AWARD NUMBER: **W81XWH-16-1-0268**

TITLE: **Targeting Fatty Acid Synthase: A Mechanism-Guided Approach to Develop a Novel Therapeutic Intervention for Drug-Resistant Breast Cancer**

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REPORT DATE: OCTOBER 2020

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2020	ANNUAL	30SEPT2019 - 29SEPT2020

4. TITLE AND SUBTITLE :
Targeting Fatty Acid Synthase: A Mechanism-Guided Approach to Develop a Novel Therapeutic Intervention for Drug-Resistant Breast Cancer

5a. CONTRACT NUMBER
BC151072

5b. GRANT NUMBER
W81XWH-16-1-0268

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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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 NOTE

14. ABSTRACT

Resistance to trastuzumab and HER2-directed therapy remains an unmet clinical need for patients with HER2+ breast cancer, and currently there are no FDA-approved drugs that can reverse resistance to trastuzumab or other HER2-directed therapies. Our preliminary data show that Fatty Acid Synthase (FASN) plays a major role in the maintenance of an aggressive breast cancer phenotype, and that FASN inhibition reduces tumor growth and augments the cytotoxicity of trastuzumab and paclitaxel. In this proposal we will evaluate TVB-2640, a FASN inhibitor that targets cancer metabolism and inhibits breast cancer growth. We will conduct a phase II trial of TVB-2640 in combination with paclitaxel and trastuzumab in patients with metastatic breast cancer who have disease resistant to trastuzumab. We will evaluate the safety and clinical efficacy of TVB-2640, as well as the value of serum and tissue FASN as novel biomarkers of response in HER2+ breast cancer

15. SUBJECT TERMS:
Breast cancer, Trastuzumab, Paclitaxel, HER2, Fatty Acid Synthase (FASN), TVB-3199, Cancer metabolism, Drug resistance, Apoptosis, Biomarkers

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	16	19b. TELEPHONE NUMBER *(include area code)*

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1.**INTRODUCTION:**

The development of HER2-targeted therapies has altered the natural course of HER2+ metastatic breast cancer (MBC) with a more favorable trajectory. The monoclonal HER2-directed antibody, trastuzumab (Trz), in combination with taxane-based chemotherapy such as paclitaxel (PXL) has an established clinical benefit for the treatment of HER2+ MBC. However, resistance inevitably ensues even for those with initial response, and novel approaches to overcome Trz-resistance remain an unmet clinical need. ***No FDA-approved drug that reverse resistance to trastuzumab (Trz) or other HER2-directed therapies* are currently available.**

Our preliminary data show that Fatty Acid Synthase (FASN) plays a major role in the maintenance of an aggressive BC phenotype. FASN inhibition interferes with BC tumor growth and augments the cytotoxicity of Trz and PXL, indicating that its inhibition has a chemo-sensitizing effect in BC. Most importantly, this is also true *in vivo* as FASN inhibition reduces tumor volume and synergizes with Trz in Trz-resistant, HER2+ BC xenograft models. ***Extending upon our prior studies of FASN and its role in tumor progression and response to therapy, we aim to develop novel, rationally-designed therapeutic approaches for BC.***

In this proposal we will evaluate a potentially revolutionary BC therapy, TVB-2640, that targets cancer metabolism and inhibits BC growth in part through induction of cellular apoptosis. Resistance to standard therapies further stimulates BC progression, and our preclinical work suggests TVB-2640 can overcome Trz- and PXL-resistance in HER2+ BC models. ***We will conduct a phase II trial of TVB-2640 in combination with PXL and Trz in patients with breast cancer who have disease resistant to Trz. We will evaluate the clinical efficacy of TVB-2640, as well as the value of serum and tissue FASN as novel biomarkers of response in HER2+ BC.***

2. **KEYWORDS:**

Breast cancer
Trastuzumab
Paclitaxel
HER2
Fatty Acid Synthase (FASN)
TVB-2640
Cancer metabolism
Drug resistance
Clinical Trial
Biomarkers

3. ACCOMPLISHMENTS:

3.1. What were the major goals of the project?

Specific Aim 1: ***To assess the clinical activity of a novel FASN inhibitor, TVB-2640, in combination with paclitaxel and trastuzumab in a phase II clinical trial of patients with HER2+ metastatic breast cancer resistant to taxane and HER2-directed therapy.***

Specific Aim 2: ***To examine the clinical value of serum and tissue FASN expression as a novel theranostic marker in HER2+ breast cancer.***

Aim 1 and 2 are under the direction of Dr. Tufia Haddad. Please see separate annual progress report for details related to Specific Aims 1 & 2.

Specific Aim 3: ***To determine the mechanistic link between FASN inhibition-induced Bcl-2 pro-apoptotic BH3-only proteins and develop preclinical models in PDX mice based on targeting FASN and Bcl-2.***

- **Major Task 8: Mechanism of apoptotic synergy between FASN inhibition and PXL**
  Milestone in progress: Study mostly completed and reported

- **Major Task 9: Linking FASN inhibition to increased ROS production**
  Milestone in progress: Completed

- **Major Task 10: Preclinical assessment of the FASN inhibitor TVB-3166 (the form of TVB-2640 for animal use) in combination with ABT263**
  Milestone in progress: Study is partially completed.

3.2: What accomplished under these goals?

- **Major Task 8: Mechanism of apoptotic synergy between FASN inhibition and PXL**

Subtask 1:

- Determine which of the BH3-only proteins is regulated by modulation of PXL and FASN
- Overexpress BH3-only proteins determine whether the synergistic effect is reversed
- Downregulate the gene of interest causes sensitization to TVB and PXL.

- **Major Task 9: Linking FASN inhibition to increased ROS production**

Subtask 1: Tumor biospecimens stained, scored and interpreted

- Determine the effect of FASN inhibition on lipid composition of the mitochondrial
- Membrane (In different models of FASN expression in breast cancer)
- Determine the effect of FASN inhibition on oxidative stress and redox unbalance (In different models of FASN expression in breast cancer)

- **Major Task 10: Preclinical assessment of the FASN inhibitor TVB-3166 (the form of TVB-2640 for animal use) in combination with ABT263**
  - The recently completed BEAUTY clinical trial (Change strategy)
  - Patient-derived xenografts (PDX) from the Metastatic Registry (Change registry to a commercially available)

REPRESENTATIVE RESULTS:

➢ **Major Task 8: Mechanism of apoptotic synergy between FASN inhibition and PXL**

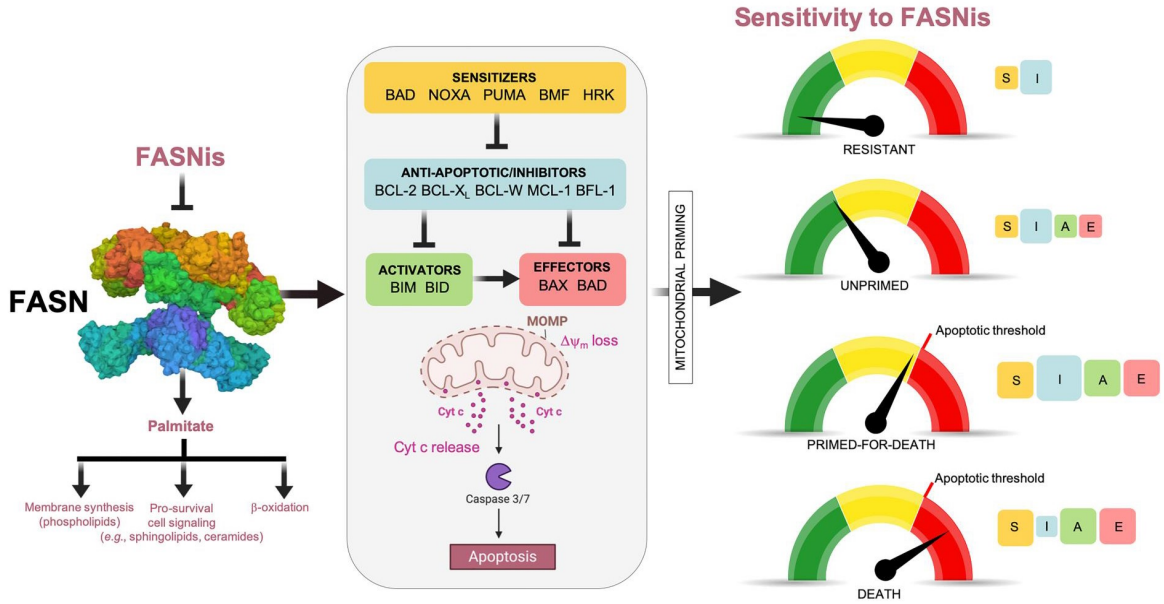
Subtask 1:

- Determine which of the BH3-only proteins is regulated by modulation of PXL and FASN
- Overexpress BH3-only proteins determine whether the synergistic effect is reversed
- Downregulate the gene of interest causes sensitization to TVB and PXL.

Milestone Achieved: Understanding how FASN inhibition promotes taxane sensitivity. Report final studies and publish results

A highly complex rewiring of metabolic pathways orchestrated to meet or even exceed the increased metabolic demands of cancer cells [1-4]. Elevated *de novo* fatty acid biogenesis driven by the overexpressionand hyperactivation of several lipogenic enzymes is one of the most common cancer-associated metabolic traits that provide proliferative and survival advantages to tumors [5-7]. Fatty acid synthase (FASN) is a key enzyme in the endogenous lipogenesis pathway that primarily catalyzes the synthesis of the long-chain saturated fatty acid palmitate from acetyl-CoA and malonyl-CoA, using NADPH as a reducing agent [8,9]. FASN activation is an early and near universal hallmark of most human carcinomas and their precursor lesions, and is enhanced in a stage-dependent manner that associates with worsened patient survival and therapeutic resistance in several cancer types. Cancer cells utilize FASN endogenously-produced free fatty acids for phospholipid synthesis of new membranes, for pro-survival signaling molecules (e.g., sphingolipids) and for obtaining energy via β-oxidation [8-11] (**Fig. 1**). Interest in FASN as a target for therapeutic intervention stemmed from findings more a decade ago that tumor cells addicted to FASN-driven lipid signaling show significantly reduced growth and viability upon FASN inhibition [reviewed in 8,9,11-14]. Since then, however, we have been unable to resolve the apparent discrepancy between the basic science-discovery *bench* aspects of FASN blockade and the awaited *bedside* effects of clinical-grade FASN inhibitors (FASNis).

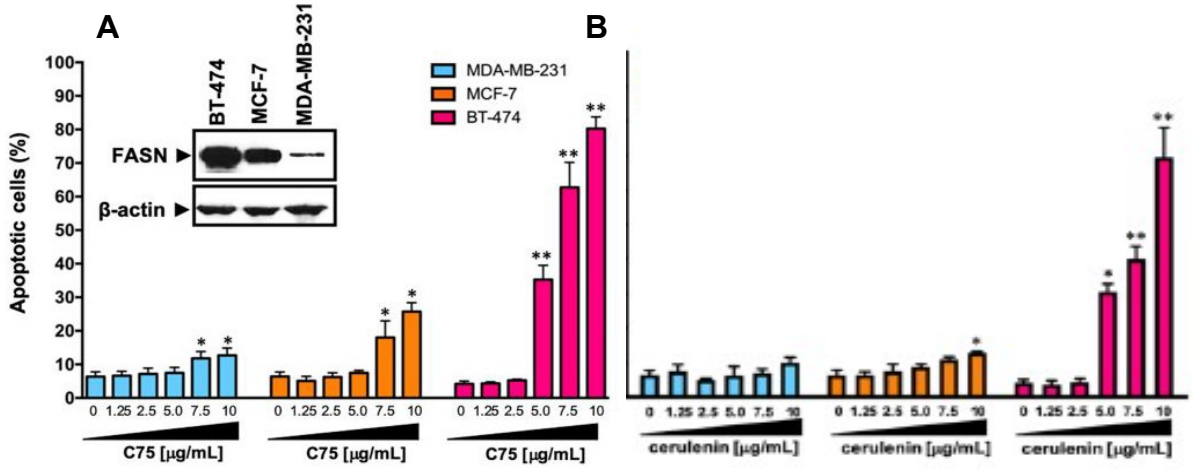
Figure 1: Proposed Uncovered linked of the so-called "mitochondrial priming" that links the redox-buffering mechanism of FASN activity to the intrinsic apoptotic threshold in breast cancer cells



The extent of FASN inhibition-induced apoptotic cell death relates to FASN expression status. Just as a recollection of our previous results.

We examined apoptotic cell death using the semi-synthetic FASNi C75 in three breast cancer cellular models expressing distinct levels of FASN: BT-474 (high expressor of FASN), MCF-7 (moderate expressor of FASN), and MDA-MB-231 (low expressor of FASN) (**Fig. 2A**, *inset*; 26,27). Apoptosis was monitored by flow cytometry after staining with annexin V, which binds phosphatidylserine that is exposed during apoptosis [28]. FASN inhibition significantly and dose-dependently increased the number of annexin V-positive BT-474 cells relative to vehicle-treated control cells (**Fig. 2A**). A smaller but still significant increase in annexin V-positive cells was observed in C75-treated MCF-7 cells, whereas MDA-MB-231 cells remained annexin V-negative following C75 treatment. Equivalent findings were identified when we used graded concentrations of the natural FASN inhibitor cerulenin (**Fig. 2B**).

Figure 2A-B: The extent of FASN inhibition-induced apoptotic cell death relates to FASN expression status



These results show that the extent of apoptosis in response to FASN inhibition reflects the baseline level of FASN expression, suggesting an augmented dependency of cancer cell survival on FASN activity.

- **Major Task 9: Linking FASN inhibition to increased ROS production**

Subtask 1: Tumor biospecimens stained, scored and interpreted

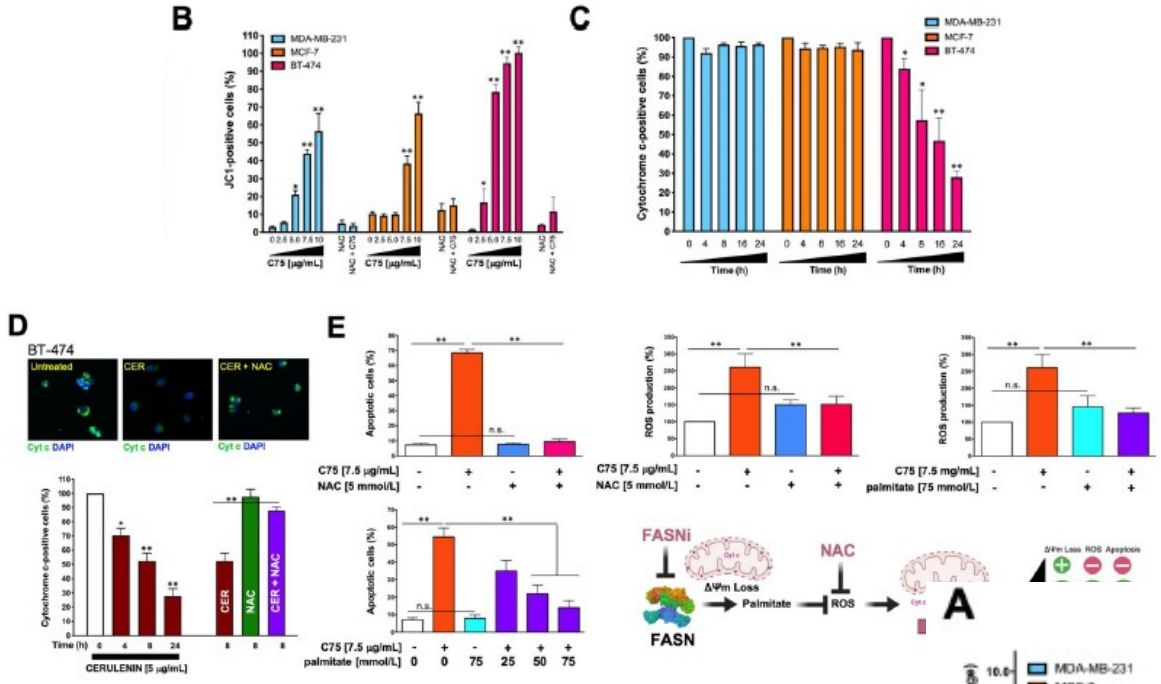
- Determine the effect of FASN inhibition on lipid composition of the mitochondrial
- Membrane (In different models of FASN expression in breast cancer)
- Determine the effect of FASN inhibition on oxidative stress and redox unbalance (In different models of FASN expression in breast cancer)

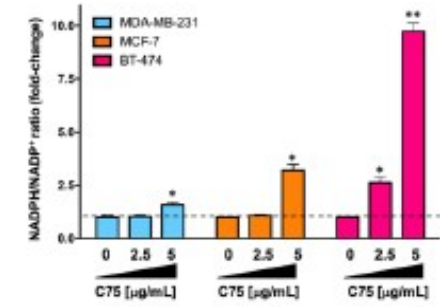
Milestone Achieved: Understanding the effect of FASN inhibition on cell stress in different breast cancer models. Report final studies and publish results

A time-dependent release of cytochrome c was observed only in FASNis-treated BT-474 cells and not in MCF-7 and MDA-MB-231 cells, as measured by flow cytometry (**Fig. 2C,D**). Co-treatment with NAC treatment blocked the ability of the FASNi to induce apoptotic cell death (**Fig. 2E**), and prevented both C75-induced ROS production and cytochrome c release in FASNis-sensitive cancer cells (**Fig. 2D**,**E**). To question whether inhibition of FASN-driven endogenous fatty acid biogenesis was a key driver of ROS production and subsequent apoptosis in response to FASN inhibitors, we performed rescue experiments using the FASN end-product palmitate. Co-treatment with palmitate largely prevented C75-induced ROS production and effectively protected BT-474 cells from apoptosis in a dose-dependent manner (**Fig. 2E**).

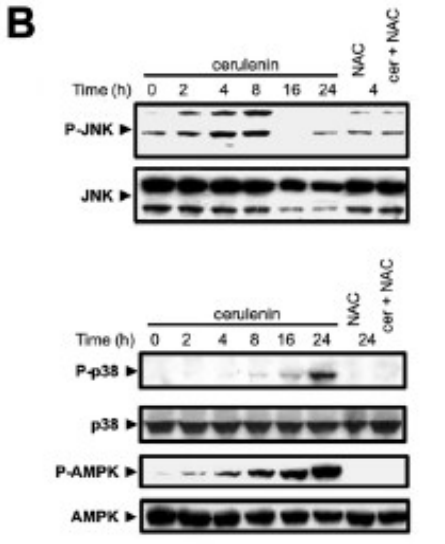
Mitochondrial depolarization appears to be a common response to FASN inhibition irrespective of the levels of FASN expression. FASNi-driven decrease in Δψm levels appears to have to reach a certain threshold to elicit the release of mitochondrial cytochrome c accompanying apoptotic cell death, which is restricted to FASNi-sensitive cancer cells in an apparently ROS-dependent manner (**Fig. 2E**).

Figure 2(B-E): The extent of FASN inhibition-induced apoptotic cell death relates to FASN expression status





FASN inhibition activates redox-sensing kinases. As ROS production commonly results from redox stress, and considering that redox-associated NADPH is consumed rapidly by FASN [24], we examined the effects of FASN inhibition on NADPH accumulation. We found a dramatic, dose-dependent accumulation of NADPH in BT-474 cells treated with C75 (**Fig. 3A**). At the highest concentration used, C75 promoted a more modest, but significant, increase in the NADPH/NADP+ ratio in both MCF-7 and MDA-MB-231 cells (**Fig. 3A**).

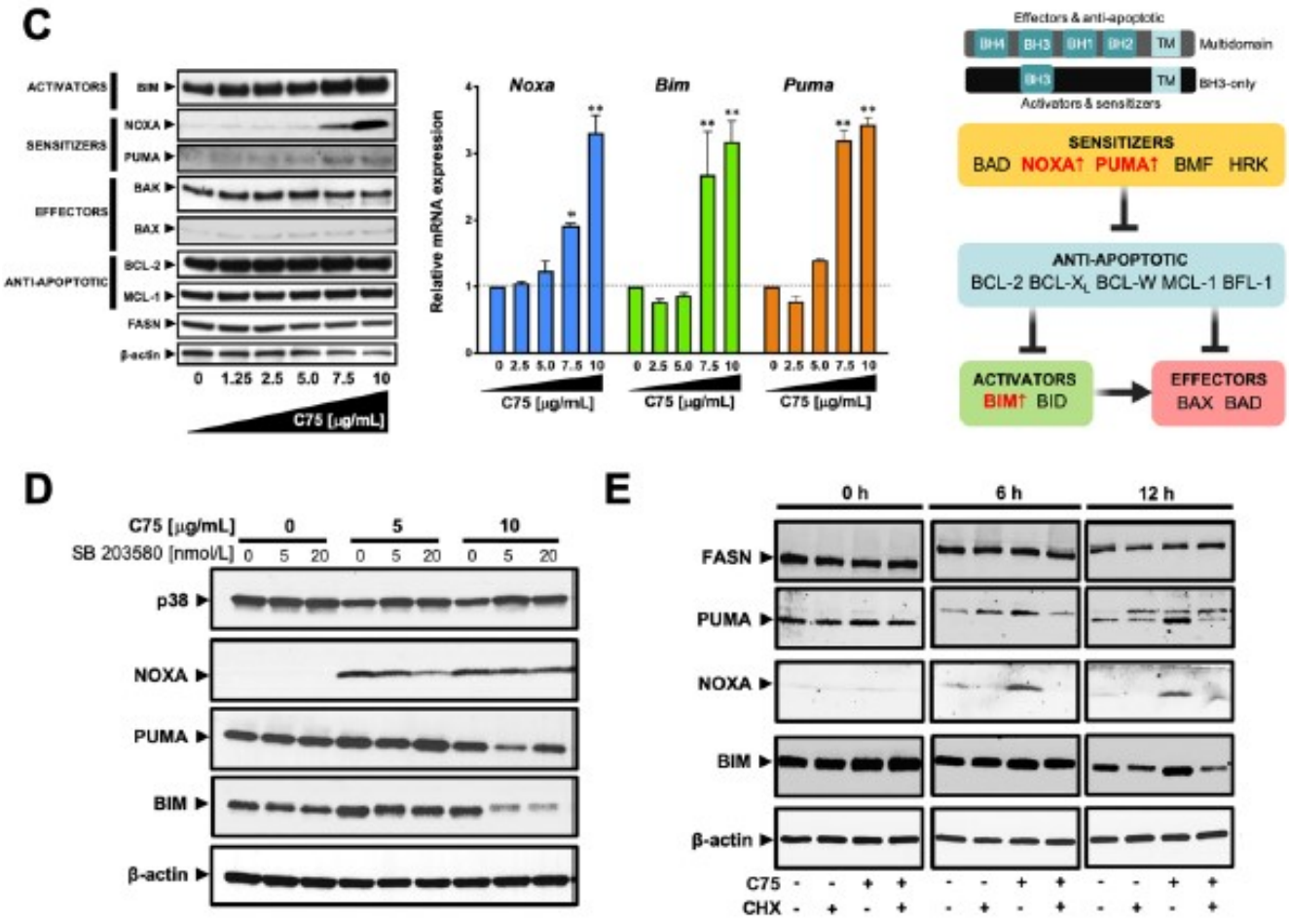


Redox imbalance causes the activation of stress-related proapoptotic kinases such as Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK) [35,36]. We thus evaluated the effects of FASN inhibition on the activation of the two kinases. FASN blockade activated both kinases in BT-474 cells, but this was markedly attenuated in cells co-treated with NAC (**Fig. 3B**). FASN inhibition also strongly activated AMP-activated protein kinase (AMPK), a key regulator of metabolism and survival during energy stress that also senses intracellular redox signals [37], and this was also prevented by co-treatment with NAC (**Fig. 3B**).

These findings suggest that FASN activity in FASNi-sensitive cells is linked to cytoprotection via the control of the NADPH/NADP$^+$ balance, ROS production, and activation of redox-sensing kinases.

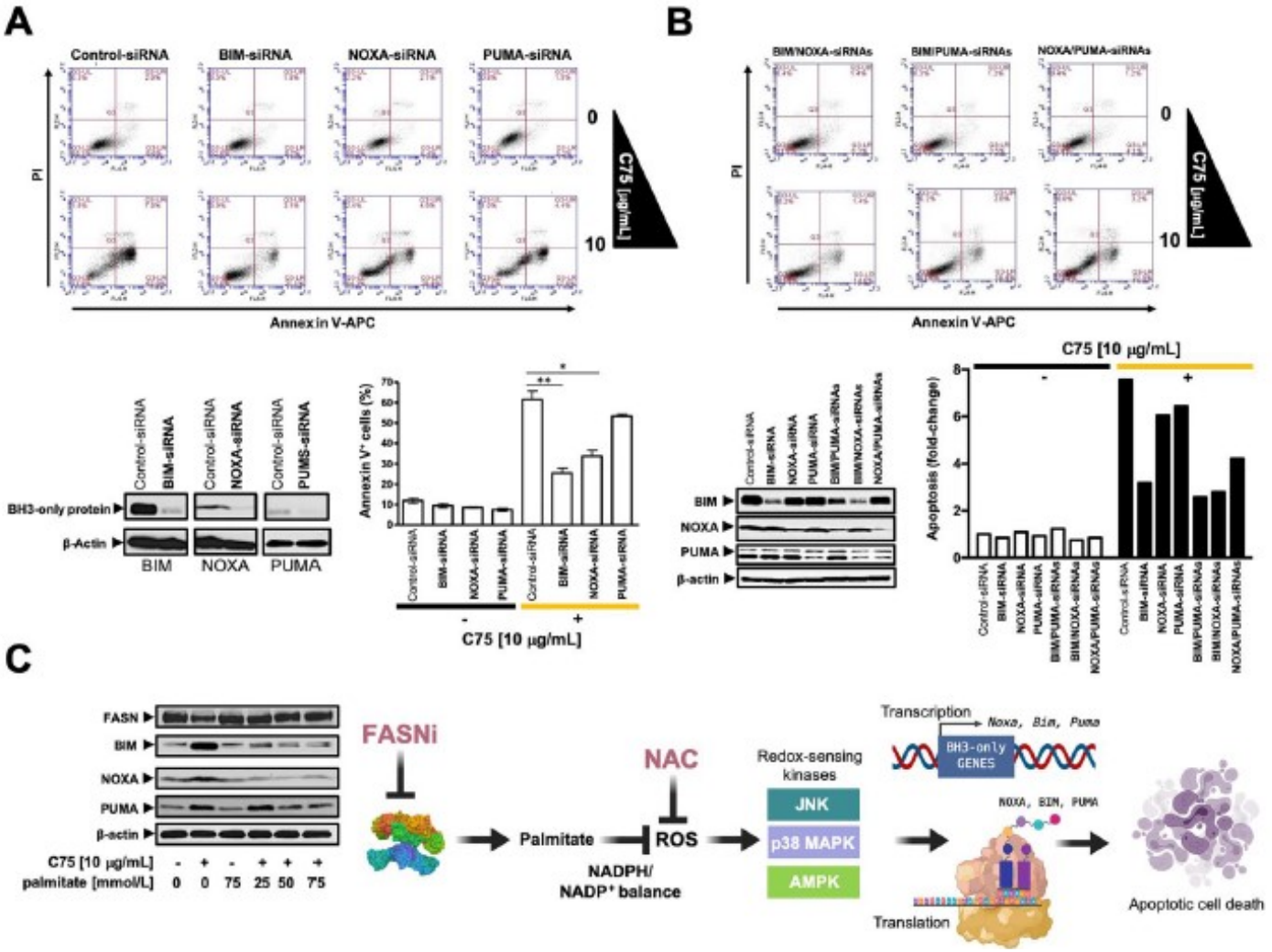
- **Major Task 10: Preclinical assessment of the FASN inhibitor TVB-3166 (the form of TVB-2640 for animal use) in combination with ABT263**
  - The recently completed BEAUTY clinical trial (Change strategy)
  - Data interpretation: see bellow

FASN inhibition up-regulates pro-death BH3-only proteins. To explore the molecular mechanisms underlying the apoptotic cell death induced by FASN inhibition, we examined the impact of FASN blockade on the death decision circuitry controlled by the BCL-2 family (**Fig. 1**). Expression of the multidomain anti-apoptotic proteins BCL-2 and MCL-1 remained unchanged following pharmacological inhibition of FASN activity (**Fig. 3C**). However, C75 treatment resulted in a robust dose-dependent up-regulation of the BH3-only BCL2 family members BIM, NOXA, and PUMA at both mRNA and protein levels (**Fig. 3C**). Inhibition of p38 MAPK activity with SB203580 lessened the ability of C75 to up-regulate BIM, NOXA, and PUMA (**Fig. 3D**), indicating that ROS-driven activation of stress-induced kinases is linked to the induction of BH3-only proteins in FASN-inhibited breast cancer cells. To investigate whether FASN inhibition regulated the stability of BH3-only proteins, we analyzed BIM, NOXA, and PUMA abundance in cells treated with cycloheximide (protein synthesis inhibitor). Of note, cycloheximide blocked the activation of BH3-only proteins in C75-treated cells (**Fig. 3E**), suggesting that their accumulation after FASN inhibition requires *de novo* protein synthesis.



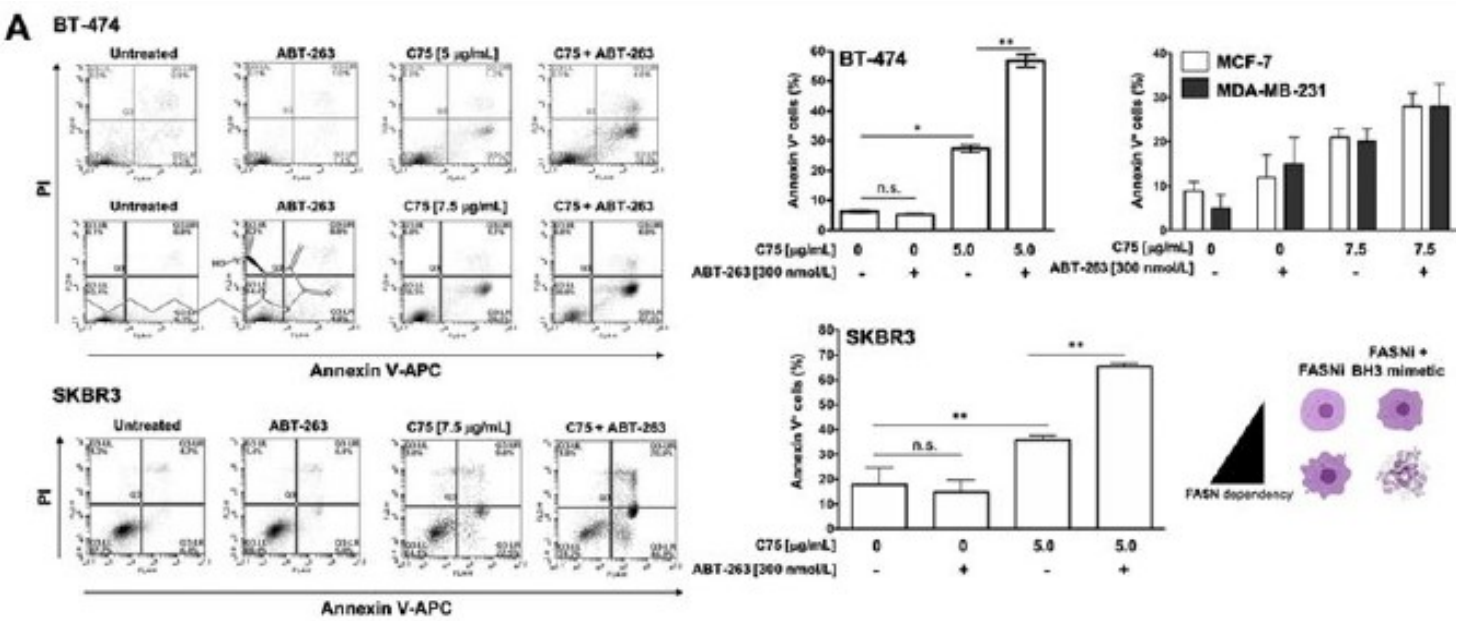
To assess the potential role of BIM, NOXA, and PUMA in FASN inhibition-induced apoptosis, we silenced their expression in BT-474 cells. All tested siRNAs robustly decreased the protein abundance of their targets. siRNA-mediated knockdown of BIM or NOXA significantly reduced (up to 60 and 40% reduction, respectively) apoptotic cell death, as measured by annexin V staining (**Fig. 4A**).

By contrast, siRNA-mediated depletion of PUMA had little effect on C75-induced apoptosis. When the siRNAs against BH3-only proteins were combined, those combinations containing the BIM-targeted siRNA were the most effective in preventing C75-induced apoptotic cell death (**Fig. 4B**). Finally, exogenous supplementation of cells with palmitate rescued the down-regulation of FASN expression and the up-regulation of BIM, NOXA, and PUMA in response to C75 (**Fig. 4C**). ***These findings underscore the inverse relationship between the status of FASN activity/expression and that of BH3-only proteins in breast cancer cells.***

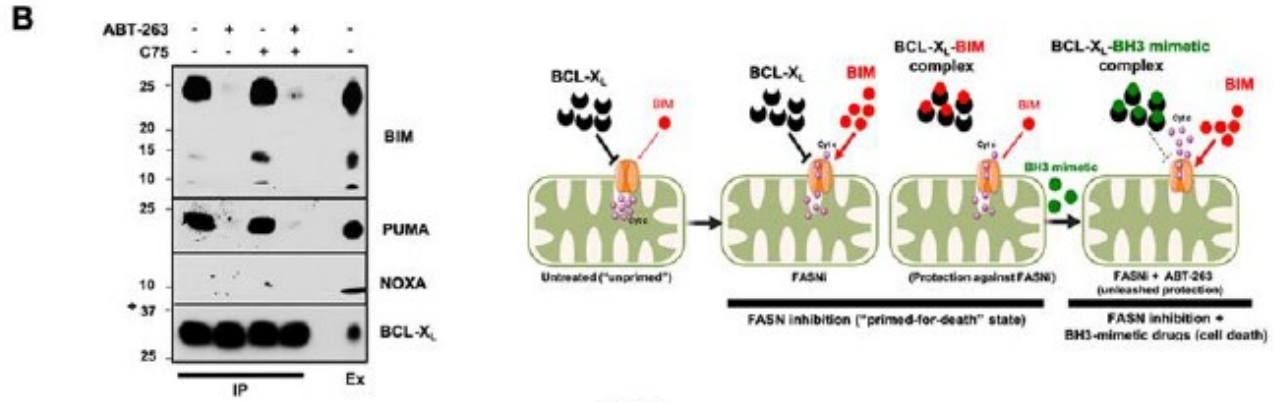


FASN inhibition enhances sensitivity to BH3 mimetic-induced apoptosis. The finding that apoptotic cell death induced by FASN inhibition was markedly diminished by the concurrent loss of the pro-apoptotic protein BIM suggests that FASN activity regulates cancer cell survival by fine-tuning the BIM-dependent mitochondrial threshold for apoptosis, known as “mitochondrial priming” [38-48]. To test this hypothesis, we questioned whether FASN-inhibited cells showed increased sensitivity to BH3 mimetic drugs such as navitoclax (ABT-263), a potent and clinically available antagonist of BCL-2, BCL-X_L and BCL-w [49,50]. Standard viability assays (MTT reduction) revealed that the combination C75 and navitoclax synergized to reduce the viability of BT-474 cells (data not shown). We then analyzed the proportion of annexin V-positive apoptotic cells in BT-474 cultures treated with navitoclax in the absence or presence of graded concentrations of C75 (**Fig. 5A**). Whereas single-agent navitoclax failed to trigger apoptotic cell death, addition of C75 synergized with navitoclax (**Fig. 5A**). This ability involved a synergistic amplification of ROS generation The apoptosis-resistant phenotype of MCF-7 and MDA-MB-231 treated with navitoclax remained unaltered by the addition of C75 (**Fig. 5A**), indicating that C75 needs to alter pro-apoptotic BH3-only family members in order to enhance navitoclax sensitivity. To further confirm the FASN-dependent nature of the synergistic interaction between FASN inhibitors and BH3 mimetics, we employed SKBR-3 cells, which express the highest cellular levels of FASN

(up to 28% by weight of the cytosolic proteins) yet described in human established cell lines [26,27,51,52]. While ABT263 had no impact on these cells by itself, synergism was observed too when C75 was added to ABT263 (**Fig. 5A**).

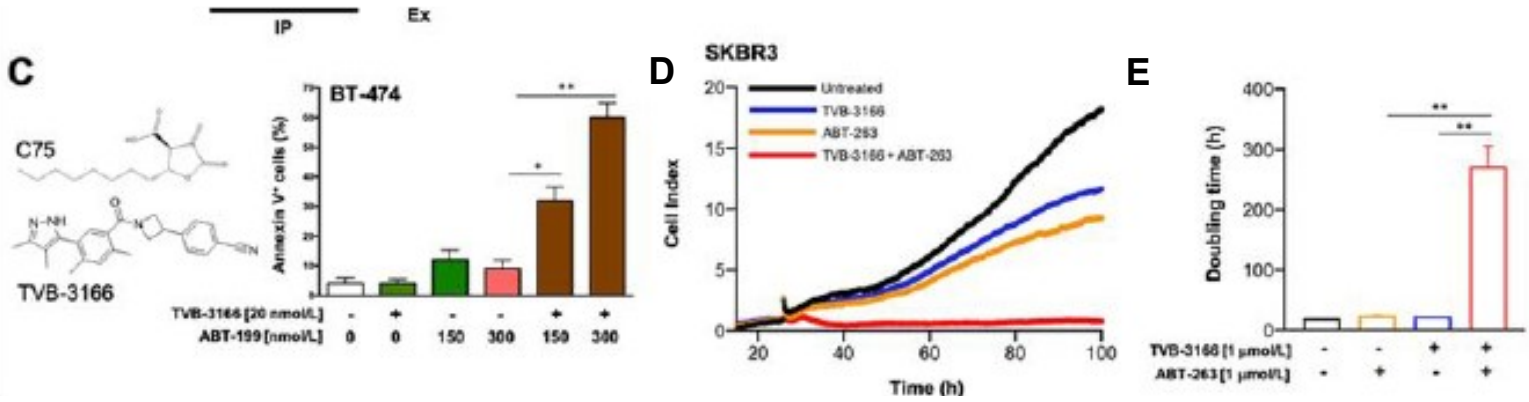


We next immunoprecipitated BCL-x_L and assessed how the FASNi C75 impacted the ability of BCL-x_L to bind PUMA, NOXA, and BIM in the absence or presence of navitoclax. Immunoblotting revealed that binding of BIM_L and BIM_S to BCL-x_L was increased in FASN-inhibited BT-474 cells (**Fig. 5B**, *left*). The addition of navitoclax markedly decreased the binding of BCL-x_L to BIM_L/BIM_S despite the noteworthy up-regulation of the total levels of BIM in FASN-inhibited cells (**Fig. 5B**, *left*). These findings suggest that FASN inhibition heightens mitochondrial priming, shifting cells towards a primed-for-death state that is addicted to the anti-apoptotic protein BCL-X_L to sequester BIM and ensure survival. Counteracting the binding of BIM to BCL-X_L with BH3-mimetics abolished this protected state by freeing BIM, leading to increased apoptosis in FASN-inhibited cells (**Fig. 5B**, *right*).



To substantiate the potential clinical relevance of BH3 mimetics to enhance apoptosis sensitivity upon FASN inhibition-heightened mitochondrial priming, we explored the nature of the interaction between the recently developed small-molecule FASN inhibitor TVB-3166 [12] and venetoclax (ABT-199), an FDA-approved BH3 mimetic that circumvents the adverse effect of navitoclax on platelets by specifically targeting BCL-2 rather than multiple BCL proteins [53-55]. Whereas single-agent venetoclax failed to induce any significant level of apoptotic cell death, addition of TVB-3166 dramatically enhanced (up to 4-fold) the capacity of ABT-199 to promote apoptotic cell death in BT-474 cells (**Fig. 5C**, *left*). We finally employed the impedance-based RTCA platform (xCELLigence), a label-free environment for cancer cells that accurately informs on the characteristics

of the response to treatment without the use of toxic/end-point assays leading to the termination of the experiments [56,57]. Using this platform, we captured real-time kinetic data on cell growth after treatment of SKBR-3 cells with TVB-3166, ABT-263/navitoclax, or their combination (**Fig. 5C**, *right*) and calculated cell proliferation rates and doubling times as the slope of the growth curve of best fit from cell index recording between the 24 and 100 hour-interval. A highly significant, supra-additive increase in cell doubling time observed in SKBR-3 cells simultaneously exposed to TVB-3166 and ABT-263/navitoclax (**Fig. 5D**, *right*).



These findings show that targeted apoptosis with FASN inhibitors and BH3 mimetic drugs might be a promising therapeutic strategy for the treatment of FASN-addicted breast cancer cells.

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

Nothing to report

How were the results disseminated to communities of interest?

Nothing to report

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

- **Major Task 8: Mechanism of apoptotic synergy between FASN inhibition and PXL**
  - Downregulate the gene of interest causes sensitization to TVB and PXL. (continue)
- **Major Task 10: Preclinical assessment of the FASN inhibitor TVB-3166 (the form of TVB-2640 for animal use) in combination with ABT263**
  - Continues preclinical studies *in vivo* studies to assess TVB3166+ ABT199 and TVB3166+ ABT263
  - Histopathological assessment of Tumor derived from the *in vivo* studies

4. **IMPACT:**

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

Nothing to report at this time

- **What was the impact on other disciplines?**

Nothing to report at this time

- **What was the impact on technology transfer?**

Nothing to report at this time

- **What was the impact on society beyond science and technology?**

Nothing to report at this time

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

Nothing to report at this time

- **Actual or anticipated problems or delays and actions/plans to resolve them**

Tasks related to tissue and serum specimens will be delayed due to delay in the clinical trial (Explained in Dr. Tufia Haddad's progress report)

- **Changes that had a significant impact on expenditures**

Nothing to report at this time

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

  Nothing to report
  - **Significant changes in use or care of vertebrate animals**

  Nothing to report
  - **Significant changes in use of biohazards and/or select agents**

  Nothing to report

5. **PRODUCTS:**

Publications, conference papers, and presentations

Abstract submitted and ACCEPTED to the Annual conference of the American Association for Cancer Research (April 2019) Fatty Acid Synthase: A Therapeutic Target: Travis Van der Steen, George Kemble, and Ruth Lupu

Journal publications

Manuscripts Published

1) Papadimitropoulou A, Vellon L, Atlas E, Steen TV, Cuyàs E, Verdura S, Espinoza I, Menendez JA, **Lupu R.** Heregulin Drives Endocrine Resistance by Altering IL-8 Expression in ER-Positive Breast Cancer. Int J Mol Sci. 2020 Oct 19;21(20):7737. doi: 10.3390/ijms21207737.
2) Menendez JA, Mehmi I, Papadimitropoulou A, Vander Steen T, Cuyàs E, Verdura S, Espinoza I, Vellon L, Atlas E, **Lupu R.** Fatty Acid Synthase Is a Key Enabler for Endocrine Resistance in Heregulin-Overexpressing Luminal B-Like Breast Cancer. Int J Mol Sci. 2020 Oct 16;21(20):7661. doi: 10.3390/ijms21207661

Manuscripts accepted for Publication

1) Menendez JA, Peirce, KS, Papadimitropoulou A, Cuyàs E, Verdura S, Steen TV, Vellon L, Chen, WY, **Lupu R.** Progesterone receptor isoform-dependent cross-talk between prolactin and fatty acid synthase in breast cancer. Aging, Accepted for publication, November 2020.

Manuscripts submitted for Publication

1) Espinoza I, Vander Steen T, Schroeder B, Cuyàs E, Kurapaty Venkatapoorna CM, X. Wei Meng, Schneider PA, Regan K, Flatten KS, Verdura S, Kaufmann SH, Menendez, JA, **Lupu R.** Fatty acid synthase regulates the mitochondrial primed-for-death state in breast cancer cells. Submitted to: Cell Dead and Differentiation.

Books or other non-periodical, one-time publications

Nothing to report

Other publications, conference papers, and presentations

Nothing to report

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Ruth Lupu*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	0000-0001-8226-3581
Nearest person month worked:	1.8
Contribution to Project:	Authored the Translational research and contributed all the preliminary data for the research proposal except the clinical trial data. Led training and logistics review for the laboratory study personnel; facilitated contract completion with 3V Biosciences; active oversight the research and the collaborative studies
Funding Support:	

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

No Change

What other organizations were involved as partners?

We continue collaboration with 3V-Biosciences, Inc. (Renamed SAGIMET Inc.)

Organization Name: SAGIMET, Inc.
Location of Organization: 3715 Haven Ave. Suite 220, Menlo Park, CA 94025

Partner's contribution to the project: 3V Biosciences is providing the investigational agent, TVB-2640, and the company will oversee serum FASN and tissue pAKT and pS6 correlative studies

Financial support: Financial support from 3V Biosciences is not provided to Mayo Clinic, Dr. Haddad, or the clinical trial participant's
In-kind support:

Facilities:
Not applicable
Collaboration: Scientists from 3V Biosciences will

- Review study safety data and assist with safety monitoring
- Participate in data interpretation, as appropriate

Personnel exchanges:
Not applicable

Other:
Not applicable

Pending

Department of Defense Breast Cancer Research Program Expansion Award
W81XWH-20-BCRP-EA: Expansion to the current award
Title: "Targeting Fatty Acid Synthase Intervention for Endocrine Resistant
Funding Period: 09-31-20121– 08-31-2024
HER2 positive Breast Cancer"

P50 CA102701: To be submitted January 2021
Mayo Clinic SPORE in Pancreatic Cancer
National Cancer Institute.

Title: “Targeting Fatty Acid Synthase: A Mechanism-Guided Approach to Target Pancreatic Adenocarcinoma and the Tumor Microenvironment”

Funding Period: 09/1/2021 – 08/ 31/2026

Overall PI: Billadeau D.

Role: PI- Project # 2

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS;

Dr. Ruth Lupu, PhD. Principal Investigator (PI)

Dr. Haddad is the Partnering PI.

QUAD CHARTS:

Nothing to report

APPENDICES:

No Appendices