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TITLE: Targeting Drivers of Aggressive Triple-Negative Breast Cancer in African Americans

PRINCIPAL INVESTIGATOR: Cynthia Ma, MD PhD

CONTRACTING ORGANIZATION: The Washington University, St. Louis, MO

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Triple-negative breast cancer (TNBC) is an overly aggressive breast cancer subtype that disproportionately affects African American women. In our preliminary studies, we found that p53 mutations in TNBC often coincided with deletion/silencing of the CDKN2A locus that encodes both the ARF and INK4A tumor suppressors. The purpose of this study is to investigate the potential of targeting JAK1 (through loss of p53 and ARF) and CDK4 (through INK4A loss) activity in treating TNBC and the biomarkers predictive of response. In this project period, we have been focusing on the construction of our Tissue Microarray (TMA). We have reviewed 377 of our 525 desired cases, and have succeeded in placing 180 case specimens in the TMA. We anticipate the completion of the TMA sample collection in the next six months.

15. SUBJECT TERMS
TP53, ARF, INK4A, JAK1 inhibitor, CDKN2A, CDK4 inhibitor, TNBC, Patient-derived xenograft models, Tissue microarray, Immunohistochemistry

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

Triple-negative breast cancer (TNBC) is an overly aggressive breast cancer subtype that disproportionately affects African American women. In our preliminary studies, we found that p53 mutations in TNBC often coincided with deletion/silencing of the *CDKN2A* locus that encodes both the ARF and INK4A tumor suppressors. The purpose of this study is to investigate the potential of targeting JAK1 (through loss of p53 and ARF) and CDK4 (through INK4A loss) activity in treating TNBC and the biomarkers predictive of response.

2. KEYWORDS:

TP53, ARF, INK4A, JAK1 inhibitor, CDKN2A, CDK4 inhibitor, TNBC, Patient-derived xenograft models, Tissue microarray, Immunohistochemistry.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 2: Analyze 525 primary TNBC tumors and 30 PDX TNBC tumors

Subtask 1: Generate tumor microarray from 525 TNBC samples (months 1-12)

Subtask 2: Immunostain tumor microarray (months 1-12)

Subtask 3: Analyze tumor microarray staining (months 12-24)

What was accomplished under these goals?

Dr. Ma's team has completed all the subtasks listed in the Major Task 2. Major activities included identifying eligible TNBC tissues, followed by sectioning for H&E for pathologist review, Coring for Tissue Microarray (TMA) construction, and clinical annotation of these cases. TMA composed of tumor tissue cores from 501 patients is now available for analysis. 441 (89%) cases have cores available for DNA/RNA extraction, which is ongoing. Immunostains of TMA sections for ARF, TP53, ISG15 have been complete by Dr. Weber's team which showed 74% of patients exhibited elevated ADAR1 expression, 26% displayed high p14ARF expression, and 58% exhibited high p53 expression.

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

Nothing to Report

How were the results disseminated to communities of interest?

We have disseminated this project and the TNBC TMA resource that this project is generating to the scientific community through our monthly breast cancer research seminars as well as patient advocates to the public.

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

N/A

4. **IMPACT:**

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

The TNBC TMA offers an outstanding resource for studies in TNBC biology and biomarker development. The analysis of the TMA in this project have uncovered a novel pathway underlying the aggressive TNBC.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

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

None

Changes that had a significant impact on expenditures

Nothing to Report

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

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

The work was presented at the following conferences:
• Dean's Council, Washington University (Oral Presentation)
• Alumni Council, Washington University (Oral Presentation)
• San Antonio Breast Cancer Meeting (Poster Presentation)
• Cancer Biology Training Consortium, Baltimore, MD (Oral Presentation)

- **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**

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Cynthia Ma*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Ma supervised the execution and coordination of the TNBC TMA case identification, path review, clinical annotation and construction.*

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

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. **SPECIAL REPORTING REQUIREMENTS**
   COLLABORATIVE AWARDS:
   QUAD CHARTS:

9. **APPENDICES:**