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**

PRINCIPAL INVESTIGATOR: **Ruth Lupu, PhD**

CONTRACTING ORGANIZATION: Mayo Clinic, Rochester, MN 55905

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Ruth Lupu, PhD , PI
E-Mail: Lupu.ruth@mayo.edu

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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.

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

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1.**INTRODUCTION:**

The clinical and translational research associated with this Award was significantly impacted by the COVID-19 pandemic, specifically to the expected timeline to achieve clinical trial accrual goals. As has been previously detailed in quarterly and annual progress reports: On March 22, 2020, in response to the COVID-19 pandemic and the executive 'stay at home' order, new patient enrollment to all Mayo Clinic clinical trials (at all sites), was suspended. These orders subsequently expired on variable dates at all Mayo sites (MN, FL and AZ) in May/June 2020. On May 27, 2020, the Mayo Clinic Dean of Research facilitated communication that all trials may resume enrollment and research-related procedures. While patient volumes returned to normal in Q4 of Period 4, some patients expressed concerns with trial participation due to the need for nearly all care and treatment to be administered at a Mayo Clinic site. This persisted in Period 5 (October 2020 – September 2021) as regional COVID-19 surges occurred throughout the year, most notably in Florida (Q3-4) and the Midwest (Q4). The pandemic and trial logistics (frequent visits and travel) was cited as the most common reason for patients declining study participation in Period 5 (5 of 13 screen failures). This has persisted into the current no cost extension year (beginning October 1, 2021 – to date) with the Delta and subsequent Omicron variant surges. The latter also significantly impacted clinical care team staffing with downstream effects of reduced patient access/appointments. As of March 7, 2022, these issues have resolved across all Mayo Clinic sites; however, the public health emergency remains in place.

Concurrent with challenges and delays to patient recruitment and accrual goals in the past 2 years, 4 new therapies for HER2+ metastatic breast cancer were FDA-approved. This also impacted trial participation and referrals to Mayo Clinic for clinical trials as new standard treatment options became available. In response to these practice changes, and based on emerging research from Dr. Lupu's laboratory, study amendment #4 was prepared and implemented June 9, 2021. This established a new cohort of patients with ER+/HER2+ metastatic breast cancer and trastuzumab/endocrine therapy resistance who may be eligible to receive treatment with TVB-2640 in combination with trastuzumab and endocrine therapy (Cohort B). The initial two cohorts were combined into one (Cohort A). No change in the study analysis design or statistical plan was required. Similarly, no changes to the grant aims, procedures, or budget were required.

2. **KEYWORDS:**

Breast cancer
Trastuzumab
Paclitaxel
HER2
Fatty Acid Synthase (FASN)
TVB-2640
Cancer metabolism
Drug resistance
Clinical Trial
Biomarkers
Venetoclax (ABT-199)
Nnavitoclax (ABT-263).

3. ACCOMPLISHMENTS:

3.1. What were the major goals of the project?

The aims of the project based on the COVID-19 relief information for Award: W81XWH-16-1-0269/BC151072P1.

Specific Aim 2: To examine the clinical value of serum and tissue FASN expression as a novel theranostic marker in HER2+ breast cancer. The same correlative studies will be performed for the Endocrine-Resistant metastatic patients.

Major Task 6-7: Correlative Studies and Analysis:

Subtask 1: Tumor biospecimens stained, scored and interpreted: Blood and Tumor Biospecimen Collection from Participants of the Phase II Clinical Trial Evaluating TVB-2640 in Combination with PXL and TRZ (current anti-HER2 drugs will be considered) in Patients with HER2+ MBC Resistant to Taxanes and HER2-directed Therapy: The correlative study objectives associated with the trial described in Section D.2.1 are to:

- Assess changes in tumor expression of FASN , phospho-AKT, phospho-S6 (pS6) and HER2 (performed by the Pathology Research Core) after first cycle of treatment and their association with clinical outcome.
- Determine the percentage of apoptotic cells and its association with FASN expression and clinical outcome; and
- Assess the changes in serum FASN (performed in Dr. Lupu's Laboratory) and malonyl carnitine (performed by the Pathology Research Core) after the first cycle of treatment and their association with clinical outcome.

Mandatory blood and tumor biopsies will be collected prospectively for research purposes from all trial patients at two time points: baseline pre-treatment and after completion of the first cycle of therapy. All biospecimens collected will undergo on-site initial processing and then be sent to the Mayo Clinic Cancer Center, Pathology Research Core for final processing, preparation for analysis and staining.

- Statistical Analysis: All patients will undergo a blood draw and tumor biopsy during pre-registration period and at the completion of one cycle of treatment. Analyses will be performed for each patient cohort separately. The primary endpoint of interest for these analyses is the clinical benefit at 6 months which will be defined as remaining on study treatment and progression-free at least through 6 cycles of treatment. To assess whether clinical benefit rate at 6 months differs with respect to FASN or HER2 expression after one cycle of treatment, a 95% confidence binomial interval for the difference in the 6-month clinical benefit rate among those whose expression level is 0-2+ after one cycle of treatment and those whose expression level is 2+ or 3+ will be constructed. A Wilcoxon rank sum test will assess if the percent change after one cycle of treatment in pAKT H Score, pS6 H score, in serum FASN levels or in serum malonyl carnitine levels differs among those who remained on study treatment and progression-free at least through 6 cycles of treatment and those who did not. Spearman rank correlation coefficients will be used to assess the relationship between percentage of apoptotic cells and FASN expression after one cycle of treatment. Statistical support will be provided by study biostatistician.

Specific Aim 3: 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 3: Assessment of the efficacy of the combination of FASNi with Navitoclax in PDX derived from tumors derived from patients enrolled in the BEAUTY clinical trial.

Subtask C: The BEAUTY clinical trial: ***A unique approach to identifying individualized therapies:*** The BEAUTY trial combined multiple scientific approaches to evaluate treatment for aggressive breast cancer. Tumor biopsies from 140 patients with aggressive breast cancer were collected before patients were treated with chemotherapy. Preclinical assessment of the FASN inhibitor TVB-3166 or TVB-3664 (FASNi analogues of the clinical FASNi-TVB-2640) in combination with ABT-263 in patient-derived tumor xenografts (PDX). The PDX's, are mice in which a sample of a patient's tumor is injected into a mouse, resulting in a biological model duplicating the patient's tumor.

We hypothesize that inhibition of FASN re-sensitizes breast cancer to the Bcl-2 pro-apoptotic pathway to induce cell death, and that dual blockade of FASN using TVB-3166 or TVB-3664) in combination with Navitoclax (ABT-263) would result in a synergistic anti-tumor effect. ABT-263 synergistically induce anchorage independent growth and apoptosis of FASN expressing BC cells. We have also shown to inhibition of FASN sensitizes tumors to anti-HER2 therapies. Thus, we will design studies to resensitize tumor to Trastuzumab (Trz). To do so, we will use NSG mice and introduce a very small portion of the patient tumor directly, generating a PDX. The NSG mice engrafted with viable tumor from consenting patients will "mimic" the tumor growth in the patient. Thus, will recapitulate the individuality of human cancers and allow better prediction of response to therapy. Thus, this approach-directed therapy is projected to guide treatment selection, improve treatment response rates, and minimize delivery of non-effective agents to patients. Since we are working on the premise that inhibition of FASN chemosensitises tumors to chemotherapeutic and biological drugs, we will test at this point any advanced BC molecular –subtype, post chemotherapy.

The BEAUTY clinical trial: For an immediate start, we have been granted access to 12 PDX models of HER2+ tumors (10 PDX mice that are Trz/taxane-sensitive and 2 PDX mice that are Trz/taxane-resistant) through the recently completed BEAUTY clinical trial. *For all the studies we will need to supplement mice with estradiol and/or Tamoxifen and the combination of both.* Additional Avatar models of the HER2+ subtype are available through the BEAUTY trial and we are currently gathering all the necessary information regarding the availably and variety of these existing mice. The studies were performed under the consortium IACUC and the ACURO protocols. *The proposed experiments are as follows:*

•*To assess the first experiment we used TBV-3166 to target FASN which inhibits tumorigenicity*: *This task was accomplished and presented in the Annual Report of Y6P6: we presented data demonstrating that* a clinical grade FASNi enhances sensitivity to navitoclax *in vivo*: We finally sought to determine the efficacy of combining navitoclax/ABT-263 and TVB-3664 using BT-474 human breast cancer xenografts in nude mice. BH3 mimetics and TVB-3664 were administered by oral gavage to mimic human oral drug administration. Both navitoclax and venetoclax failed to elicit any tumor growth delay of BT-474 xenograft tumors; notably, single agent TVB-3664 was notably efficacious in producing a tumor response (44% tumor growth inhibition). The completely lack of anti-tumor efficacy of navitoclax and venetoclax as single agents, were fully circumvented when FASN activity was pharmacologically targeted in BT-474 tumor xenografts; thus, when administered in combination with the FASNi TVB-3664, navitoclax and venetoclax caused strong tumor growth inhibition (80% and 78%, respectively). Combination therapy were well-tolerated, with mice maintaining normal body weight. ***The studies were completed using BT-474 breast cancer Xenograft tumors treated with inhibitor of FASNi (TVB3664) in combination with* navitoclax [Bcl2 and Bclxl inhibitor (ABT-263)] report for Y6P6.**

REPRESENTATIVE RESULTS (From the new SOW)

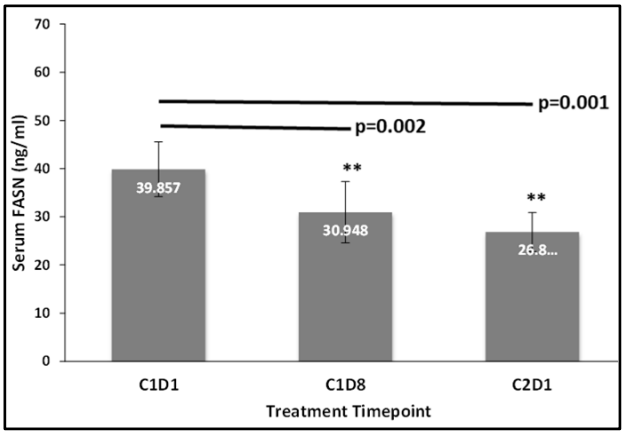
Specific Aim 2: To examine the clinical value of serum and tissue FASN expression as a novel theranostic marker in HER2+ breast cancer. The same correlative studies will be performed for the Endocrine-Resistant metastatic patients.

Major Task 6-7: Correlative Studies and Analysis:

Subtask 1: Tumor biospecimens stained, scored and interpreted: Assess the changes in serum FASN (performed in Dr. Lupu's Laboratory)

FASN Expression in Serum: Determination of FASN expression in serum samples from all the patients enroll in our clinical trial. Since the FAS-detect ELISA from ImmTech, usually used in the laboratory, was discontinued, we had the evaluate different alternatives to test expression of FASN in serum. Based on the literature we identified three alternative kits: (1) Cloud-Clone Corp, (2) Elabscience and (3) Cusabio. After serious evaluation we determined that the Cusabio FASN ELISA had the best sensitivity of 0.39ng/ml and a dynamic range of 1.56-100ng/ml which we anticipate all samples to fall within that range.

Subtask 1: Tumor biospecimens stained, scored and interpreted: ***We examine the clinical value of serum FASN expression as a novel theranostic marker in HER2+ breast cancer.*** A decrease in the FASN serum levels (<-2%) in eleven of the thirteen patient samples from C1D1 to C2D1, one sample we observed no change (+/- 2%), and one sample an increase (>2%) in Serum FASN. There was an average decrease in FASN serum levels by 40%, with a median decrease of 36%. While there was no change in one sample (1% increase) and an 11% increase in one patient sample. Overall, there was a significant decrease in the C1D1 FASN levels (39.9 ng/ml) to the C2D1 (26.8ng/ml) with a p=0.001. Deidentified Serum samples from patients were coded as follows: Cycle 1 Day 1 (C1D1), cycle 2 Day 1 (C2D1) samples were tested in serial dilutions were tested for the expression of FASN. All patient serum samples were deidentified and labeled C10-C48. For example, the first patient was C10 (C1D1), C11 (C1D8) and C12 (C2D1) samples. Student T. Test was completed to determine significance. Paired t Test. Two-tailed. I am not sure if this was the correct method for statistics



Given the success of the First set of experiments we embarked on the second set of experiments.

Specific Aim 3: 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 3: *Assessment of the efficacy of the combination of FASNi with Navitoclax in PDX derived from tumors derived from patients enrolled in the BEAUTY clinical trial.*

Subtask C: The BEAUTY clinical trial: ***A unique approach to identifying individualized therapies:*** The BEAUTY trial combined multiple scientific approaches to evaluate treatment for aggressive breast cancer. Tumor biopsies from 140 patients with aggressive breast cancer were collected before patients were treated with chemotherapy. Preclinical assessment of the FASN inhibitor TVB-3166 or TVB-3664 (FASNi analogues of the clinical FASNi-TVB-2640) in combination with ABT-263 in patient-derived tumor xenografts (PDX). The PDX's, are mice in which a sample of a patient's tumor is injected into a mouse, resulting in a biological model duplicating the patient's tumor. We hypothesize that inhibition of FASN re-sensitizes breast cancer to the Bcl-2 pro-apoptotic pathway to induce cell death, and that dual blockade of FASN using TVB-3166 or TVB-3664) in combination with Navitoclax (ABT-263) would result in a synergistic anti-tumor effect. ABT-263 synergistically induce anchorage independent growth and apoptosis of FASN expressing BC cells. We have also shown to inhibition of FASN sensitizes tumors to anti-HER2 therapies. Thus, we will design studies to resensitize tumor to Trastuzumab (Trz). To do so, we will use NSG mice and introduce a very small portion of the patient tumor directly, generating a PDX. The NSG mice engrafted with viable tumor from consenting patients will "mimic" the tumor growth in the patient. Thus, will recapitulate the individuality of human cancers and allow better prediction of response to therapy. Thus, this approach-directed therapy is projected to guide treatment selection, improve treatment response rates, and minimize delivery of non-effective agents to patients. Since we are working on the premise that inhibition of FASN chemosensitises tumors to chemotherapeutic and biological drugs, we will test at this point any advanced BC molecular –subtype, post chemotherapy.

- *To assess the second set of experiments the* Mayo Clinic BEAUTY consortium provided our laboratory, initially, with two humans HER2+ breast cancer PDX tiny tumors (namely BJ-11 and BJ-07). The tiny tumors where immediately implanted, **for expansion**, in the immunodeficient mouse model NSG mice.

A) The BJ07 tumors were implanted (~4mm^3) in NSG mice to expand to tumor: BJ07 tumor obtained from Mayo Clinic BEAUTY Consortium. BJ07 tumor slices (4mm^3) were implanted into the 4th mammary fat pad and allowed grow. Mice

were monitored several times a week to ensure tumor growth and mouse wellness. Tumors volumes were determined by measuring length and width of tumor and calculating the tumor volume (V=1/2(length x width^2) was implanted into one NSG mouse (Day 0) and was monitored for tumor growth. Calipers were used to measure the tumor length and width. Tumor volume was determined by the equation V=1/2(length x width^2).

B) The BJ11 tumors were implanted (~4mm^3) in NSG mice to expand to tumor: BJ11 tumors were monitored and measured by calipers by measuring length and width to determine tumor volume (volume=0.5*(length x width^2). Upon tumor reaching about 1.8 mm^3, mice were sacrificed, and tumors were diced-up and implanted for the expansion and the additional studies. The additional studies include two NSG mice (Mouse A and B) were implanted with BJ11 slices (4mm^3) into the 4th mammary fat pad and allowed to grow. Mice were monitored several times a week to ensure tumor growth and mouse wellness. Tumors volumes were determined by measuring length and width of tumor and calculating the tumor volume (V=1/2(length x width^2). Upon tumors reached up to no more than 1.8 mm^3. At that point, mice were sacrificed, tumors were removed and 4mm^3 slices were re-implanted into 3-4 old week female NSG mice for propagation of tumors in additional 15 mice to further generate tumor bearing mice to begin the experiments detailed in Task 3.

Once tumor volume reached 1500mm^3, the mouse was sacrificed, and the tumor was removed. The tumor was cut into 2 mm^3 pieces and immediately implanted into 20 NSG mice for further expansion of BJ11 tumor. Based upon experimental design. Once again when the tumor volume reaches 1500 mm^3, mice were sacrificed, and tumors were removed. Tumors were cleaned to remove mouse tissue/cells and dissected into 2mm^3 pieces. BJ11 tumor pieces were then implanted into NSG mice. Mice were monitored weekly and tumor volumes were recorded. Once the tumor volumes reached ~150-200mm^3 mice were randomized into 9 groups (shown in Table 1). Mice were randomized on day 20 into 9 treatment groups, see Table 1. Mice were treated daily via oral gavage (100 µl) with each group treatments and tumor volumes were measured twice weekly. Tumor volumes at day 41 are recorded as the mean and standard error and then mice were sacrificed. Tumor Growth Inhibition (TGI) for each treatment was determined using the following equation: TGI = (1-(mean volume of Tx)/ (mean volume of control) * 100%. When control group tumor volume reach ~2,000mm^3, mice were sacrificed, tumors were removed and processed. Tumors were partitioned to develop paraffin sections for further studies via immunohistochemistry (IHC), flash frozen for RNA isolation, for protein, and remaining tumor was flash frozen.

Group Treatments **Table 1**

Group 1: vehicle control
Group 2: TVB-3664 2mg/kg
Group 3: TVB-3664 4mg/kg
Group 4:ABT263 25mg/kg
Group 5:ABT263 50mg/kg
Group 6: TVB-3664 2mg/kg + ABT263 25mg/kg
Group 7: TVB-3664 2mg/kg + ABT263 50mg/kg
Group 8:TVB-3664 4mg/kg + ABT263 25mg/kg
Group 9: TVB-3664 4mg/kg + ABT263 50mg/k

A combination of FASNi sensitizes HER2+PDX to a BH3 mimetics and improved Tumor Growth Inhibition: will address whether adding a Bcl2 (ABT263) inhibitor add to TBV-3166's ability to inhibit tumorigenicity. Mice will be randomized to each of the following treatment groups when their tumors have reached a size of 100 mm^3: TVB-3166 dose from experiment 1 (TD1), TD1+ABT263 150 nM and TD1+ABT263 300 nM. Mice will be sacred when the tumor reaches a size of 2.0 cm^2 or appears in distress. For each dose of ABT263, the difference in the rate of change in tumor size (from pre-treatment to the time of sacrifice) with ABT263 TD1 and the rate of change in tumor size with TD1 alone will be assessed either using a two-sample t-test or a Wilcoxon rank sum test. The difference in the rate of change in tumor size with the combination and that vehicle will be examined. The dose level of ABT263+D1 that differs most from TD1 alone will be carried forward into the next experiment (see table 2)

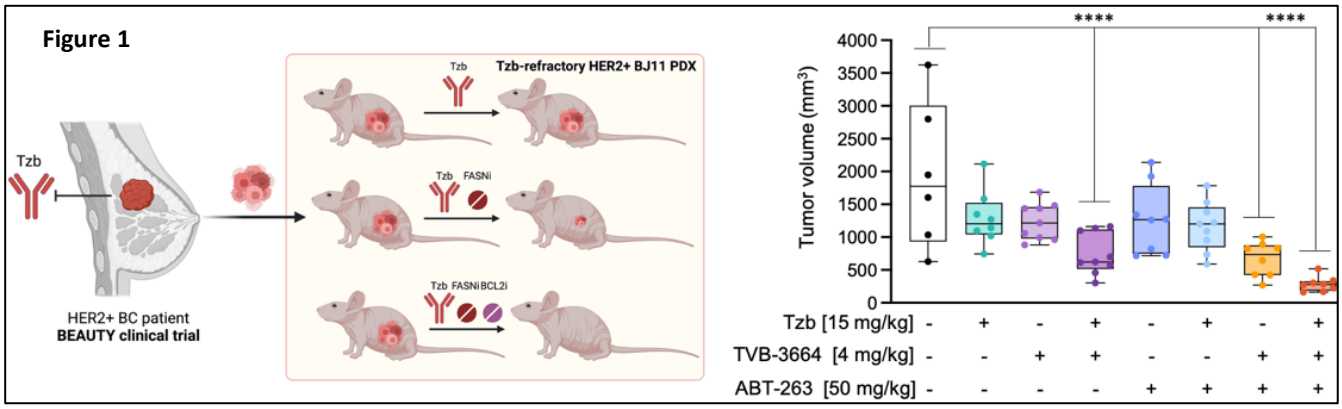
Treatment	Mean (mm^3)	Std. Error	TGI	p Values	Significant
Control	2292.7	286.6	--	--	--
2mg/kg TVB	1171.7	208.2	50.5%	0.0414	yes
4mg/kg TVB	1162.5	209.4	44.3%	0.0254	yes
25mg/kg ABT	1274.8	147.7	48.0%	0.0610	no
50mg/kg ABT	1199.0	260.8	55.3%	0.0341	yes
2mg/kg +25mg/kg	917.9	115.5	53.9%	0.0054	yes
2mg/kg+50mg/kg	854.0	329.9	63.7%	0.0067	yes
4mg/kg+25mg/kg	587.8	131.3	72.8%	0.0003	yes
4mg/kg+50mg/kg	544.8	97.6	77.8%	0.0005	yes

Table 2: Tumor Growth Inhibition (TGI): was determined using the following equation: TGI= (1-(mean vol of Tx)/(mean volume of control) *100%. Statistical analysis was calculated with GraphPad Prism via ANOVA analysis, significance has a p-value <0.05. All samples were significant (p<0.05 for all treatments compared to control except for ABT263 25mg/kg (see table 2 for p values and significance).

Given the success of the Second set of experiments we embarked on the third set of experiments.

- *To assess the third set of experiments we tested whether the optimal combination of TVB3664 and ABT-263 based on previous experiments (Table 2) could sensitizes tumors to HER-2 inhibitors.* Patient-derived xenografts (PDX) – also known as "avatar" or "mirror" models– can better predict both the development of resistance to first-line therapy and response to second-line therapy before they occur in the donor patient. BJ11 PDX, which was derived from a HER2+/hormone receptor-negative BC patient prior to receiving neoadjuvant chemotherapy (weekly taxane ± trastuzumab [Tzb] and anthracycline-based chemotherapy) in the BC Genome Guided Therapy Study (BEAUTY) clinical trial, to evaluate the ability of a FASNi to overcome BC resistance to Tzb. **The Tzb-unresponsive BJ11 PDX model regained sensitivity to Tzb in the presence of FASNi and, more importantly, showed dramatic tumor shrink (>90% reduction) when co-treated with a combination of TVB-3664 and the pan-BCL2 inhibitor navitoclax (Fig. 1).** *The combination of BH3 profiling with BH3 mimetic toolkits has the potential to maximize the anti-BC activity of FASNis and to identify new treatment options, even for BC patients who are refractory to targeted therapy.*

Figure 1. Tzb resistance in HER2+ FASN is reversed by FASNi TVB-2664 plus a pan-Bcl2 inhibitor. The horizontal line inside each box represents the median value (final tumor volume, day 38). The top and bottom of each box represent the 25% and 75% percentiles, respectively. (****, p<0.001)



For each of the 3 experimental studies we will use 10 mice per treatment group, a two-sided α=0.01 t-test of the difference in two means will have a 90% change of detecting a 2 STD difference in treatment means. To elucidate the correlation between FASN expression, treatment outcome and cell death, tumors will be stained for in vivo apoptosis using ApopTag Kit. Ki67 expression will be assessed to determine proliferation. Additional markers could be stained as we see them fit during the study. Tumor measurements and metastasis will be followed by the Fluor Vivo system for Fluorescent signal (cells labeled with GFP) and Xenogen system for luminescent signals (cells labeled with Luciferase).

***The work associated with Major Tasks 6-7 requires completion of correlative blood and tumor tissue collection.** These tasks will be completed following last patient enrolled and last biospecimen collected; if accrual goals are not fulfilled, the tasks will be completed with all tissue and blood biospecimens collected. The correlative studies will be completed in the laboratory of Dr. Ruth Lupu. Co-investigators, Dr. Carter (Pathologist) and Dr. Suman (Biostatistician) will aid in the completion of the studies and subsequent analysis and interpretation of results.

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.

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.**

The specimens for the correlative studies are currently being collected form all three Mayo sites and will be conducted in the next month or two.

- **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

Journal publications

1. Menendez JA, Cuyàs E, Encinar JA, Steen TV, Verdura S, Llop-Hernández À, López J, Serrano-Hervás E, Osuna S, Martin-Castillo B, **Lupu R.** The Fatty Acid Synthase (FASN) signalome: A molecular guide for precision oncology. Mol Oncol. 2023 Dec 29. doi: doi: 10.1002/1878-0261.13582.
2. Cuyàs E, Fernández-Arroyo S, Verdura S, **Lupu R**, Joven J, Menendez JA. Metabolomic and Mitochondrial Fingerprinting of the Epithelial-to-Mesenchymal Transition (EMT) in Non-Tumorigenic and Tumorigenic Human Breast Cells. Cancers (Basel). 2022 Dec 16;14(24):6214. doi: 10.3390/cancers14246214.PMID: 36551699

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: Sagimet is providing the investigational agent, TVB-3166, TVB3446, TVB-2640. A pathologist 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 participants.

In-kind support:
Not applicable
Facilities:
Not applicable

Collaboration: Scientists from Sagimet (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 Proposals:

Department of Defense BCRP Breakthrough Award - Funding Level 2 - Partnering PI Option (Javier Menendez)
BC210816P1: Title: "Unknown yet"
Funding Period: to be announced.

RO1-NIH/NCI- To be submitted by Feb 5th, 2024.
Title: Co-Targeting Fatty Acid Synthase (FASN) and Sphingosine Phosphate Kinase 1 (SphK1)/Sphingosine 1-Phosphate (S1P) Axis in Hormone Receptor Positive (HR+)/Hormone-Resistant Metastatic Breast Cancer

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