducible Fak kinase dead mutant. This experiment will mimic genetically the action of a pharmacologic inhibitor of Fak and will discriminate whether the Fak kinase activity or its scaffolding function is important for tumorigenesis.

What do you plan to do during the next reporting period to accomplish the goals? These experiments are in progress and should mature during the no cost extension period.

Goal #2. Identification of strategies that synergize with inhibition of FAK to induce the death of NSCLC expressing oncogenic KRAS.

We proposed to use genetic and pharmacologic approaches to identify strategies to optimize the therapeutic outcome of inhibition of FAK in KMLC cells mutant for either CDKN2A or p53.

Subtask 2a. Identification of combination therapies that synergize with pharmacologic inhibition of FAK;
Major activity: testing the effects of drug combinations in cultured lung cancer cells.
Specific Objectives: identification of combination therapies that synergize with inhibition of FAK.
Significant results: We prioritized our efforts to determine whether FAK inhibitors synergize with inhibitors of proteins that interact with FAK, such as c-MET, EGFR, SRC, PI3K, MEK1/2 or mTORC1/2. We have not identified synergistic relationships, but only additive relationships. This finding may indicate that in NSCLC cells, FAK signals though non-canonical pathways. This hypothesis is consistent with the observation that FAK silencing/inhibition leads to radiosensitization (refer to subtask 1a). This finding reveals a novel and unexpected function of FAK, which could be harnessed for therapeutic purposes in KMLC.
This task is completed.

Other achievements: NA

What do you plan to do during the next reporting period to accomplish the goals? This task is completed.

Subtask 2b. Complete the validation of a whole genome siRNA screening to identify oncogenic KRAS synthetic lethal interactions in NSCLC cells.
Major activity: To perform experiments to identify genes that when inactivated cause the death of KMLC cells.
Specific Objectives: Identification of additional KM synthetic lethal interaction that could represent therapeutic targets.
Significant results:
This task is completed.
Other achievements: NA

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

NA

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

This project was not intended to provide training and professional development opportunities.
Dr. Mahesh Padanad (post-doctoral fellow), Dr. Ke-Jing Tang (Associate Professor at Sun Yat-sen University, Guangzhou, China, Visiting professor) and Niranjan Venkateswaran, MS (Research technician) conducted the research described in this progress report. Their involvement in this project is part of their research training under the mentorship of Dr. Scaglioni, MD

3.3 How were the results disseminated to communities of interest?

Part of these data were presented at the:

- 15th Annual Targeted Therapies of Lung Cancer Meeting. The Fairmont Miramar Hotel, Santa Monica, CA. Sponsored by the IASLC. February 18-21, 2015

- 10th symposium " Mechanisms and Models of Cancer" at the Salk Institute, La Jolla CA, August 5-8, 2015

- 16th World Conference on Lung Cancer" in Denver, Colorado, September 6-9, 2015.

In addition, we are preparing manuscripts detailing our findings. The newly acquired data regarding the role of FAK in DNA damage repair provide the framework for further development of FAK inhibitors in radiation therapy protocols.

4. Impact.

With this research we have identified FAK as a novel targetable vulnerability of KMLC. Our preclinical data provided the rationale for the design and execution of a Phase II multi-institutional clinical trial in lung cancer patients, which has completed the target enrolment of 55 KMLC patients so far.

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

Our research project indicates that KMLCs that are mutant for either CDKN2A or for p53 are vulnerable to FAK silencing or pharmacologic inhibition both in cultured cells and in transgenic mice of high-grade lung adenocarcinoma.

This oncogenotype is of clinical relevance. We have determined that mutant KRAS;CDKN2A deficiency occurs in about 50% of mutant KRAS lung cancers. Mutant KRAS is present in 25% of the 175,000 newly diagnosed lung cancers that are diagnosed yearly in the USA yearly. Thus, the mutant KRAS;CDKN2A deficient genotype is present in about 20,000 to 25,000 patients/year in the USA. Mutant KRAS;p53 deficiency has a similar prevalence (13, 14).

We also identified a novel function of FAK, namely its ability to promote the repair of DNA damage. Our preliminary data indicate that FAK silencing or pharmacologic inhibition lead to defective DNA double-strand break repair causing significant radiosensitizing effects. Accordingly, FAK inhibition/silencing

overcomes radioresistance of KMLC cells cultured in vitro. We are currently pursuing the hypothesis that FAK exerts its effect on the DNA damage repair machinery through the SUMO E3 ligase PIAS1.

Our data provided the rationale for the execution of the first clinical trial of a small molecule inhibitor of FAK in lung cancer patients (ClinicalTrials.gov Identifier: NCT01951690). This is a multicenter Phase 2 trial of the FAK inhibitor defactinib (VS-6063) to treat KRAS-mutated non-small cell lung cancer (NSCLC). This trial has completed its targeted accrual of 55 patients. Treatment outcomes will be correlated to the presence of CDKN2A or p53 mutations.

4.2. What was the impact on other disciplines?

Our data indicate that KMLC, which was considered a homogenous disease, can be further sub-classified based on co-occurring mutations and that specific oncogenotypes may dictate response to targeted therapy. It is conceivable that this paradigm may apply to cancer of other histological origins.

4.3. What was the impact on technology transfer?

A phase II multicentrer clinical trial sponsored by Verastem is ongoing (ClinicalTrials.gov Identifier: NCT01951690).
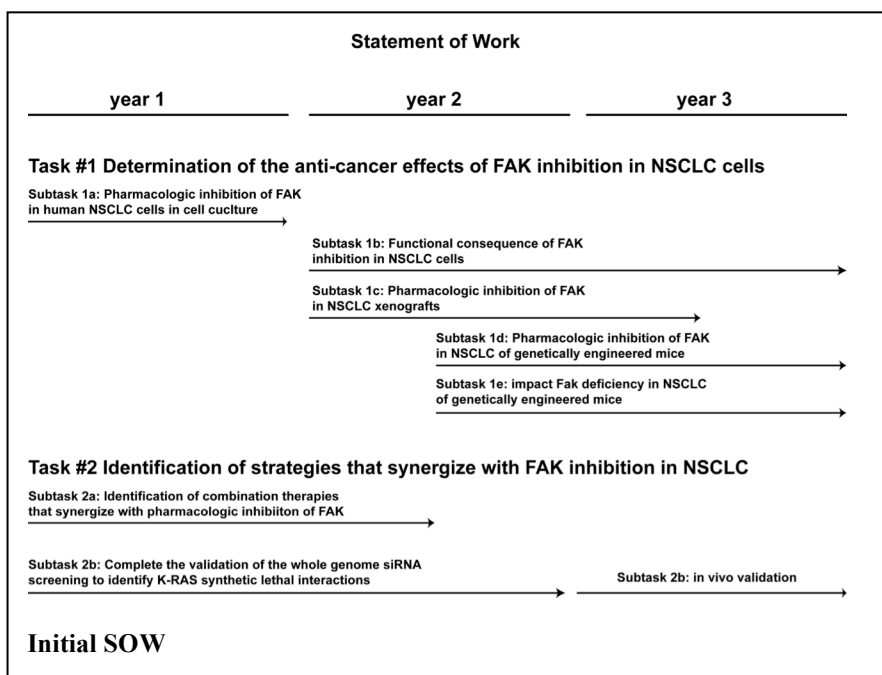
4.4. What was the impact on society beyond science and technology?

None to report

5. Changes/Problems.

There are no changes to the original SOW.

There are some delays in the original time-table, but the project is essentially on track.

Statement of Work

year 1	year 2	year 3

Task #1 Determination of the anti-cancer effects of FAK inhibition in NSCLC cells

Subtask 1a: Pharmacologic inhibition of FAK in human NSCLC cells in cell cuclture

Subtask 1b: Functional consequence of FAK inhibition in NSCLC cells

Subtask 1c: Pharmacologic inhibition of FAK in NSCLC xenografts

Subtask 1d: Pharmacologic inhibition of FAK in NSCLC of genetically engineered mice

Subtask 1e: impact Fak deficiency in NSCLC of genetically engineered mice

Task #2 Identification of strategies that synergize with FAK inhibition in NSCLC

Subtask 2a: Identification of combination therapies that synergize with pharmacologic inhibiiton of FAK

Subtask 2b: Complete the validation of the whole genome siRNA screening to identify K-RAS synthetic lethal interactions

Subtask 2b: in vivo validation

Initial SOW

6. Products.

6.1. Publications, conference papers, and presentations.

Manuscripts:

Manuscripts in preparation:

Focal Adhesion Kinase regulates the DNA damage response and its inhibition radiosensitizes mutant KRAS lung cancer. Submitted to Clinical Cancer Research.

FAK-PIAS1 Interaction Promotes the Survival and Migration of Lung Cancer cells. In preparation.

Manuscripts published during prior phases of the award:

Konstantinidou G, Ramadori G, Torti F, Kangasniemi K, Ramirez RE, Cai Y, et al. RHOA-FAK is a required signaling axis for the maintenance of KRAS-driven lung adenocarcinomas. Cancer Discov. 2013;3(4):444-57. doi: 10.1158/2159-8290.CD-12-0388. PubMed PMID: 23358651; PubMed Central PMCID: PMC3625467.

Schuster K, Venkateswaran N, Rabellino A, Girard L, Pena-Llopis S, Scaglioni PP. Nullifying the CDKN2AB Locus Promotes Mutant K-ras Lung Tumorigenesis. Molecular cancer research : MCR. 2014;12(6):912-23. doi: 10.1158/1541-7786.MCR-13-0620-T. PubMed PMID: 24618618; PubMed Central PMCID: PMC4058359.

Abstracts at national of international meetings:

P.P. Scaglioni.
Focal adhesion kinase (FAK) is a therapeutic target in KRAS mutant lung cancer. 15th Annual Targeted Therapies of Lung Cancer Meeting. The Fairmont Miramar Hotel, Santa Monica, CA. Sponsored by the IASLC. February 18-21, 2015.

D.E. Gerber, D.R. Camidge, D. Morgensztern, J. Cetnar, R.J. Kelly, S.S. Ramalingam, D.R. Spigel, W. Jeong, P. Scaglioni, M. Li, M. Keegan, J. C. Horobin, T. F. Burns.
Focal adhesion kinase (FAK) inhibition for KRAS mutant non-small cell lung cancer (NSCLC): a single-arm phase 2 clinical trial. International Association for the Study of Lung Cancer (IASLC) 15th Annual Targeted Therapies of Lung Cancer Meeting. Santa Monica, California. February 18-21, 2015.

D.E. Gerber, D.R. Camidge, D. Morgensztern, J. Cetnar, R.J. Kelly, S.S. Ramalingam, D.R. Spigel, W. Jeong, P. Scaglioni, M. Li, M. Keegan, J. C. Horobin, T. F. Burns.
Phase II study of Defactinib, VS-6063, a focal adhesion kinase (FAK) inhibitor, in patients with KRAS mutant non-small cell lung cancer (NSCLC). 16th World Conference on Lung Cancer. Denver, Co. September, 6-9, 2015

J. D. Constanzo, K.J. Tang, S. Rindhe, M. Melegari, N. Venkateswaran, and P.P. Scaglioni.
FAK and PIAS1 genes promote the survival and progression of aggressive metastatic lung cancer by engaging DNA repair networks and mitochondria metabolism. The 10th Symposium, Cancer Models and Mechanisms. The Salk institute, LA Jolla, CA. August 5-8, 2015.

Abstracts presented during prior phases of the award

1. G. Konstantinidou, G. Ramadori, F. Torti, C. Behrens, I. I. Wistuba, A. Heguy, D. Gerber, J. Teruya-Feldstein, P.P. Scaglioni. Identification of Focal Adhesion Kinase (FAK) as a Therapeutic Target in KRAS Mutant Lung Cancer. Mechanisms and Models of Cancer. Salk Institute, La Jolla, CA. August 7-10 2013. **Note that this abstract was selected for oral presentation.**

2. K. Schuster, N. Venkateswaran, S. Peña-Llopis and P.P. Scaglioni. Loss of the CDKN2AB Tumor Suppressor Locus Promotes Mutant KRAS Lung Tumorigenesis. Mechanisms and Models of Cancer. Salk Institute, La Jolla, CA. August 7-10 2013.

3. J.D. Constanzo, A. Rabellino, G. Konstantinidou, K. Schuster and P.P. Scaglioni. SUMO Ligase PIAS1: An Unexpected Role In Cancer Cell Initiation And Survival. Mechanisms and Models of Cancer. Salk Institute, La Jolla, CA. August 7-10 2013.

3. P.P. Scaglioni. Identification of Focal Adhesion Kinase (FAK) as a therapeutic target in KRAS mutant lung cancer. Lung Spore Workshop. National Cancer Institute., Rockville, MD. July 11-12, 2013. **Note that this abstract was selected for oral presentation.**

4. P.P. Scaglioni. Inhibiting Focal Adhesion Kinase in Mutant KRAS NSCLC. Lung Cancer Summit. Ritz Carlton Dallas, Texas 12/15/2013.

5. K.J. Tang, J. D. Constanzo, N. Venkateswaran, M. Melegari, J.C. Morales, D.A. Boothman, P.P. Scaglioni. Pharmacologic inhibition or genetic ablation of Focal Adhesion Kinase (FAK) is radiosensitizing in KRAS mutant lung cancer. Lung Cancer SPORE Workshop. Rockville, MD. 6/15-6/16 2014.
Note that this abstract was selected for oral presentation.

Presentations at Academic Institutions. Presenter, Pier Paolo Scaglioni, MD.

None this year

Presentations to academic institutions during prior phases of the award

Metabolic and Signaling Vulnerabilities of KRAS-driven lung adenocarcinoma. European Institute of Oncology, Milano, Italy. Grand Rounds. 1/22/2013.

Metabolic and Signaling Vulnerabilities of KRAS-driven lung adenocarcinoma. University of California, Division of Hematology/Oncology. Irvine, CA. 1/31/2013.

Metabolic and Signaling Vulnerabilities of KRAS-driven lung adenocarcinoma. Division of Hematology/Oncology. UT Health Science Center. San Antonio, TX. 2/21/2013.

Genotype-Specific Cancer Vulnerabilities: The case of PML-RARA and mutant KRAS. Indiana University Medical Center. Indianapolis, IN. 4/18/2013.

Genotype-Specific Cancer Vulnerabilities: The case of PML-RARA and mutant KRAS. Vanderbilt University Medical Center. Nashville. TN. 5/14/2013.

Genotype-Specific Cancer Vulnerabilities: The case of PML-RARA and mutant KRAS. Case Comprehensive Cancer Center. Cleveland, OH. 5/22/2013.

Genotype-Specific Cancer Vulnerabilities: The case of PML-RARA and mutant KRAS. City of Hope, Duarte, CA. 10/04/2013.

6.2 Website(s) or other Internet site(s)

NA

6.3 Technologies or techniques

We are generating genetically engineered lung cancer models: we will make them available to the scientific community as detailed in the appropriate section of the funded grant.

6.4 Inventions, patent applications, and/or licenses

NA

6.5 Other Product

NA

7. Participants and other collaborating organizations.

7.1. what individuals have worked on the project?

Name:	Mahesh Padanad
Project Role:	Post-doctoral fellow
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Execution of Cell biology Experiments
Funding Support:	CPRIT Institutional Training Grant (since 3/2014)

Name:	Ke-Jing
Project Role:	Post-doctoral fellow
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Execution of Cell biology Experiments
Funding Support:	Visiting Scholar supported by the Sun Yat-sen University, Guangzhou, China.

Name:	Niranjan Venkateswaran
Project Role:	Research technician II
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Management of mouse colony and execution of experiments with mouse lung cancer models
Funding Support:	DOD

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

The following are the research funds received by Dr. Scaglioni, the PI of this project.

Texas 4000 (PI: Scaglioni)   One time gift 2015   0.4 cal. Month
                                                                $50,000
Title: From the clinic to the laboratory: a pipeline to identify and target the intracellular metabolic networks that sustain acute leukemia.
Project Goal: this research grant will identify BCR-ABL-dependent metabolic network in acute lymphoblastic leukemia.

7.2. What other organizations were involved as partners?

None to report

8. Appendices: Attach all appendices that contain information that supplements, clarifies or supports the text.

Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

1.   CV of Dr. Pier Paolo Scaglioni.

9. References

1.   Konstantinidou G, Ramadori G, Torti F, Kangasniemi K, Ramirez RE, Cai Y, et al. RHOA-FAK is a required signaling axis for the maintenance of KRAS-driven lung adenocarcinomas. Cancer discovery. 2013;3(4):444-57. Epub 2013/01/30. doi: 2159-8290.CD-12-0388 [pii]10.1158/2159-8290.CD-12-0388. PubMed PMID: 23358651; PubMed Central PMCID: PMC3625467.

2.   Roberts WG, Ung E, Whalen P, Cooper B, Hulford C, Autry C, et al. Antitumor activity and pharmacology of a selective focal adhesion kinase inhibitor, PF-562,271. Cancer Res. 2008;68(6):1935-44. Epub 2008/03/15. doi: 68/6/1935 [pii]10.1158/0008-5472.CAN-07-5155. PubMed PMID: 18339875.

3.   Tanjoni I, Walsh C, Uryu S, Tomar A, Nam JO, Mielgo A, et al. PND-1186 FAK inhibitor selectively promotes tumor cell apoptosis in three-dimensional environments. Cancer biology & therapy. 2010;9(10):764-77. PubMed PMID: 20234191; PubMed Central PMCID: PMC2933317.

4.   Kadare G, Toutant M, Formstecher E, Corvol JC, Carnaud M, Boutterin MC, et al. PIAS1-mediated sumoylation of focal adhesion kinase activates its autophosphorylation. The Journal of biological chemistry. 2003;278(48):47434-40. doi: 10.1074/jbc.M308562200. PubMed PMID: 14500712.

5.   Galanty Y, Belotserkovskaya R, Coates J, Polo S, Miller KM, Jackson SP. Mammalian SUMO E3-ligases PIAS1 and PIAS4 promote responses to DNA double-strand breaks. Nature. 2009;462(7275):935-9. doi: 10.1038/nature08657. PubMed PMID: 20016603; PubMed Central PMCID: PMC2904806.

6.   Boothman DA, Greer S, Pardee AB. Potentiation of halogenated pyrimidine radiosensitizers in human carcinoma cells by beta-lapachone (3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]pyran- 5,6-dione), a novel DNA repair inhibitor. Cancer research. 1987;47(20):5361-6. Epub 1987/10/15. PubMed PMID: 3652040.

7.   Konstantinidou G, Bey EA, Rabellino A, Schuster K, Maira MS, Gazdar AF, et al. Dual phosphoinositide 3-kinase/mammalian target of rapamycin blockade is an effective radiosensitizing strategy for the treatment of non-small cell lung cancer harboring K-RAS mutations. Cancer Res. 2009;69(19):7644-52. Epub 2009/10/01. doi: 0008-5472.CAN-09-0823 [pii] 10.1158/0008-5472.CAN-09-0823. PubMed PMID: 19789349; PubMed Central PMCID: PMC2760010.

8.   Mukherjee B, Tomimatsu N, Amancherla K, Camacho CV, Pichamoorthy N, Burma S. The dual PI3K/mTOR inhibitor NVP-BEZ235 is a potent inhibitor of ATM- and DNA-PKcs-mediated DNA damage responses. Neoplasia. 2012;14(1):34-43. PubMed PMID: 22355272; PubMed Central PMCID: PMC3281940.

9.   Fairchild A, Harris K, Barnes E, Wong R, Lutz S, Bezjak A, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. J Clin Oncol. 2008;26(24):4001-11. Epub 2008/08/20. doi: 26/24/4001 [pii] 10.1200/JCO.2007.15.3312. PubMed PMID: 18711191.

10.   Iwasa T, Okamoto I, Suzuki M, Nakahara T, Yamanaka K, Hatashita E, et al. Radiosensitizing effect of YM155, a novel small-molecule survivin suppressant, in non-small cell lung cancer cell lines. Clin Cancer Res. 2008;14(20):6496-504. Epub 2008/10/18. doi: 14/20/6496 [pii] 10.1158/1078-0432.CCR-08-0468. PubMed PMID: 18927289.

11.   Jackson EL, Willis N, Mercer K, Bronson RT, Crowley D, Montoya R, et al. Analysis of lung tumor initiation and progression using conditional expression of oncogenic K-ras. Genes Dev. 2001;15(24):3243-8. Epub 2001/12/26. doi: 10.1101/gad.943001. PubMed PMID: 11751630.

12. Beggs HE, Schahin-Reed D, Zang K, Goebbels S, Nave KA, Gorski J, et al. FAK deficiency in cells contributing to the basal lamina results in cortical abnormalities resembling congenital muscular dystrophies. Neuron. 2003;40(3):501-14. Epub 2003/12/04. doi: S0896627303006664 [pii]. PubMed PMID: 14642275; PubMed Central PMCID: PMC2758566.

13. Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, Hodis E, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell. 2012;150(6):1107-20. doi: 10.1016/j.cell.2012.08.029. PubMed PMID: 22980975; PubMed Central PMCID: PMC3557932.

14. Schuster K, Venkateswaran N, Rabellino A, Girard L, Pena-Llopis S, Scaglioni PP. Nullifying the CDKN2AB Locus Promotes Mutant K-ras Lung Tumorigenesis. Molecular cancer research : MCR. 2014;12(6):912-23. doi: 10.1158/1541-7786.MCR-13-0620-T. PubMed PMID: 24618618; PubMed Central PMCID: PMC4058359.

Appendix

BIOGRAPHICAL SKETCH -			
Provide the following information for collaborators listed on this application. Follow this format for each person.			

NAME		POSITION TITLE	
Scaglioni, Pier Paolo, MD		Associate Professor	

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Modena, Italy	M.D.	10/1989	Medicine
University of Modena, Italy	Resident	1989-1994	Internal Medicine
Massachusetts General Hospital	Research	1994-1998	Virology
Montefiore Medical Center, Bronx, NY	Resident	1998-2001	Internal Medicine
Memorial Sloan-Kettering Cancer Center, NY	Clinical Fellow	2001-2005	Medical Oncology

A. Personal Statement.

I am a medical oncologist and physician-scientist trained in molecular virology and cancer biology. I am interested in understanding how genetic alterations contribute to tumorigenesis, modify response to cancer treatment or create vulnerabilities that may be targeted by therapeutics. To enable our research, we integrate the use of mouse cancer models, cell lines generated from human tumors, small molecule inhibitors and RNAi libraries and CRISPR technology. We have been working on mutant KRAS lung tumorigenesis and on acute promyelocytic leukemia because these cancer types depend on their initiating oncogenes. With our lung cancer research program, we have identified several vulnerabilities of mutant KRAS including a novel RHOA-FAK axis, which is essential for the maintainance of mutant KRAS adenocarcinoma. This work led to a clincial trial to investigate the effectivenes of FAK inhibitors in lung cancer (NCI identifier NCT01951690). In related work, we found mutant KRAS reprograms lipid homeostasis establishing a reliance on fatty acids metabolism and β-oxidation. With our work on the promyelocytic tumor suppressor, we have found that the PIAS1 SUMO E3 ligase is a critical regulator of PML, PML-RARA. As a PI of Project 3 of the University of Texas Lung cancer SPORE, I have long-standing and productive interactions with a network of investigators dedicated to the study of lung cancer. These efforts have led to several fellowships for trainees working in my lab. Thus, I believe I am optimally positioned to contribute to the success for this research proposal.

B. Positions and Honors. List in chronological order previous positions, concluding with your present position.
List any honors. Include present membership on any Federal Government public advisory committee.

Positions

-1993-1998 Research Fellow in Medicine, Massachusetts General Hospital, Boston, MA. Research Advisor: J. Wands, MD.

-1998-2001 Resident in Medicine, Montefiore Medical Center, The University Hospital for the Albert Einstein College of Medicine, Bronx, NY. Program Director: Joan Casey, MD.

-2001- 2005: Fellow in Hematology/Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY. Program Directors: D. Bajorin, MD & M. Heaney, MD.

-2002-2005: Post-Doctoral Fellow, Department of Pathology and Cancer Biology & Genetics Program, Sloan-Kettering Institute, New York, NY. Research Advisor: Pier Paolo Pandolfi, MD, Ph.D.

-2005-2006. Instructor in Medicine, Memorial Sloan-Kettering Cancer, Department of Medicine, Division of Hematologic Oncology, Hematology Service, New York, NY.

-2006-2014. Assistant Professor, Department of Medicine, Division of Hematology/Oncology, UT Southwestern Medical Center. Dallas, TX.

-2014-Present. Associate Professor, Department of Medicine, Division of Hematology/Oncology, UT Southwestern Medical Center. Dallas, TX.

-2015-Present. Co-Leader, Cancer cell Networks program, Simmons Cancer Center, UT Southwestern Medical Center. Dallas, TX.

Honors

1989 Medicina Prize for Italian Researchers younger than 35 years of age; 1991 Terme di Chianciano S.p.a. Fellowship; 2001 Montefiore Medical Center/A. Einstein College of Medicine: Citation in recognition as an outstanding House Officer; 2003 ASCO Young Investigator Award; 2003 CALGB Oncology Fellows Award; 2003 ASH Travel Award; 2004 Michael and Ethel L. Cohen Fellow; 2004 Charles A. Dana Fellow, Clinical Scholars Training Program in Biomedical Research; 2004 Doris Duke Dinner Award; 2004 ASH Travel Award; 2008 Gibbie Award Ryan Gibson Foundation ; 2012 Gibbie Award Ryan Gibson Foundation; 2013 UT Southwestern Friends of the Cancer Center Award; 2014 and 2015 Texas 4000 for Cancer Award.

Peer review Committees

2013-Present AACR Basic Cancer Research Fellowships Scientific Review Committee
2014-Present NCI Study Section J. Ad hoc reviewer

C. Selected peer-reviewed publications, in chronological order (earliest to recent selected from 40 publications listed in Pubmed). List does not include publications submitted or in preparation.

1. R. Bernardi, **P. P. Scaglioni**, S. Bergmann, H.F. Horn, K.H. Vousden and P. P. Pandolfi. PML regulates p53 stability by sequestering Mdm2 to the nucleolus. Nat. Cell. Biol. 2004. 6:665-672. PMID: 15195100.

2. H. Matsushita, **P.P. Scaglioni**, M. Bhaumik, E.M. Rego, L.F. Cai, Hayato Miyachi, A. Kakizuka, W.H. Miller, P.P. Pandolfi. In vivo analysis of the role of aberrant histone deacetylase recruitment and RARalpha blockade in the pathogenesis of acute promyelocytic leukemia. J Exp Med. 2006. 17:821-828. PMID: 16549595.

3. L.C. Trotman, A. Alimonti, **P.P. Scaglioni**, J.A. Koutcher, C. Cordon-Cardo, P.P. Pandolfi. Identification of a tumour suppressor network opposing nuclear Akt function. Nature. 2006. 25:523-527. PMID: 16680151.

4. **P.P Scaglioni**, T. Yung, L. F. Cai, H. Erdjument-Bromage, P. Tempst, J. Teruya-Feldstein, P. P. Pandolfi. A CK2-dependent pathway for PML degradation upon cellular and oncogenic stress. Cell. 2006. 126:269-83. PMID: 16873060.

5. T.H. Shen, H.K. Lin, **P.P. Scaglioni**, T.M. Yung, P.P. Pandolfi. The Mechanisms of PML-Nuclear Body Formation. Mol Cell. 2006. 24:331-9. PMID: 17081985.

6. G. Konstantinidou, E.A. Bey, A. Rabellino, K. Schuster, M.S. Maira, A.F. Gazdar, D. Boothman, **P.P. Scaglioni**. Dual PI3K/mTOR blockade is an effective radiosensitizing strategy for the treatment of non-small cell lung cancer. Cancer Research. 2009. 69:7644-52. PMID: 19789349.

7. J.P. Sullivan, M. Spinola, M. Dodge, M.G. Raso, C. Behrens, B. Gao, K. Schuster, C. Shao, J.E. Larsen, L.A. Sullivan, S. Honorio, Y. Xie, **P.P. Scaglioni**, J.M. DiMaio, A.F. Gazdar, J.W. Shay, I.I. Wistuba, J.D. Minna. Aldehyde dehydrogenase activity selects for Notch signaling dependent non-small cell lung cancer stem cells. Cancer Research. 2010. 70:9937-48. PMID: 21118965.

8. **P.P. Scaglioni***, A. Rabellino, T.M. Yung, R. Bernardi, S. Choi, G. Konstantinidou, C. Nardella, K. Cheng, P.P. Pandolfi*. ***Co-corresponding authors**. Translational-dependent mechanisms lead to PML upregulation and mediate oncogenic K-RAS induced cellular senescence. EMBO Molecular Medicine. 2012. 4:594-602. PMID: 22359342.

9. A. Rabellino, B. Carter, G. Konstantinidou, S.Y. Wu, A. Rimessi, L. A. Byers, J.V. Heymach, Luc Girard, C.M Chiang, J. Teruya-Feldstein and **P. P. Scaglioni**. The SUMO E3-ligase PIAS1 regulates the tumor suppressor PML and its oncogenic counterpart PML-RARA. Cancer Research, 2012. 72:2275-84. PMID: 22406621.

10. G. Konstantinidou, A. Heguy, F. Torti, G. Ramadori, K. Kangasniemi, R.E. Ramirez, Y. Cai, C. Behrens, M.T. Dellinger, I.I. Wistuba, R.A. Brekken, J. Teruya-Feldstein and **P.P. Scaglioni**. RHOA-FAK signaling is required for the maintenance of K-RAS-driven adenocarcinomas. Cancer Discovery, 2013. 3:444-57. Article **featured in World Biomedical Frontiers**.

11. A. Rabellino and **P.P. Scaglioni**. PML degradation: multiple ways to eliminate PML. Front. Oncol. PMID: 2013:3:60. PMID: 23526763.

12. K. Schuster, N. Venkateswaran, A. Rabellino, L. Girard, S. Peña-Llopis and **P.P. Scaglioni**. Loss of the *CDKN2AB* locus promotes mutant *KRAS* lung tumorigenesis. Molecular Cancer Research, 2014 Mar 11. [Epub ahead of print].

PMID: 24618618.

13. G. Ramadori, G. Konstantinidou, N. Venkateswaran, T. Biscotti, L. Morlock, M. Galié, N.S. Williams, M. Luchetti, A. Santinelli, **P.P. Scaglioni***, R. Coppari*. ***Co-corresponding authors**. Diet-induced unresolved ER stress hinders KRAS-driven lung tumorigenesis. Cell Metabolism, 2015. 21:117-25. PMID: 25533479.

14. K.N. Rajagopalan, R.A. Egnatchik, M.A. Calvaruso, A.T. Wasti, M.S. Padanad, L.K. Boroughs, B. Ko, C.T. Hensley, M. Acar, Z. Hu, L. Jiang, J.M. Pascual, **P.P. Scaglioni**, R.J. DeBerardinis. Metabolic plasticity maintains proliferation in pyruvate dehydrogenase deficient cells. Cancer Metabolism, 2015. 3:7. PMID: 26137220.

Research Support.
Ongoing Research Support

CPRIT RP140672 (Scaglioni)   8/31/2014-8/30/2017
Individual Investigator Research Award
Mutant KRAS reprograms lipid metabolism exposing beta-oxidation as a novel therapeutic target in lung cancer lung cancer.
Major goal: with this grant we propose to determine the role of fatty acid beta-oxidation in metabolic reprogramming of mutant KRA sung cancer cells.
Role: PI

Grant # LC110229 (Scaglioni)   9/1/2012-NCE
CDMRP LCRP Investigator-Initiated Research Award
Deconstruction of oncogenic K-RAS signaling reveals focal adhesion kinase as a novel therapeutic target in NSCLC
Major Goal: with this grant we will characterize the role of FAK signaling in mutant K-RAS induced NSCLC tumorigenesis
Role: PI

Grant #13-068-01-TBG (Scaglioni)   1/1/2013-12/31/2016
American Cancer Society Scholar Award
Identification of critical components of the K-RAS network in lung cancer
Major Goal: with this grant we will identify vulnerabilities of mutant K-RAS lung cancer.
Role: PI

5P50 CA70907-15 (Minna)   9/1/1998-4/30/2019
NIH/NCI
University of Texas SPORE (Special Program of Research Excellence) in Lung Cancer
The overall goal is the translation of findings to and from the laboratory and the clinic to result in improvement in the diagnosis, treatment, and prevention of lung cancer. It is a joint effort of UTSW and MDACC.
Role: Co-PI of Project #3 "Preclinical Development and Clinical Testing of MEK and PI3K Targeted Therapy for KRAS-mutant NSCLC as a Method of Radiosensitization and Metastasis Inhibition"

Grant #RP101251 (Mangelsdorf)
Cancer Prevention and Research Institute of Texas (CPRIT)   9/1/2012-8/31/2017
Development of Nuclear Receptor and Coregulator Profiles for Diagnostic and Therapeutic for diagnostic and therapeutic (theragnostic) targeting of breast and lung cancers.
Role: collaborator
Major goal: this grant proposes to determine whether nuclear receptors and nuclear co-receptors can be used as risk stratifiers or therapeutic targets in lung and breast cancers.

Texas 4000 (Scaglioni)   One time gift 2015

Title: From the clinic to the laboratory: a pipeline to identify and target the intracellular metabolic networks that sustain acute leukemia.
Major Goal: this research grant will identify BCR-ABL-dependent metabolic network in acute lymphoblastic leukemia.

Completed Research Support

Texas 4000   One time gift 2014
Exploitation of Fatty Acid b-oxidation as a novel therapeutic target in lung cancer
This research grant will test whether inhibition of fatty acid beta-oxidation is a novel therapeutic strategy in lung cancer.
Role: PI

The Ryan Gibson Foundation   6//1/2012-5/31/2013
Private Foundation
Role of the PIAS1 E3 SUMO ligase in APL
Major Goal: this grant proposes to characterize the role of SUMOylation in promoting APL leukemogenesis and response to arsenic trioxide treatment.
Role: PI

RO1 CA 137195A1   7/1/2009-6/30/2015 (NCE)
NIH/NCI
Characterization and Drug Targeting of the PML Tumor Suppressor in Lung Cancer.
Major Goal: this grant proposes studies to identify the mechanisms that mediate PML tumor suppressive function with an approach that integrates a biochemical and molecular approach with studies in mouse models of lung cancer.
Role: PI