AWARD NUMBER: W81XWH-15-1-0101

TITLE: Phase 1B Clinical Trial of a Candidate Breast Cancer Prevention Vaccine

PRINCIPAL INVESTIGATOR: William E. Gillanders

RECIPIENT: Washington University
St. Louis, MO 63110-1010

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6. AUTHOR(S)
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5e. TASK NUMBER

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

Washington University, The
One Brookings Drive
Saint Louis MO 63130-4862

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

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13. SUPPLEMENTARY NOTES

14. ABSTRACT This project involves a phase 1b clinical trial in breast cancer patients undergoing neoadjuvant endocrine therapy. Sixty subjects with mammaglobin-A-expressing breast cancer will be randomized in a 1:1 ratio to neoadjuvant endocrine therapy alone, or neoadjuvant endocrine therapy plus mammaglobin-A DNA vaccination. The primary objective is to assess the safety of the mammaglobin-A DNA vaccine. The secondary objective is to assess the ability of the mammaglobin-A DNA vaccine to induce an immune response to mammaglobin-A. During the first year of the project most efforts focused on optimizing patient awareness and accrual. Several protocol amendments were implemented earlier in the year to improve accrual. Additionally, we implemented screening of both medical and surgical oncologists' clinic schedules, and added Dr. Bisi Ademuyiwa, a Breast Cancer Medical Oncologist, to the trial team. To increase awareness a patient information package was prepared that explains the goal and details of the clinical trial. To date, a total of 12 patients signed the screening consent. Of these, 5 patients were eligible and 4/5 were randomized to the trial.

15. SUBJECT TERMS Phase 1b, neoadjuvant, endocrine, DNA vaccine, mammaglobin-A, immune response

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

1. INTRODUCTION:

This project involves a phase 1b clinical trial in breast cancer patients undergoing neoadjuvant endocrine therapy or chemotherapy. Forty six subjects with mammaglobin-A-expressing breast cancer will be randomized to neoadjuvant endocrine therapy alone (n=8); neoadjuvant endocrine therapy plus mammaglobin-A DNA vaccination (n=15), neoadjuvant chemotherapy (n=8) or neoadjuvant chemotherapy plus mammaglobin-A DNA vaccination (n=15). The primary objective is to gain additional information about the safety of the mammaglobin-A DNA vaccine. Safety will be closely monitored after injection with eight or more clinical and laboratory assessments in the first 24 weeks of the trial. The secondary objective is to assess the ability of the mammaglobin-A DNA vaccine to induce an immune response to mammaglobin-A. The immune response will be measured in the peripheral blood (ELISPOT analysis, multi-parameter flow cytometry), and in the primary tumor (imaging mass cytometry, IHC and RT-PCR).

2. KEYWORDS:

Breast, cancer, neoadjuvant, therapy, mammaglobin-A, DNA, vaccine, endocrine, chemo, phase 1b, ELISPOT, T-cells, microenvironment

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Subtask1: Manufacture mammaglobin-A DNA vaccine. Complete manufacture, product release tests, and other IND –enabling studies of the mammaglobin-A DNA vaccine.
Subtask 2: Obtain regulatory approval for phase 1b clinical trial. Obtain FDA approval, RAC approval, Institutional Biosafety Committee approval, PRMC approval and IRB approval. All approvals have been obtained.
Subtask 3: Patient enrollment. Enroll patients to the phase 1b clinical trial.
Subtask 4: Screening studies. Complete screening studies including HLA type and mammaglobin expression levels.
Subtask 5: Assessment of safety. The primary endpoint is safety of the mammaglobin-A DNA vaccine. Safety will be closely monitored after injection and toxicity will be graded according to the NCI CTCAE version 4.0.
Subtask 6: Immune monitoring. The secondary objective is immune response in the peripheral blood. PBMC will be analyzed for the presence of mammaglobin-A-specific T cells by ELISPOT and multi-parameter flow cytometry. Tetramer staining will also be combined with intracellular cytokine staining (IFNγ, TNFα).
Subtask 7: Manuscript Preparation. Safety and immune response to the mammaglobin-A DNA vaccine are the primary and secondary objectives of the trial and will be published together.

All tasks will take 4-5 years.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Accrual and treatment: During the past year of the project most efforts focused on optimizing patient accrual to the trial. **Appendix #1** presents an overview of all patients consented to date; changes from last year are highlighted and reflect a total of 11 new patients and a status update in 3 additional patients. Of the 11 new patients, 4 patients were eligible and 2 of those received neoadjuvant endocrine therapy plus mammaglobin DNA vaccine (WU-061 and WU-065). The other 2 patients preferred an alternative treatment. An additional patient is undergoing screening for eligibility (WU-069). The other 6 new patients dropped out because of a mammaglobin-negative tumor (n=2); Ki67 levels being too high (n=1) or because the patients preferred an alternative treatment (n=3). In total, 14 patients have completed therapy; 8 patients with neoadjuvant endocrine therapy alone, and 6 patients with neoadjuvant endocrine therapy plus vaccine. Neoadjuvant endocrine therapy plus vaccine is ongoing in an additional patient.

During the past year we continued our efforts to optimize patient accrual to the trial. After discussion with DOD staff, a protocol amendment was submitted to include patients undergoing neoadjuvant *chemotherapy* in addition to patients undergoing neoadjuvant *endocrine* therapy. This amendment was approved on March 13 by the Human Research Protection Office at Washington University and on March 22 by the Office of Research Protections at the USAMRMC. According to the amendment, there will be four cohorts: neoadjuvant endocrine therapy alone (n=8), neoadjuvant, neoadjuvant endocrine therapy + mammaglobin-A DNA vaccine (n = 15), neoadjuvant chemotherapy alone (n = 8), and neoadjuvant chemotherapy + mammaglobin-A DNA vaccine (n=15). It should be noted that we completed recruitment to the neoadjuvant endocrine therapy group (n=8).

Safety and toxicity: In all 15 patients that received therapy, toxicity was restricted to mostly grade 1 and 2, and none of the patients experienced toxicity that required discontinuation of treatment.

Immune monitoring: We reported last year on a pilot study to assess gene expression in human breast cancer samples using the NanoString platform nCounter PanCancel Immune Profiling platform, and presented quality control data after isolation of RNA from tissue samples. RNA was isolated from tumor areas containing $\geq$30% leukocyte infiltrate, immune-dense areas, and from areas with <30% leukocyte infiltrate (immune-sparse) areas, based on H&E evaluation by a pathologist. The majority of the samples passed the RNA quality control and were used for gene expression analysis. Samples from 7 patients with triple-negative breast cancer were further analyzed. As expected, all immune cell subsets analyzed were more prominently expressed in immune-dense areas compared to immune-sparse areas (**Appendix 2, Figure 1**). Comparing normalized gene expression in leukocytes from immune-dense versus immune-sparse areas suggested leukocytes in immune-dense areas have a more activated phenotype (**Appendix 2, Figure 2 and Table**).

In addition to gene expression analysis we explored imaging mass cytometry. This technique uses metal-tagged antibodies and allows for simultaneous imaging of up to 37 protein markers in tissue sections. The technique is part of a comprehensive effort to construct tumor atlasses of human breast and pancreas cancer, and is supported by a U01 grant to Washington University. We plan to implement imaging mass cytometry to analyze the tumor samples from patients before and after treatment. Representative examples of imaging mass cytometry are presented in **Appendix 3**.

Combined, the NanoString gene expression analysis and imaging mass cytometry permit detailed characterization of tissues. We plan to incorporate both techniques for the analysis of trial patient samples, before and after treatment. Of all 13/14 patients that completed treatment, we obtained 1-3 tissue cores pre-study, and from 12/14 patients we obtained tissue post-treatment (two patients had an insufficient amount of tumor tissue at the time of surgery).

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

While accrual to the trial has been challenging, we hope that opening up the trial to patients undergoing neoadjuvant chemotherapy will increase accrual. Additionally, we will continue with the correlative studies. Specifically, we will continue with the immune monitoring assays using peripheral blood samples from trial patients collected at multiple time points, and gene – and protein expression analysis in tissue samples collected pre – and post treatment, as outlined above in section 3.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

As patients are treated in the neoadjuvant setting prior to undergoing surgery, it is still too early to assess the impact of the vaccine

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

As described above, accrual has been slow, but we anticipate that broadening the trial to include patients undergoing neoadjuvant chemotherapy will increase accrual.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Nothing to report

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation);*

status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to report

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*

- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

William Gillanders
No change

S. Peter Goedegebuure
No change

Lijin Li
No change

Nancy Myers
No change

Narendra Sankpal
No change

Mark Sturmoski
No change

John Herndon
No change

Xiuli Zhang
No change

Lincoln Muhoro
No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

WILLIAM GILLANDERS

NEW AWARDS

U2CCA233303 (Ding/Achilefu/Fields/Gillanders) 9/1/2018-8/31/2023 1.2
National Institutes of Health calendar

Washington University Human Tumor Atlas Research Center
Molecular, Cellular, and Tissue Characterization Unit (Gillanders/Chen/Li/Oh/Shoghi)
The over-arching goal of the Characterization Unit at the Washington University Human Tumor Atlas Research Center (WU-HTARC) is to subject the samples collected by the Biospecimen Unit to a well-coordinated battery of analyses among three broad classes: imaging, omics, and phenotypic characterization. This will help us better understand the clonal evolution of the cancer cells, the tumor ecosystem, the development of drug resistance and metastasis.

Specific Aims
Aim 1: Employ radiomic pipelines to characterize structure and function of both the tumor and tumor microenvironment at the tissue and cellular levels.
Aim 2: Characterize the tumor and tumor microenvironment using high throughput "omics" technologies.
Aim 3: Define cellular phenotypes, intracellular protein activation states, and immune cell signatures, and ascribe these features to specific spatial locations.

Program Official: Admin Official:
Jerry Li Alania Foster

U2CCA233303 (Ding/Achilefu/Fields/Gillanders) 0.30
9/30/2018-8/31/2023 National Institutes of Health calendar

Washington University Human Tumor Atlas Research Center
Administrative Core (Li)
The goal of the Administrative Core is to provide executive oversight and administrative support for the construction of the tumor atlases for TNBC, Pancreas and Glioblastoma by the Washington University Human Tumor Atlas Research Center (WU-HTARC). The Administrative Core will also provide the infrastructure for communications across the three disease groups that are the focus for the atlases and also for scientific collaborations within the Human Tumor Atlas Network and other companion NCI initiatives.

Specific Aims
Aim 1: Facilitate executive oversight of the HTARC and each of the Units.

Aim 2: Provide administrative and fiscal oversight for all HTARC components.
Aim 3: Coordinate all HTARC meetings.
Aim 4: Facilitate HTARC -HTANet communications and collaborations.
Aim 5: Coordinate and manage the HTARC.
Aim 6: Provide general administrative support for HTARC investigators.

Program Official: Admin Official:
Jerry Li Alania Foster

(Gillanders/Curiel) 1/1/2019-12/31/2020
Alvin J. Siteman Cancer Research Fund 0.24 calendar

Evaluation of a Novel Personalized Vaccine Strategy for Breast Cancer
The goal is to activate immune cells capable of recognizing and killing breast cancer using the "prime/boost" neoantigen vaccines, and then take the "brakes" off these immune cells using checkpoint blockade therapy.
This combination has the potential to be a synergistic and highly effective strategy in TNBC, and in other cancers, particularly cancers resistant to checkpoint blockade therapy alone.
Specific Aims
Aim 1: Test the safety, feasibility, and immunogenicity of a neoantigen vaccine strategy consisting of a simian adenovirus vaccine "prime," followed by a plasmid DNA vaccine "boost" in a phase 1 clinical trial.
Aim 2: Test the hypothesis that specifically targeting tumor-associated macrophages (TAM) will enhance the efficacy of breast cancer neoantigen vaccines in the setting of established disease.
Admin Official:
Jennifer Lodge

EXPIRED AWARDS

KG111025 (Gillanders/Mardis) 10/5/2011-10/4/2017 0.96 calendar
Susan G. Komen for the Cure
Personalized Breast Cancer Vaccines Based on Genome Sequencing
Next-generation sequencing technologies with the ability to process millions of sequence reads in a single run have revolutionized genetics, providing the ability to answer questions with unimaginable speed [69]. The vision of the Breast Cancer Research Program at WUSM is that breast cancer genome sequencing will be used in the future to tailor therapies to individual breast cancer patients, and The Genome Center is one of only a few centers worldwide with the sequencing capacity and analytical prowess to explore this vision. The flexibility of the DNA vaccine platform, and the experience of investigators at WUSM provides the opportunity to rapidly translate a personalized breast cancer vaccine strategy into a phase I clinical trial.
Specific Aims
Aim 1: Test the hypothesis that genetic changes identified by breast cancer genome sequencing predict unique tumor antigens.
Aim 2: Optimize polyepitope DNA vaccines for unbiased presentation of unique tumor antigens identified by genome sequencing.
Aim 3: Compare personalized breast cancer vaccines to conventional vaccines in a preclinical breast cancer model.

Aim 4: Produce durable breast cancer immunity by combinatorial targeting of the intrinsic and extrinsic pathways that control CD8 T cell memory.
Aim 5: Test the safety and immunogenicity of personalized breast cancer DNA vaccines in a phase I clinical trial.

Research Grants Manager

Stephanie Bunt, Ph.D.

PETER GOEDEGEBUURE

NEW AWARDS

U2CCA233303 (Ding/Achilefu/Fields/Gillanders) 0.12
9/30/2018-8/31/2023 National Institutes of Health calendar
Washington University Human Tumor Atlas Research Center
Biospecimen Acquisition, Processing, and Classification Unit (Fields/Kim/Watson)
The over -arching goal of the Biospecimen Unit for the Washington University Human Tumor Atlas Research Center (WU-HTARC) is to collect human tumor biospecimens for use by the Characterization and Data Analysis Units to construct the proposed tumor atlases.

Specific Aims

Aim 1: Identify patients with TNBC, GBM, and PDAC for inclusion in the WU-HTARC program.
Aim 2: Collect biospecimens for use in constructing the proposed human tumor atlases.
Aim 3: Create a comprehensive database of all patients and tissue included in the WU-HTARC program.

Program Official:	Admin Official:
Jerry Li	Alania Foster

OC170200 (Curiel) 6/1/2018-11/30/2019 1.2
Department of Defense calendar
Novel Ovarian Cancer Therapy
These studies will test a hypothesis regarding the biologic basis of virotherapy action that is of field-wide relevance. In addition, we will realize the database rationalizing translational development of a novel virotherapy agent for carcinoma of the ovary.

Specific Aims

Aim 1: To construct an ovarian cancer CRAd based upon gorilla adenovirus.
Aim 2: To characterize the tumor selectivity of the gorilla CRAd in vitro and in vivo.
Aim 3: To evaluate the ability of CRAd-based virotherapy to induce anti-tumor immunity in a syngeneic immunocompetent murine model of carcinoma of the ovary.

Program Official:	Admin Official:
not yet available	not yet available

(Gillanders/Curiel) 0.6
1/1/2019-12/31/2020 Alvin J. Siteman Cancer Research Fund calendar
Evaluation of a Novel Personalized Vaccine Strategy for Breast Cancer
The goal is to activate immune cells capable of recognizing and killing breast cancer using the

"prime/boost" neoantigen vaccines, and then take the "brakes" off these immune cells using checkpoint blockade therapy. This combination has the potential to be a synergistic and highly effective strategy in TNBC, and in other cancers, particularly cancers resistant to checkpoint blockade therapy alone.

Specific Aims

Aim 1: Test the safety, feasibility, and immunogenicity of a neoantigen vaccine strategy consisting of a simian adenovirus vaccine "prime," followed by a plasmid DNA vaccine "boost" in a phase 1 clinical trial.

Aim 2: Test the hypothesis that specifically targeting tumor-associated macrophages (TAM) will enhance the efficacy of breast cancer neoantigen vaccines in the setting of established disease.

Program Official:
not yet available

Admin Official:
not yet available

P19-00559 (Perlmutter) 4/1/2019-3/31/2022 0.6
Centene Corporation calendar

Research in the Field of Personalized Medicine - Cancer (Breast and Pancreatic), Alzheimer's Disease, Obesity and DiabetesP102 Next Generation of Personalized Vaccines for PDAC (Hawkins/Goedegebuure/Gillanders)

The Centene Corporation contract supports the Washington University-Centene Personalized Medicine Initiative (PMI) which awards funding to internal Washington University (WU) research projects in four disease specific areas. This project is funded under the WU-Centene PMI Pancreatic Cancer Program. The overall objective of this project is to test second generation personalized vaccines incorporating both neoantigens and immune modulatory molecules in mouse models of pancreatic cancer.

Specific Aims

Aim 1: Develop and credential a neoantigen vaccine preclinical model.

Aim 2: Optimize the neoantigen vaccine.

Aim 3: Multidimensional profiling of the tumor following neoantigen vaccine therapy.

Program Official:
Rebecca Evans; evansb@wustl.edu

P19-00559 (Perlmutter) 4/1/2019/31/2022 1.2
Centene Corporation calendar

Research in the Field of Personalized Medicine - Cancer (Breast and Pancreatic), Alzheimer's Disease, Obesity and DiabetesB101 Personalized Breast Cancer Vaccines (Breast Project 1: Gillanders)

The Centene Corporation contract supports the Washington University-Centene Personalized Medicine Initiative (PMI) which awards funding to internal Washington University (WU) research projects in four disease specific areas. This project is funded under the WU-Centene PMI Breast Cancer Program.

The goal of this proposal is to validate an in vivo model to evaluate human tumors in the context of an intact human immune system in a completely personalized and autologous fashion.

Specific Aims

Aim 1: Test innovative neoantigen vaccine platforms in a preclinical model of breast cancer.

Aim 2: Optimize neoantigen vaccines.

Aim 3: Multidimensional profiling of the tumor microenvironment following neoantigen vaccine therapy.

Program Official:
Rebecca Evans

EXPIRED AWARDS

KG111025 (Gillanders/Mardis) 10/5/2011-10/4/2017 0.96
Susan G. Komen for the Cure calendar

Personalized Breast Cancer Vaccines Based on Genome Sequencing

Next-generation sequencing technologies with the ability to process millions of sequence reads in a single run have revolutionized genetics, providing the ability to answer questions with unimaginable speed [69]. The vision of the Breast Cancer Research Program at WUSM is that breast cancer genome sequencing will be used in the future to tailor therapies to individual breast cancer patients, and The Genome Center is one of only a few centers worldwide with the sequencing capacity and analytical prowess to explore this vision. The flexibility of the DNA vaccine platform, and the experience of investigators at WUSM provides the opportunity to rapidly translate a personalized breast cancer vaccine strategy into a phase I clinical trial.

Specific Aims

Aim 1: Test the hypothesis that genetic changes identified by breast cancer genome sequencing predict unique tumor antigens.
Aim 2: Optimize polyepitope DNA vaccines for unbiased presentation of unique tumor antigens identified by genome sequencing.
Aim 3: Compare personalized breast cancer vaccines to conventional vaccines in a preclinical breast cancer model.
Aim 4: Produce durable breast cancer immunity by combinatorial targeting of the intrinsic and extrinsic pathways that control CD8 T cell memory.
Aim 5: Test the safety and immunogenicity of personalized breast cancer DNA vaccines in a phase I clinical trial.

Research Grants Manager

Stephanie Bunt, Ph.D.

FOLUSO ADEMUYIWA

NEW AWARDS

Barnes Jewish Hospital Foundation

NEK9-MAP2K4: A Novel Signaling Axis Promoting Breast Cancer Growth and Chemotherapy Resistance

Specific Aims: 1) To test the hypothesis that NEK9-MAP2K4 axis is important for mitotic cell cycle progression and tumor cell growth in breast cancer cells, particularly TNBC; 2) To test the hypothesis that NEK9-MAP2K4 contributes to chemotherapy resistance and to determine the cell cycle checkpoint(s) that NEK9-MAP2K4 participates in; and 3) To establish the clinical relevance of NEK9 and MAP2K4 signaling axis in TNBC.
Grant officer: Donald Buckner

(Ademuyiwa) 8/1/2018-7/31/2019 0.12 Calendar
NeoImmune Tech, Inc.
Correlative Studies of a Phase 2 Clinical Trial of Neoadjuvant Chemotherapy with Docetaxel and Carboplatin for Triple Negative Breast Cancer (TNBC)
Grant officer: Jeong Gu Kang

U2C CA233303 (Ding) 9/30/2018-8/31/2023 0.12 Calendar
National Institutes of Health
Washington University Human Tumor Atlas Research Center - Biospecimen Unit
The over -arching goal of the Biospecimen Unit for the Washington University Human Tumor Atlas Research Center (WU-HTARC) is to collect human tumor biospecimens for use by the Characterization and Data Analysis Units to construct the proposed tumor atlases.

Specific Aims:
Aim 1: Validate the ability to model tumor behavior in a microphysiological platform that supports a comprehensive TME using autologous primary tumor and non-tumor TME cellular subsets from PDAC specimens collected via our U2C grant.
Aim 2: Use multidimensional analyses to characterize the autologous TOC platform at molecular, cellular, and tissue levels, and to further validate the ability of our platform to recapitulate key features of parental PDAC tumors.

Admin Official:
Alania Foster

EXPIRED AWARDS
R01 CA195450 (Dehdashti) 5/1/2015 - 4/30/2019 0.18 calendar
NIH
Assessment of Functional Status of Estrogen Receptors in Breast Cancer by PET
The overall goal of this study is to develop a noninvasive PET-based examination for identifying patients with breast cancer who have functional estrogen receptors and may benefit from endocrine therapy.

Specific Aims:
1. Evaluate whether the change in tumor uptake of FFNP following a 1-day estradiol challenge differs among patients who respond to ET versus those who do not respond.
2. Evaluate the heterogeneity of tumor FFNP uptake at baseline and after estradiol challenge in patients with multiple metastatic foci.

Admin Official:
Lori Henderson, hendersonlori@mail.nih.gov, (240) 276-5930

CTRFP (Ademuyiwa) 3/1/2018 - 2/28/2019 0.12 calendar
Institute of Clinical and Translational Sciences $50,000
Study of Molecular Analyses to Predict Disease Recurrence in Breast Cancer
The risk of the cancer returning is high for those triple negative breast cancer (TNBC) patients whose cancers are not eradicated by chemotherapy. Once the TNBC returns, it ultimately kills. We will study blood markers to identify those at high risk for recurrence. Our plan is to develop new ways to accurately determine which TNBC patients are at a high risk of relapsing, so that such patients may be treated differently and have better outcomes.

Specific Aims: Not Available Grant Officer: Not Available

FENG GAO

NEW AWARDS

R21CA234640 (Ratner) 12/10/2018-11/30/2020 0.48
National Institutes of Health Calendar

Immune Checkpoint Blockade Promotes Adult T Cell Leukemia

The goal of this proposal is to define the molecular mechanisms underlying this paradoxical effect, in order to better understand the potential benefits and risks of immune checkpoint blockade in cancer, especially T cell malignances.

Specific Aims

Aim 1: Define the effect of immune checkpoint blockade on tumor cell clonality.
Aim 2: Define the effects of immune checkpoint blockade on T cell signaling pathways: a) Proliferation rate, b) PD-1, PD-L1 levels, c) PI3K and RAS/MAPK pathways. We will assess the effects of immune checkpoint blockade in culture, in PDX models in mice, and in patients by FACS to assess proliferation, apoptosis, AKT and ERK activation.
Aim 3: Define the effect of immune checkpoint blockade on T cell proliferation: a) In culture and b) In NSG mice.

Program Official: William D. Merritt Admin Official: Viviana Knowels

P50CA171963 (Link) 2.4
7/1/2018-6/30/2023 National Institutes of Health calendar

Specialized Program of Research Excellence (SPORE) in Leukemia Biostatistics Core (Colditz)

The Biostatistics Core facility provides the statistical design, data management, and computational support for all Leukemia SPORE investigators. The Core will support consultation and collaboration on all aspects of study design, database development and quality control, and analysis and interpretation of data.

Specific Aims

Aim 1: Provide biostatistical and bioinformatics collaboration for Projects, Developmental Research Program and Cores in the SPORE, to assure robust statistical methods support the projects.
Aim 2: Provide biostatistical and bioinformatics support and training to junior investigators through CEP.

Program Official: Igor Kuzmin, Admin Official: Viviana Knowles

(Gillanders/Curiel) 1/1/2019-12/31/2020 Alvin 0.12
J. Siteman Cancer Research Fund calendar

Evaluation of a Novel Personalized Vaccine Strategy for Breast Cancer

The goal is to activate immune cells capable of recognizing and killing breast cancer using the "prime/boost" neoantigen vaccines, and then take the "brakes" off these immune cells using

checkpoint blockade therapy.
This combination has the potential to be a synergistic and highly effective strategy in TNBC, and in other cancers, particularly cancers resistant to checkpoint blockade therapy alone.
Specific Aims
Aim 1: Test the safety, feasibility, and immunogenicity of a neoantigen vaccine strategy consisting of a simian adenovirus vaccine "prime," followed by a plasmid DNA vaccine "boost" in a phase 1 clinical trial.
Aim 2: Test the hypothesis that specifically targeting tumor-associated macrophages (TAM) will enhance the efficacy of breast cancer neoantigen vaccines in the setting of established disease.
Admin Official:
Jennifer Lodge

Team Science SIP (Fehniger/Kahl) 1/1/2019-12/31/2020 0.6
Siteman Cancer Center Calendar
Advancing Therapies for Incurable Lymphomas via Translational Team Science (SCC) Biostats Core A
In this team science program, we will 1) leverage and connect expertise in immunology, immunotherapy, genomics, cancer biology, and clinical trial design to develop new biomarkers and treatments for lymphoma in 5 translational projects, and 2) integrate and enhance infrastructure that supports translational lymphoma research.
Specific Aims
Aim 1: Leverage and connect expertise in immunology, immunotherapy, genomics, cancer biology, and clinical trial design to develop new biomarkers and treatments for lymphoma in 5 translational projects. Aim 2: Integrate and enhance infrastructure that supports translational lymphoma research.
Program Official:
not yet available
Admin Official:
not yet available

P19-00559 (Perlmutter) 4/1/2019-3/31/2022 0.6
Centene Corporation Calendar
Research in the Field of Personalized Medicine - Cancer (Breast and Pancreatic), Alzheimer's Disease
The Centene Corporation contract supports the Washington University-Centene Personalized Medicine Initiative (PMI) which awards funding to internal Washington University (WU) research projects in four disease specific areas. This project is funded under the WU-Centene PMI Breast Cancer Program.
The goal of this proposal is to validate an in vivo model to evaluate human tumors in the context of an intact human immune system in a completely personalized and autologous fashion.
Specific Aims
Aim 1: Test innovative neoantigen vaccine platforms in a preclinical model of breast cancer.
Aim 2: Optimize neoantigen vaccines.
Aim 3: Multidimensional profiling of the tumor microenvironment following neoantigen vaccine therapy.
Program Official:
Rebecca Evans; evansb@wustl.edu

EXPIRED AWARDS

R01CA182746 (Watson/Govindan) 7/1/2014-5/31/2019 0.6
National Institutes of Health Calendar

Genomic Harbingers of Brain Metastasis in Non-Small Cell Lung Cancer

We will utilize exome and RNA sequencing technology, a carefully identified cohort of NSCLC patients, and an innovative analytical approach to identify genomic and transcriptome alterations that are both enriched in metastatic cell populations and highly recurrent in patients with brain metastases. The alterations identified will be used to build a risk-based model for brain metastasis using an independent validation cohort, ultimately defining a multi-marker genomic assay for more accurate prediction of metastatic behavior and improved therapeutic management of NSCLC patients.

Specific Aims

Aim 1: To identify somatic mutations and corresponding gene expression patterns that are enriched and recurrent in NSCLC which is metastatic to brain.

Aim 2: To build a predictive model of brain metastasis using the combined set of genomic and transcription biomarkers identified in aim 1, in combination with metastasis biology gene network data, and external NSCLC genomic data sets.

Aim 3: To independently validate the clinical significance of the predictive network model of brain metastasis in primary NSCLC.

Program Official: Kelly Y. Kim Admin Official: Alania Foster

R01 CA194552 (DiPersio) 05/01/2015-04/30/2020 0.4
National Institutes of Health Calendar

Retargeting Agents to Treat AML

One major goal of this project is to conduct a "first-in-human" Phase I clinical trial of MGD006, a CD123×CD3 Dual Affinity Re-Targeting (DART) bi-specific antibody-based molecule, in patients with high risk AML. In correlative studies using samples obtained from this clinical trial, we will evaluate the immunomodulatory activity and potential anti-tumor activity of MGD006.

Specific Aims

Aim 1: To conduct a “first-in-human” Phase 1 clinical trial of MGD006, a CD123xCD3 Dual Affinity Re-Targeting (DART) bicpecific antibody-based molecule, in patients with high risk AML.

Aim 2: We will characterize the immunomodulatory activity and potential anti-tumor activity of MGD006 in patients with AML.

Aim 3: We will identify novel targets of immunotherapy in human AML and test the efficacy of new retargeting agents to kill AML blasts expressing CD123 or these novel targets.

Contracting/Grants Officer

Siliva Torres / torresspc@mail.nih.gov / 240-276-6322

Dr. Gao’s effort ended 4/30/18

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

None

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Appendix 1: Overview of trial patients through July 15, 2019

Patient ID	Eligible	Treatment Arm	Treatment Status
WU-001	No (MGB negative)		
WU-002	Yes	Neo-adj + vaccine	discontinued
WU-003	No (MGB negative)		
WU-004	No (BMI)		
WU-005	No (Ki-67 too high)		
WU-006	No (MGB negative)		
WU-007	No (MGB negative)		
WU-008	No (MGB negative)		
WU-009	Yes	Other*	
WU-010	No (ineligible for neo-adj therapy)		
WU-011	No (MGB negative)		
WU-012	No (MGB negative)		
WU-013	No (MGB negative)		
WU-014	No (MGB negative)		
WU-015	Yes	Neo-adj	completed
WU-016	Yes	Neo-adj + vaccine	completed
WU-017	No (Ki67 too high)		
WU-018	No (MGB negative)		
WU-019	No (MGB negative)		
WU-020	Yes	Other*	
WU-021	Yes	Neo-adj	completed
WU-022	Yes	Neo-adj	completed
WU-023	No (Ki67 too high)		
WU-024	No (patient not compliant)		
WU-025	No (patient chose alternate trial)		
WU-026	No (patient chose surgery)		
WU-027	Yes	Neo-adj	completed
WU-028	No (patient chose surgery)		
WU-029	Yes	Neo-adj + vaccine	completed
WU-030	Yes	Other*	
WU-031	No (MGB negative)		
WU-032	Yes	Neo-adj + vaccine	completed
WU-033	Yes	Neo-adj	completed
WU-034	No (MGB positive, Ki67 not tested)	Other*	
WU-035	No (patient chose surgery)		
WU-036	No (MGB negative)		
WU-037	No (MGB negative)		
WU-038	No (MGB negative)		
WU-039	No*		
WU-040	No (MGB negative)		
WU-041	No (MGB negative)		
WU-042	Yes	Neo-adj + vaccine	completed
WU-043	No (MGB negative)		
WU-044	No (MGB negative)		
WU-045	No (Ki67 too high)		

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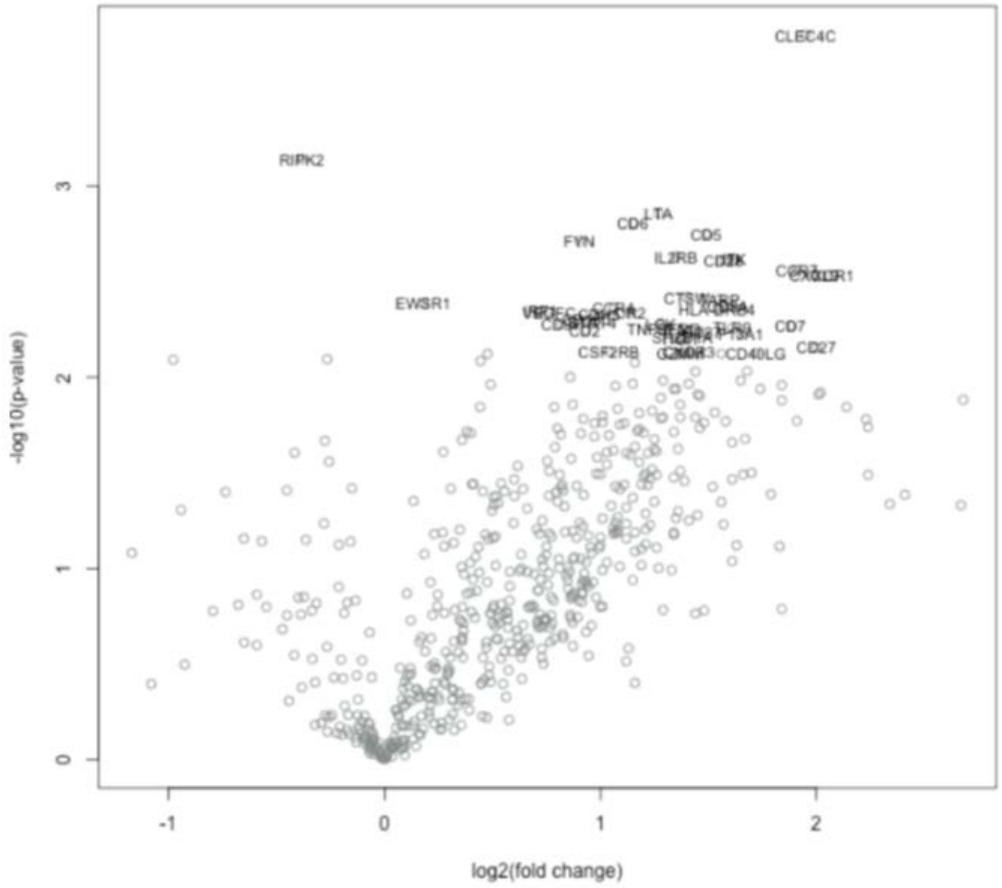
WU-046	Yes	Neo-adj	completed
WU-047	No (MGB negative)		
WU-048	Yes	Neo-adj	completed
WU-049	Yes	Neo-adj	completed
WU-050	Yes	Other*	
WU-051	No (MGB negative)		
WU-052	No (MGB negative)		
WU-053	No*		
WU-054	Yes	Other*	
WU-055	No*		
WU-056	Yes	Neo-adj + vaccine	completed
WU-057	Yes	Other*	
WU-058	No (MGB negative)		
WU-059	No (Ki67 too high)		
WU-060	No (MGB negative)		
WU-061	Yes	Neo-adj + vaccine	completed
WU-062	No	Other*	
WU-063	No (MGB negative)		
WU-064	Yes	Other*	
WU-065	Yes	Neo-adj + vaccine	ongoing
WU-066	No	Other*	
WU-067	No	Other*	
WU-068	Yes	Other*	
WU-069	pending		

* Patient declined to be on trial

Changes from the previous Annual Report are highlighted; all neoadjuvant therapy is endocrine therapy

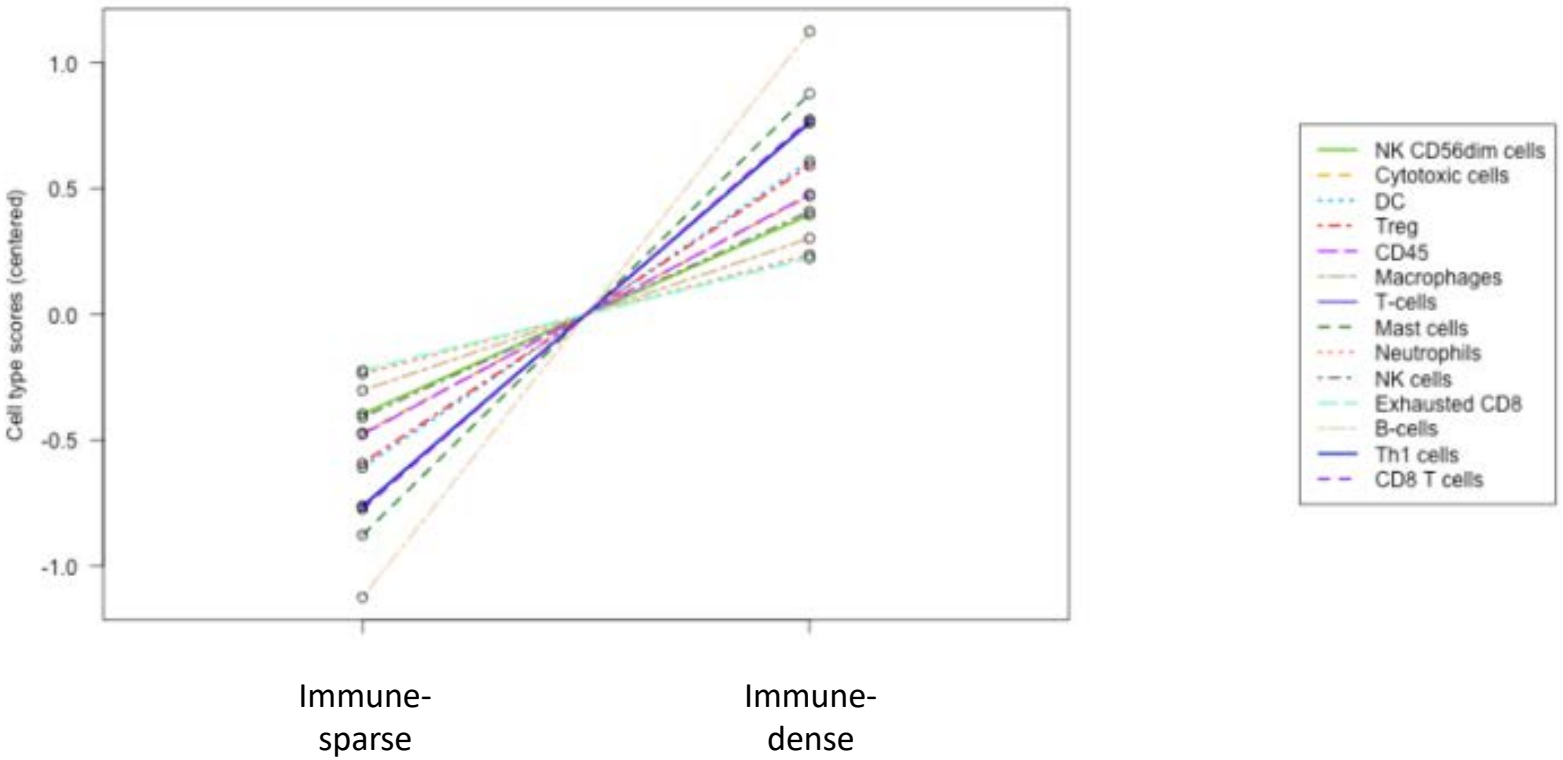
Appendix 2: Gene expression analysis in human breast cancer by NanoString's nCoulter® PanCancer Immune Profiling Panel: Comparison of immune-dense vs immune-sparse sections of triple negative breast cancer (TNBC) tumors



Gene Name	Log2 Fold Change
CLEC4C	1.95
LTA	1.27
CD6	1.15
CD5	1.49
IL2RB	1.35
ITK	1.62
CD28	1.57
CCR7	1.91
CXCL9	1.99
XCR1	2.08
CTSW	1.4
TARP	1.55
CD8A	1.59
CCR4	1.06
HLA-DRB4	1.54
CR2	1.14
LCK	1.28
CD7	1.88
TLR9	1.61
TNFSF11	1.28

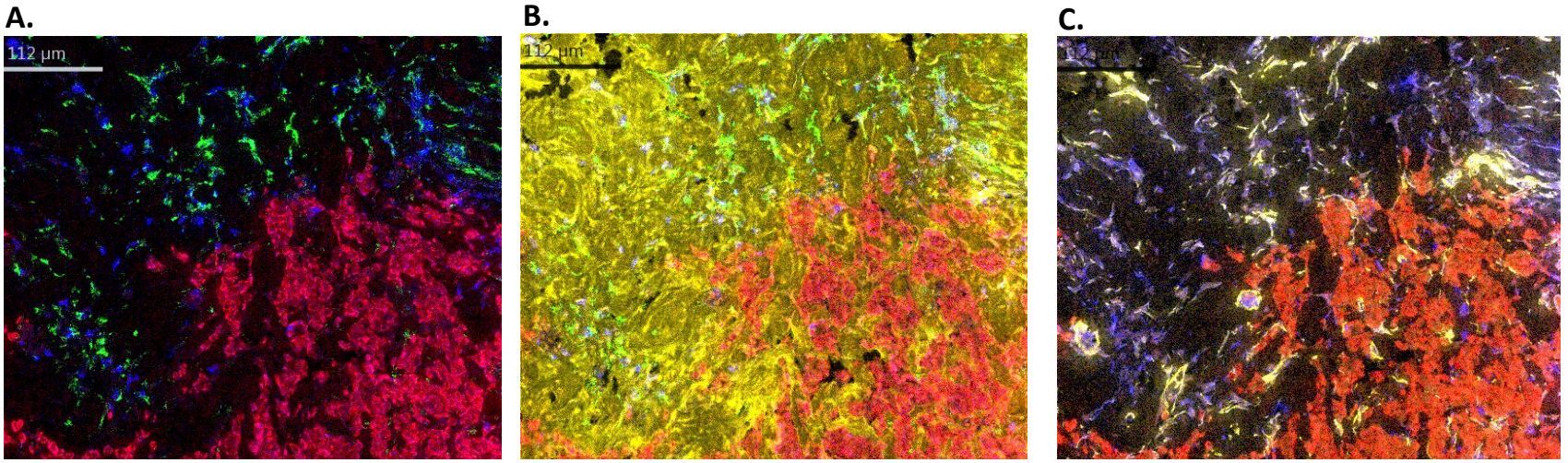
RNA collected from immune-dense, defined as ≥ 30% tumor-infiltrating lymphocyte (TIL) infiltration within a field of view at 100x magnification, and immune-sparse, < 30% TIL infiltration, regions of surgical specimens from 7 TNBC patients were analyzed with Nanostring's nCounter ® PanCancer Immune Profiling Panel, which evaluates the expression of > 770 immune-related genes. Normalized expression levels of various immune-related genes from immune-dense sections relative to corresponding levels from immune-sparse sections are shown here. Genes with greatest fold-differences in expression levels are listed in the table.

Comparison of immune-dense vs immune-sparse sections of triple negative breast cancer (TNBC) tumors



All immune cell subsets were more prominent in immune-dense sections of tumor compared to corresponding immune-sparse areas.

Appendix 3: Representative example of imaging mass cytometry analysis



Representative mass cytometry images of an invasive lobular carcinoma with tumor cells stained by Pan-Keratin (red). Additional staining includes (A): CD8+ T cells (blue) and tumor associated macrophages (CD163, green); (B): collagen (yellow), and (C): vimentin (blue) and α–smooth muscle actin (yellow).