AWARD NUMBER: W81XWH-21-1-0011

TITLE: Nanotechnology-Based Targeting of Breast Cancer Liver Metastases

PRINCIPAL INVESTIGATOR: Biana Godin

CONTRACTING ORGANIZATION: Methodist Hospital Research Institute, Houston, TX

REPORT DATE: March 2022

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
March 2022	Annual	**0**1MAR2021 – 28FEB2022

4. TITLE AND SUBTITLE

Nanotechnology-Based Targeting of Breast Cancer Liver Metastases

5a. CONTRACT NUMBER
W81XWH-21-1-0011

5b. GRANT NUMBER
BC200360

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

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 NOTES

14. ABSTRACT

This project develops a system to predict the effect of macrophage-delivered therapy on liver lesions based on tissue samples or histological slides taken from patient-resected tumors. This will help to efficiently personalize this nanomedicine-based therapy. The project will: (1) evaluate ability of different breast cancers (including commercially available human cell lines and clinically derived tumors from patients) to recruit macrophages in vitro in three dimensional breast tumor spheres, which resemble poorly vascularized liver tumors; (2) test the correlation between the number of macrophages in primary tumors and in distant tumors in the liver in vivo and in clinical samples from patients, and the ability to take up and slowly release nanotherapeutics; (3) apply computational modeling to fine-tune therapy schedules and quickly predict response based on patient tumor-specific analysis of macrophages and other markers in the tumor microenvironment. In this project period the HMRI team (Godin) focused on in vitro studies in 2D and 3D cancer cell lines and PDX as well as obtaining ACURO and HRPO approvals, finding clinical samples and initiating the analysis as well initiation of validation of mathematical model of tumor growth with UofL team. The UofL team (Frieboes) focused on development of a mathematical model of metastases that could efficiently simulate tumor growth and response to treatment. To this end, the numerical solution of the 3D model was implemented with a distributed computing approach. Further, an immune system component was implemented to simulate biologically-relevant tumor-immune interactions in the metastatic microenvironment.

15. SUBJECT TERMS
Nanomedicine; nanotherapy; immunotherapy; breast cancer; mathematical modeling

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	29	**19b. TELEPHONE NUMBER** *(include area code)*

Contents

1. INTRODUCTION

This project develops a system to predict the effect of macrophage-delivered therapy on liver lesions based on tissue samples or histological slides taken from patient-resected tumors. This will help to efficiently personalize this nanomedicine-based therapy. The project will: (1) evaluate ability of different breast cancers (including commercially available human cell lines and clinically derived tumors from patients) to recruit macrophages in vitro in three dimensional breast tumor spheres, which resemble poorly vascularized liver tumors; (2) test the correlation between the number of macrophages in primary tumors and in distant tumors in the liver in vivo and in clinical samples from patients, and the ability to take up and slowly release nanotherapeutics; (3) apply computational modeling to fine-tune therapy schedules and quickly predict response based on patient tumor-specific analysis of macrophages and other markers in the tumor microenvironment.

2. KEYWORDS

Nanomedicine; nanotherapy; immunotherapy; breast cancer; mathematical modeling

3. ACCOMPLISHMENTS

What were the major goals of the project?

Houston Methodist Research Institute (Godin) + University of Louisville (Frieboes)

Major Task 1: *In vitro* evaluation of the ability of breast tumors to recruit macrophages (30% completed)

Major Task 2: Evaluate transport of macromolecules and nanotherapeutics in hypo-perfused tumor lesions with high and low macrophage contents (10% completed)

Major Task 3: Evaluate feasibility of the proposed approach to personalize nanotherapy for patients with hypoperfused metastatic lesions based on macrophage infiltration and other parameters in the tumor microenvironment. (20% completed)

What was accomplished under these goals?

Houston Methodist Research Institute (Godin)

- **1) Major activities:**
  - In the first period we focused on in vitro studies in 2D and 3D cancer cell lines and PDX as well as obtaining ACURO and HRPO approvals, finding clinical samples and initiating the analysis as well initiation of validation of mathematical model of tumor growth with Dr. Frieboes (**Major task 1, subtasks 1-4; Major task 2, subtask 1; Major task 3, subtask 1**).
- **2) Specific objectives:**
  - In vitro, several protocols for PDX growth were tested and optimized for some PDX. Cell lines that attract macrophages were established (**Major task 1, subtasks 1-2**).
  - For in vivo studies, the ACURO approval was obtained and the studies were initiated (**Major task 1, subtask 3**).
  - For human samples HRPO approval was obtained to use commercially available clinical samples (**Major task 1, subtask 4**).

- After multiple searches, we have located and purchased the agreed number (15 patients) of primary breast tumor and matched breast cancer liver metastasis specimens (**Major task 1, subtask 4**).
- IMC and IHC/IF analysis of in vivo samples was initiated (**Major task 1, subtask 4**).
- IMC analysis of clinical specimens was initiated. Initial findings show significant similarities in the disease microenvironment between primary and metastatic lesions of the same patient (**Major task 1, subtask 4**).
- We have also started validation of mathematical model of tumor growth with Dr. Frieboes (**Major task 3, subtask 1**) and the manuscript is being prepared.

- **3) Significant results or key outcomes, including major findings, developments, or conclusions:**
  - Various breast cancer cell lines were tested for attracting macrophages in 2D and 3D cultures. Figure 1 shows a tumor spheroid produced from MCF-7 cells and incubated with fluorescently labelled macrophages (red) for 3 days. It can be clearly seen that the macrophages infiltrate into the spheroid.

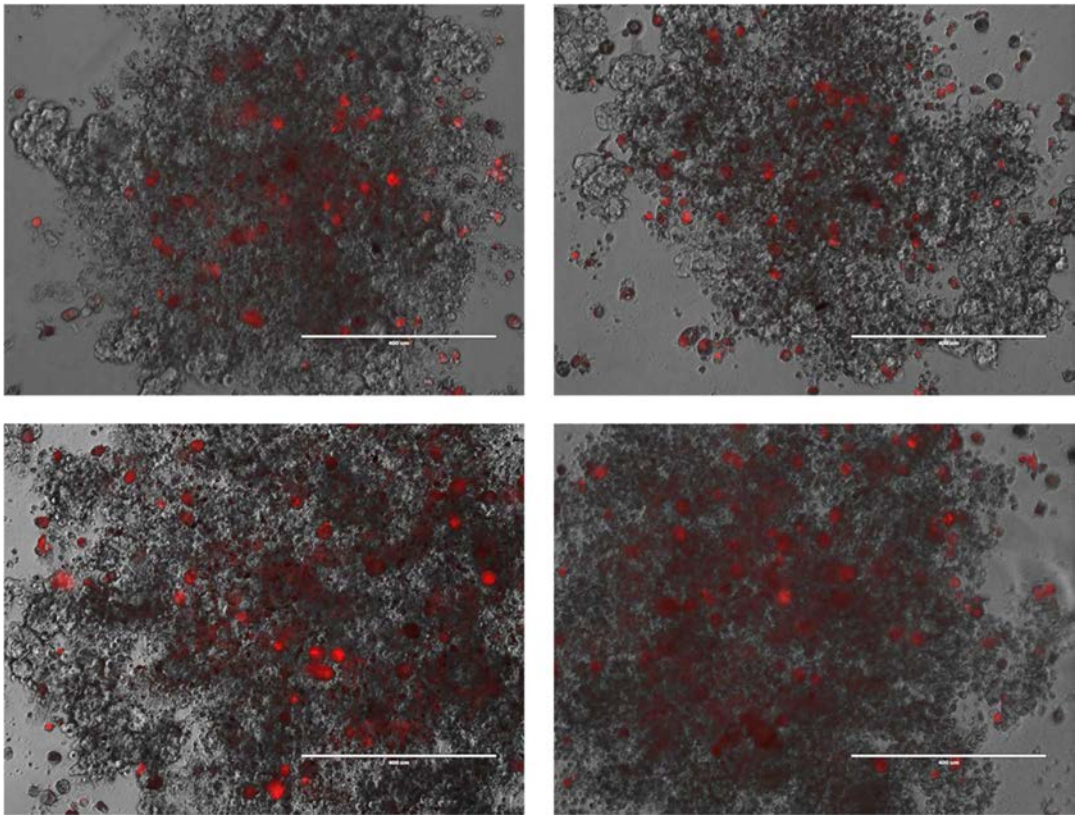


Fig. 1: Co-culture of MCF7 spheroids with labelled macrophages (Vybrant cell labelling solutions) shows that MCF7 cells efficiently recruit macrophages in the 3D structures.

- Protocols for growth of patient derived xenografts (PDX) were optimized for some PDX. **Fig. 2** shows several protocols that have been tested (various conditions, growth factors and methyl cellulose [MC] presence). Other conditions that were tested include the use of magnetic levitation with various concentrations of Nanoshuttles. Our studies show that in vitro growth of some PDX can be facilitated with 0.24% MC. Various breast cancer cell lines were tested for attracting macrophages in 2D and 3D cultures.

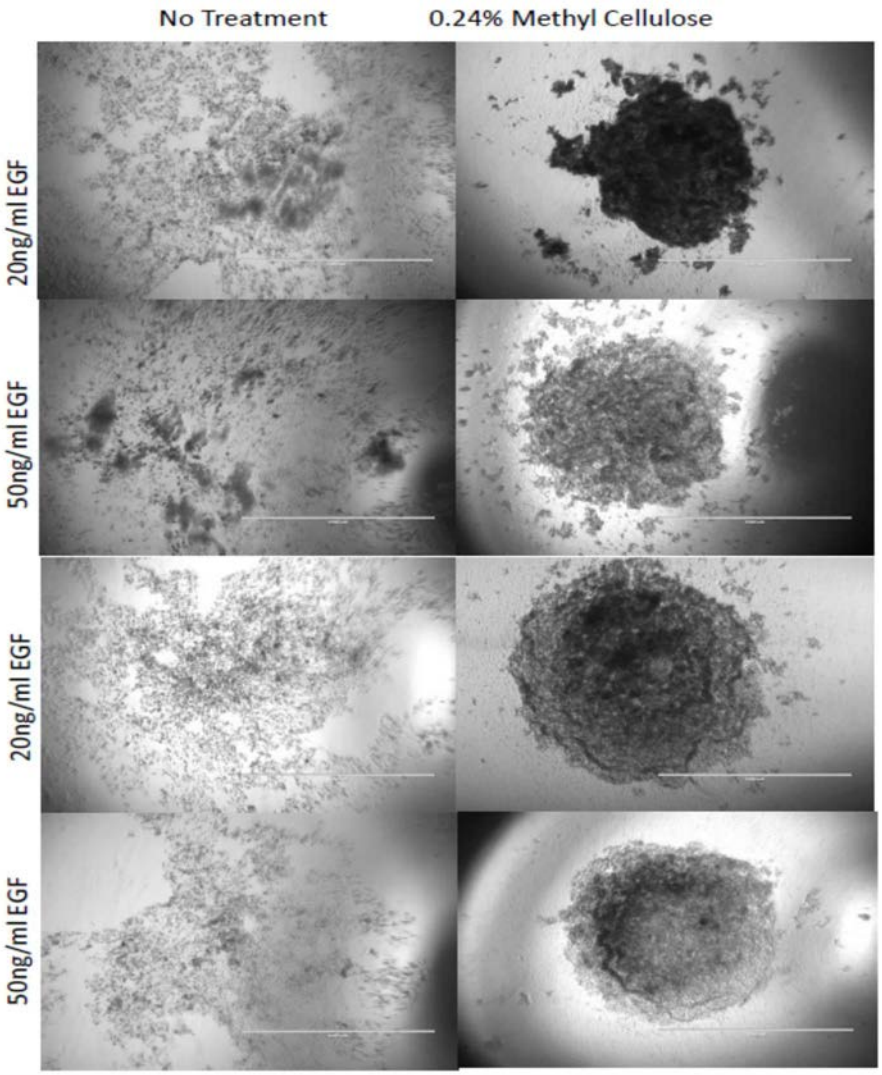


Fig. 2: Protocol for 3D culture of patient derived xenografts was optimized for some PDX. As can be seen in the Figure, protocol 2 with 0.24% methylcellulose yielded well-defined, tight spheroids.

- ACURO and HRPO approvals were obtained.
- Matched clinical samples from patients (primary breast cancers and matched liver metastasis, n=15 + normal breast and normal liver samples) were identified from a commercial vendor and purchased.
- The analysis of the clinical samples was initiated. H&E staining was performed to identify tumor cores in 3 initial patients and IMC analysis was initiated. 32 tumor and tumor microenvironment (TME) markers are being analyzed (**Fig. 3)**.
- Initial data from IMC analysis (**Fig. 4**) show that there are pronounced similarities in the microenvironment of primary lesions and liver metastasis. This points towards the feasibility of the proposed approach of personalizing the therapy based on the TME and transport variables.

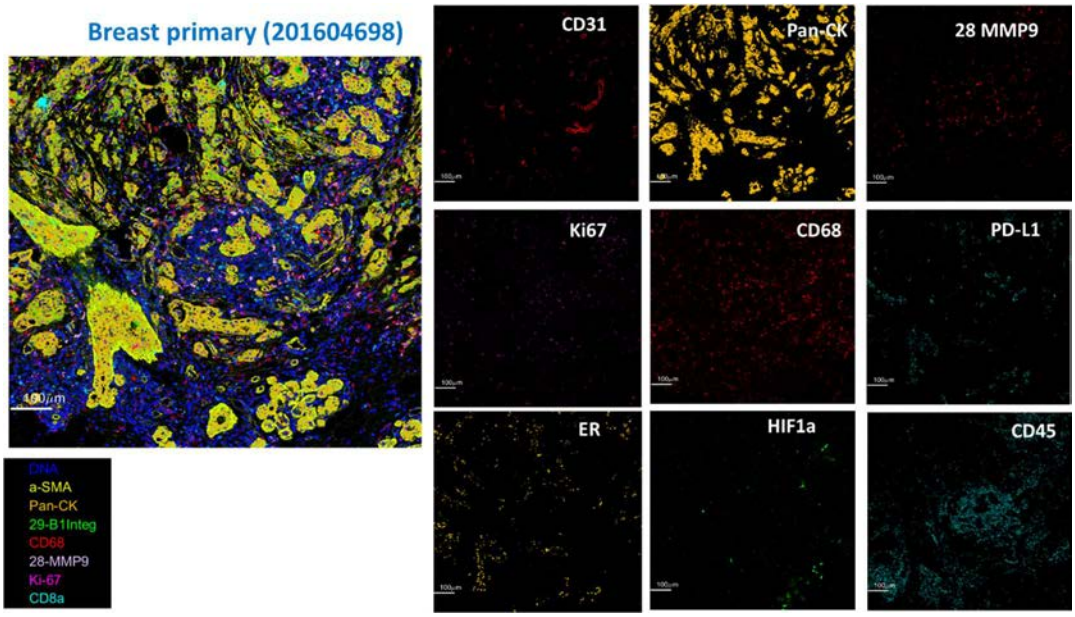
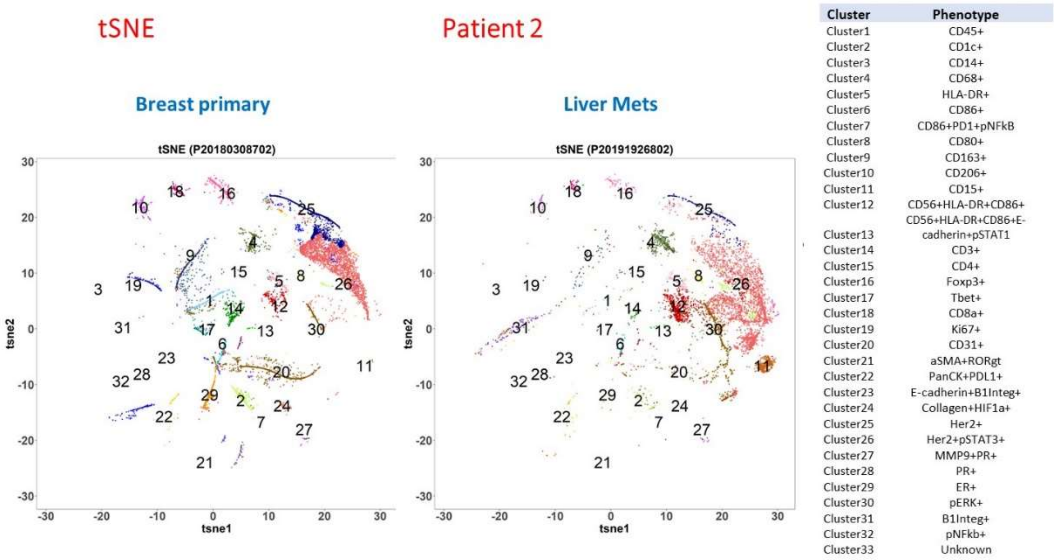


Figure 3. IMC analysis of a clinical primary breast tumor core showing expression of tumor and TME markers.



Cluster	Phenotype
Cluster1	CD45+
Cluster2	CD1c+
Cluster3	CD14+
Cluster4	CD68+
Cluster5	HLA-DR+
Cluster6	CD86+
Cluster7	CD86+PD1+pNFkB
Cluster8	CD80+
Cluster9	CD163+
Cluster10	CD206+
Cluster11	CD15+
Cluster12	CD56+HLA-DR+CD86+
Cluster13	CD56+HLA-DR+CD86+E-cadherin+pSTAT1
Cluster14	CD3+
Cluster15	CD4+
Cluster16	Foxp3+
Cluster17	Tbet+
Cluster18	CD8a+
Cluster19	Ki67+
Cluster20	CD31+
Cluster21	aSMA+RORgt
Cluster22	PanCK+PDL1+
Cluster23	E-cadherin+B1Integ+
Cluster24	Collagen+HIF1a+
Cluster25	Her2+
Cluster26	Her2+pSTAT3+
Cluster27	MMP9+PR+
Cluster28	PR+
Cluster29	ER+
Cluster30	pERK+
Cluster31	B1Integ+
Cluster32	pNFkb+
Cluster33	Unknown

Figure 4. tSNE analysis of IMC data showing the spatial proximity of various marker clusters in the TME in primary breast tumor and liver metastasis of the same patient.

University of Louisville (Frieboes)

- **1) Major activities:**
  - This first period of the project focused on the development of a mathematical model of metastases that could efficiently simulate tumor growth and response to treatment. To this end, the numerical solution of the 3D model was implemented with a distributed computing approach.
  - Further, an immune system component was implemented to simulate biologically-relevant tumor-immune interactions in the metastatic microenvironment.
- **2) Specific objectives:**

- Implement a distributed computing solution of the tumor model in order to enable efficient numerical solution of centimeter-scale tissue domains with sub-millimeter resolution.
- Implement a detailed immune system model to simulate tumor-immune system interactions

- **3) Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative):**
  - The distributed computing solution of the model was successfully implemented, enabling simulation of centimeter-scale domains (**Fig. 5**).

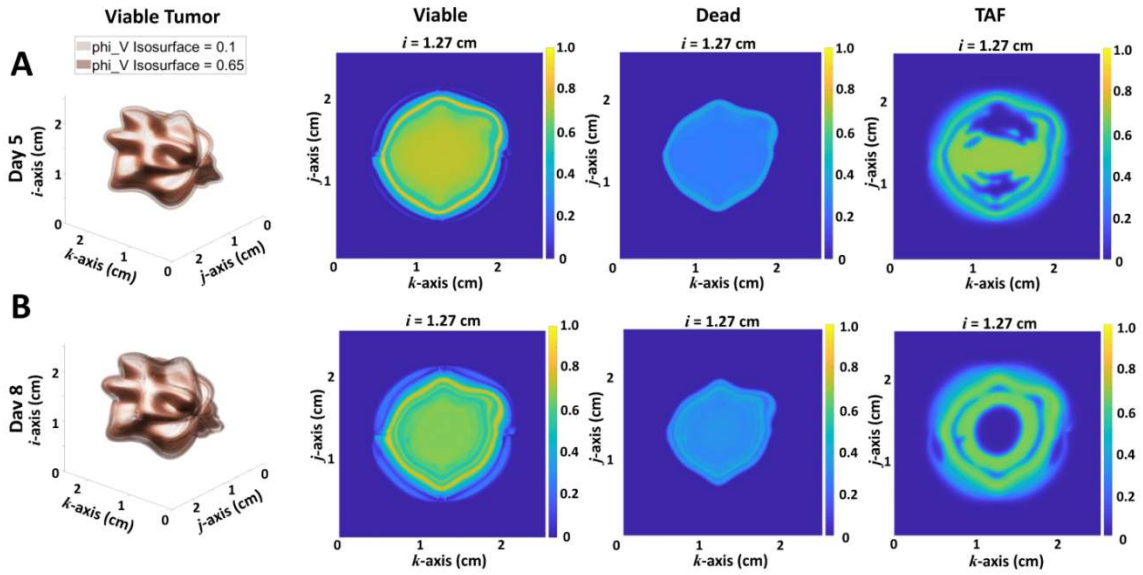


Figure 5: Evolution of ~2cm diameter tumor in 5123 domain at simulated (A) 5 days and (B) 8 days. Viable, dead, and tumor angiogenic factors (TAF) are shown (plane jk).

- Modeling of multi-metastatic tissue domains was implemented in order to simulate heterogeneous breast cancer liver metastases in the liver (**Fig. 6**).

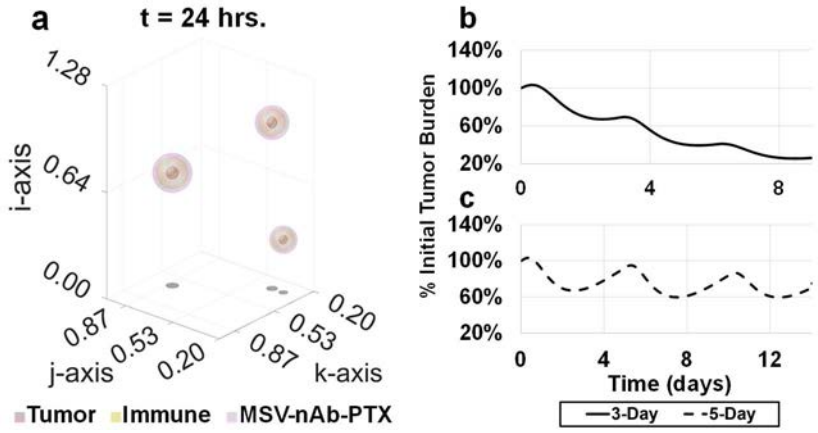
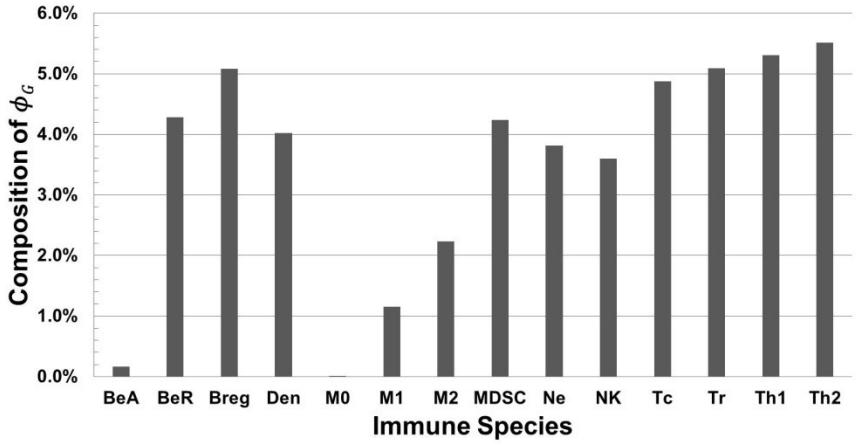


Figure 6: Model calibrated to prior BCLM modelling efforts and MSV-nab-PTX NP properties simulates response to NP-mediated immunotherapy targeting macrophages. nab-PTX was released from MSV-loaded macrophages at time t = 0 h into a 1.28 cm^3 simulated liver tissue sample containing 3 BCLM (100µm, 200µm, and 300 µm diameter). a) CLM at t = 24 h post treatment. CLM response to repetitive therapy is simulated for b) 3-day and c) 5-day intervals. All axes in a) are in cm scale.

- Simulated immune species are tracked in the large tissue domain (**Table 1** and **Fig. 7**).

Variable subscripts	Description	
M0	Monocytes	
M1	M1 macrophages	
M2	M2 macrophages	
NK	Natural killer cells	
NE	Neutrophils	
DEN	Dendrites	
MDSC	Myeloid-Derived Suppressor Cells	
B_ER	B-effector cell in resting state.	
B_EA	B-effector cell in active state.	
B_{reg}	B-regulating cell	
T_C	Cytotoxic T-cells ($CD8^+$ T-cells)	
T_R	Regulator T-cells	
T_{H1}	$CD4^+$ T-cells	Th1 cells
T_{H2}		Th2 cells

Table 1 – Immune species simulated in the tumor microenvironment.



4.

Figure 7 – Composition of immune cells within the simulated tumor microenvironment (as defined in **Table 1**).

- **4) Other achievements:**
  - Substantial progress was made to implement a machine learning approach to enable quick and efficient analysis of biological data obtained from *in vivo* experiments and from patient tumors.
- Stated goals not met: The stated goals for this first period were met.

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

- **HMRI (Godin):** One undergraduate student (summer student), one research assistant, two postdoctoral fellows received training during this period. The fellows were trained in in vitro and in vivo techniques (primary tumors, liver metastasis, spheroids, PDX).
- **UofL (Frieboes):** Two graduate research assistants (GRA), three undergraduate students, and one research assistant received training during this period. The personnel were trained in the

mathematical modeling of cancer and the analysis of cancer data. Individual Development Plans have been established for the GRAs. The plans are updated and reviewed on a yearly basis.

How were the results disseminated to communities of interest?

- Two peer-reviewed publications were completed, with one published and one in review:
  - Goodin DA, Frieboes HB. Simulation of 3D centimeter-scale continuum tumor growth at sub-millimeter resolution via distributed computing. *Computers in Biology in Medicine* 2021; 134:104507
  - Goodin DA, Frieboes HB. Simulation of tumor-immune interactions during cancer progression via a 3D continuum mixture model. *Journal of Theoretical Biology* 2022; in review.
- The findings were presented to scientific community including students and trainees:
  - Godin B., Factors in the Tumor Microenvironment Affect Transport and Efficiency of Nanotherapeutics. Biomedical Engineering Department, TAMU, College Station, Texas (Invited, Oral Presentation), April 2021.
  - Godin B. Cues in Organ Microenvironment Shape Transport and Efficacy of Nanomedicines: from Cancer to Obstetrics. HUJI Nanocenter Annual Conference, Dead Sea, Israel (Keynote Speaker), March 1, 2022.

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

The main goals for the next reporting period include:

- **Houston Methodist Research Institute (Godin)**
  - Continue evaluation of transport of macromolecules and nanoparticles in 2D and 3D tumor models in vitro.
  - In vivo evaluation of transport of macromolecules and nanoparticles in liver metastasis of breast cancer.
  - Collection of in vitro and in vivo data for calibration of the mathematical model of tumor growth and macromolecule transport.
  - Continue the IMC analysis of clinical samples- Evaluate macrophage infiltration in clinical samples taken from primary vs. metastatic sites to simulate the macrophage involvement in metastatic sites as a function of the infiltration in the primary tumor.
  - Manuscript preparation and submission.
- **University of Louisville (Frieboes)**
  - Calibrate the mathematical model of tumor growth and macromolecule transport with *in vitro* and *in vivo* tumor data.
  - Validate the mathematical model of tumor growth and macromolecule transport in liver metastasis of breast tumors.
  - Verify model-predicted tumor response as a function of therapy and macromolecule parameters in 3D co-culture and *in vivo*
  - Obtain model parameters related to tumor microenvironment in subjects *in vivo* by measuring tumor growth and performing therapy.

- Evaluate macrophage infiltration in clinical samples taken from primary vs. metastatic sites to simulate the macrophage involvement in metastatic sites as a function of the infiltration in the primary tumor.

4. IMPACT

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

- The project has contributed to an understanding of the TME in primary breast cancer lesions and liver metastasis, that can further enable a personalized and more efficient therapy of the metastatic disease. Initial clinical samples analyzed show that there is a similarity in the TME, pointing towards the ability of tumors in some patients to recruit phagocytic cells, that can be further used for retaining the macromolecules in the proximity of the tumors.
- The project has contributed to developing the capability to efficiently simulate tissue in 3D at centimeter-scale sizes with sub-millimeter resolution. This has been accomplished by implementing the mathematical model using distributed computing based on state-of-the-art cluster computing technology. Modeling of tissue at large scales with high resolution is a breakthrough in the field of cancer modeling. This achievement enables evaluation of therapy response of multiple breast cancer metastases within centimeter-sized regions of liver tissue, which provides a relevant context for clinical evaluation.

What was the impact on other disciplines?

- The implementation of a distributed computing solution to a mixture model of tumor growth is an achievement in the field of mathematical biology, enabling representation of large-scale tissue domains at high resolution.
- The numerical implementation further represents an achievement in the field of numerical computing by reporting the capability to solve coupled complex differential equations that leverage the power of distributed computing.

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

- Nothing to report

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

- Nothing to report

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

6. PRODUCTS

Publications, conference papers, and presentations

Journal publications.

- Goodin DA, Frieboes HB. Simulation of 3D centimeter-scale continuum tumor growth at sub-millimeter resolution via distributed computing. *Computers in Biology in Medicine* 2021; 134:104507. (federal support acknowledged)
- Goodin DA, Frieboes HB. Simulation of tumor-immune interactions during cancer progression via a 3D continuum mixture model. *Journal of Theoretical Biology* 2022; in review. (federal support acknowledged)
- Goodin DA, E Chau, A Tiwari, Godin B*, Frieboes HB*. Simulation of multiple breast cancer liver metastases growth and response to macrophage-mediated nanotherapy. 2022, In preparation. (federal support acknowledged)
- Frieboes HB., Chen HS, Godin B. Targeting regulation of myeloid-derived-suppressor cells with nanotherapeutics in cancer and beyond, 2022, in preparation. (federal support acknowledged)

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

- Nothing to report

Other publications, conference papers, and presentations.

- Goodin DA. Evaluation of nanoparticle-mediated immunotherapy targeting cancer liver metastases via mathematical modeling. Doctoral qualifying examination presentation, School of Interdisciplinary and Graduate Studies, University of Louisville. 11/29/2021
- Godin B., Factors in the Tumor Microenvironment Affect Transport and Efficiency of Nanotherapeutics. Biomedical Engineering Department, TAMU, College Station, Texas (Invited, Oral Presentation), April 2021.

- Godin B. Cues in Organ Microenvironment Shape Transport and Efficacy of Nanomedicines: from Cancer to Obstetrics. HUJI Nanocenter Annual Conference, Dead Sea, Israel (Keynote Speaker), March 1, 2022.

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

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Houston Methodist Research Institute

Name:	Biana Godin
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-6089-6695
Nearest person month worked:	3.5
Contribution to Project:	Dr. Godin is the lead Investigator on the project. Dr. Godin applied her expertise to establish the 2D, 3D and in vivo models of cancer, as well as to supervise the analysis of TME. She was involved in the design, planning and carrying out the proposed research and data analysis. She has supervised and coordinated this work with personnel and co-Is assigned to the project at HMRI and UoL.

Name:	Shu-Hsia Chen
Project Role:	Co-Investigator
Nearest person month worked:	0.2
Contribution to Project:	Dr. Chen served as an Immunology expert. Dr. Shu-Hsia Chen has extensive leadership experience and expertise in the field of tumor immunology, tumor microenvironment, reprogram of myeloid cell differentiation and gene therapy

	research. Her lab was responsible for conducting imaging mass cytometry (IMC) experiments.

Name:	Polly Niravath
Project Role:	Co-Investigator
Nearest person month worked:	0.2
Contribution to Project:	Dr. Niravath shares responsibility for evaluation of the clinical samples from primary tumors and metastatic sites as well as for the overall clinical perspective of the project.

Name:	Roberto Rosato
Project Role:	Co-Investigator
Nearest person month worked:	0.7
Contribution to Project:	Dr. Rosato was involved in the studies involving 3D culture of patient derived xenografts (PDX) of the breast tumors.

Name:	Eric Chau
Project Role:	Research Assistant
Nearest person month worked:	3.5
Contribution to Project:	Mr. Chau performed in vitro and in vivo studies for establishing liver metastasis models of breast cancer. He optimized the protocols for PDX growth and participated in the preparation for IMC analysis.

Name:	Anjana Tiwari
Project Role:	Research Associate
Nearest person month worked:	3.7
Contribution to Project:	Dr. Tiwari was recruited in Nov 2021 and was involved in vitro and in vivo experiments, as well as in analysis of clinical samples.

Name:	Debasish Boral
Project Role:	Research Associate
Nearest person month worked:	0.8
Contribution to Project:	Responsible for IMC analysis.

Name:	Vijaya Kumar Charaka

Project Role:	Research Associate
Nearest person month worked:	2.1
Contribution to Project:	Responsible for IMC analysis.

University of Louisville

Name:	Hermann Frieboes
Project Role:	PD/PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-5959-4286
Nearest person month worked:	4
Contribution to Project:	Dr. Frieboes applied his expertise to establish a computational model that can simulate breast cancer liver metastases. He has coordinated this work with personnel assigned to the project at The Methodist Hospital Research Institute and at UofL. He has guided the modeling work of the personnel at UofL

Name:	Dylan Goodin
Project Role:	Graduate Student
Nearest person month worked:	12
Contribution to Project:	Implementation of mathematical modeling to simulate growth and treatment of breast cancer liver metastases including interactions with the immune system

Name:	Hunter Miller
Project Role:	Graduate Student
Nearest person month worked:	12
Contribution to Project:	Implementation of modeling techniques, including machine learning, to help systematically analyze cancer data from patients and from experiments in vitro and in vivo.

Name:	Sarah Lee
Project Role:	Undergraduate Student
Nearest person month worked:	4
Contribution to Project:	Training and development of mathematical modeling to simulate and test tumor growth and response to nanotherapy

Name:	Corey Chitwood
Project Role:	Research Assistant
Nearest person month worked:	2
Contribution to Project:	Training and development of computational techniques to simulate and analyze progression of disease in order to predict clinical outcomes

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

Yes, please see attached support documents highlighting the changes to current support for Drs. Godin, Frieboes, Rosato, Chen, Xu and Niravath.

What other organizations were involved as partners?

- Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

None

9. APPENDICES

GODIN, BIANA

CURRENT SUPPORT

W81XWH2110011 (Godin) 3/1/2021 – 2/29/2024
DoD
Title: Nanomedicine for Advanced Breast Cancer Personalized to the Organ Microenvironment
In this proposal, we aim to deliver and retain nanomedicines to liver metastasis of breast tumors by exploiting innate mechanisms, such as macrophage cell infiltration.
Specific aims: 1) Evaluate the ability of specific breast tumors to recruit macrophages. 2) Evaluate proposed nanotherapeutics to deliver and retain drugs to tumor metastatic lesions with high and low macrophage content. 3) Fine-tune therapy schedules and predict therapeutic responses based on patient tumor-specific quantification of macrophages and other tumor markers.
Role: PI
Effort:

Year	Cal. Months
2021	3.6
2022	3.6
2023	3.6

Point of contact: Jodi Cardoza, 301-619-2693, jodi.l.cardoza.civ@mail.mil

(New)
(Cooke) 3/1/2021 – 8/31/2022
Avita
Title: Effects of pTERT mRNA transfected skin cells in a wound model
The goal is to regenerate skin and to treat burn wounds a split-thickness autologous skin graft can be harvested, disaggregated into single cells, followed by spraying the skin cells on the prepared burn site. In this project, we intend to improve the cell treatment using an mRNA delivered using lipid nanoparticles (LNPs) as a therapeutic for acceleration of healing of cutaneous wounds.
Role: PI
Effort:

Year	Cal. Months
2021	1.2
2022	1.2

(extended through 4/2022)
R21AI137533 (Godin/Jagannath) 5/15/2019 – 4/30/2022
NIH
Title: Study of responses to CD44 targeted nanovectors to design a novel adjunctive anti-tuberculosis host-directed therapy
The main aim of this study is to develop tuberculosis therapeutics and identify the mechanism of the immunity targeting CD44 in the tuberculosis.
Specific aims: Aim 1: To determine optimal dosage, biodistribution, efficacy and safety of inhaled CD44TA-LIP. 2: To assess the nature of the immune responses generated by short and long-term inhaled CD44TA-LIP on innate and adaptive cellular immunity.
Role: PI
Effort:

Year	Cal. Months
2019	0
2020	1.3
2021	1.3

Point of contact: Joyce Marpu Addy, joyce.addy@nih.gov, 301-761-6628

RP200619 (Cooke) 8/31/2020 – 8/30/2025
Cancer Prevention and Research Institute of Texas (CPRIT)
Title: CPRIT Core for RNA Therapeutics and Research
The goal of this proposal is to expand the current CPRIT-funded RNAcore to create state-of-the-art comprehensive CPRTI RNA Therapeutics facility that will help academic groups and biotechs in Texas and aid to translate their ideas and innovations into therapies.
Role: Co-I
Effort:

Year	Cal. Months
2020	1.2
2021	1.2
2022	1.2
2023	1.2
2024	1.2

Cancer Center Innovation (Godin/Kamat/Raghavan) 8/1/2020 – 7/31/2022
Houston Methodist Hospital Cancer Center
Nano-immunotherapy targeting macrophages to arrest liver metastasis in ovarian cancer
The goal is to utilize engineered liver biomatrices to design efficient nanomedicine strategies for macrophage checkpoint immunotherapy in advanced ovarian carcinoma (OvCa).
Specific aims: 1) Establish role of CD47-SIRPα in OvCa liver metastasis using OvCa/macrophage spheroids and engineered liver biomatrices. 2) Design and evaluate nanomedicines for disrupting CD47-SIRPα interaction.
Role: Co-I
Effort:

Year	Cal. Months
2020	0.24
2021	0.24

Point of contact: Tamim Malbari, tmalbari@houstonmethodist.org

(New)
(Sukhovershin/Godin/Nasir) 1/1/2022 – 12/31/2022
George and Angelina Kostas Cardiovascular Nanomedicine Foundation
Project title: RNA-based Therapy for Familial Hypercholesterolemia
The major goals of this project are: 1) To develop an optimal LNP formulation for delivering RNA therapeutics to liver. 2) To assess the effectiveness and short-term safety of LDLR and anti-PCSK9 mRNA therapy in vivo.
Role: co-PI
Effort: 0.12 calendar
Point of contact: Connie Green, cgreen@hosutonmethodist.org

FRIEBOES, HERMANN

CURRENT SUPPORT

DOD Department of the Army (Godin/Frieboes) 3/01/2021 – 2/29/2024
Nanotechnology-based targeting of breast cancer liver metastases
This project develops a system to quickly determine which patients will likely benefit from macrophage-delivered nanotherapy to breast cancer liver metastatic lesions.
Role: Partnering PI
Effort:

Year	Cal. Months
2021	3.6
2022	3.6
2023	3.6

Overlaps: None
Program Manager: Gayle Vaday, Ph.D.
Congressional Directed Medical Research Programs
Department of Defense
1077 Patchel Street
Fort Detrick, MD 21702
E-mail: gayle.g.vaday.civ@mail.mil

(NEW)
NIH/NIAID R01AI168475 (Steinbach-Rankins/Frieboes/Lewis) 2/25/2022 – 1/31/2027
3D-bioprinting of sustained- and phased-release antibiotic and probiotic scaffolds to treat bacterial vaginosis
This project uses 3D-printing and computational modeling, iteratively enabled by functional investigation of prototype scaffolds, to design long-acting products that sustain phased-delivery of antibiotics and probiotics to treat bacterial vaginosis.
Role: MPI
Effort:

Year	Cal. Months
2022	3.6
2023	3.6
2024	3.6
2025	3.6
2026	3.6

Overlaps: None
Program Official: Thomas J. Hiltke, PhD
National Institute of Allergy and Infectious Diseases
BG 5601 Fishers Lane Rm 8F31
5601 Fishers Ln
Rockville MD 20852
thiltke@niaid.nih.gov

PREVIOUS SUPPORT

(REMOVED)

NIH/NCI R15CA203605 (Frieboes) 6/01/2016 – 3/31/2021

Integrated framework to predict chemotherapy response post lung tumor resection

This project develops a framework to predict lung cancer patient response to chemotherapy by integrating metabolomics analysis, imaging evaluation, biopsy data, and advanced mathematical modeling.

Role: PI, 10% effort

Overlaps: None

Financial/Grants Officer: Jennifer Couch, PhD
Chief
Structural Biology and Molecular Applications Branch (SBMAB)
9609 Medical Center Drive, Room 6W332
Rockville, MD 20850-9747
Email: couchj@mail.nih.gov

ROSATO, ROBERTO R

CURRENT SUPPORT

Title: Nanotechnology-Based Targeting of Breast Cancer Liver Metastases
BC200360 (Godin)
DoD BCRP
6/1/2020 – 5/31/2023
Budget:
Overlap: None
Effort: 0.72 calendar
Role: Co-Investigator
Goal: In this proposal, we aim to deliver and retain nanomedicines to liver metastasis of breast tumors by exploiting innate mechanisms, such as macrophage cell infiltration.
Specific Aims:
Aim 1. Evaluate the ability of specific breast tumors to recruit macrophages.
Aim 2. Evaluate proposed nanotherapeutics to deliver and retain drugs to tumor metastatic lesions with high and low macrophage content.
Aim 3. Fine-tune therapy schedules and predict therapeutic responses based on patient tumor-specific quantification of macrophages and other tumor markers.

(New)
Title: A phase II multi-center trial evaluating dual targeting of the PI3K/AKT and NOS pathways for treating metaplastic breast cancer (MpBC)
U01 (MPI: Chang, Meric, Lipkwitz, Wink, Wong)
NIH
12/1/2021 – 11/30/2026
Budget:
Overlap: None
Effort: 2.4 calendar
Role: Co-Investigator
Goal: In the proposal, we propose a multi-center phase II clinical trial with a targeted combinatorial approach by inhibiting two major pathways implicated in metaplastic breast cancer (MpBC), namely the phosphoinositide 3-kinase pathway (PI3K/AKT) and nitric oxide synthase (NOS) pathways. Our proposal further includes mechanistic investigation and identification of biomarkers of resistance and cell-cell interactions using specimens derived from MpBC patients.

(New)
Title: Novel Potential drug targets for treatment of triple negative breast cancer (Chang)
Breast Cancer Research Foundation
10/1/15 – 09/30/22
Budget:
Overlap: None
Effort: 4.2 calendar
Role: Co-Investigator
Goal: The goal of this study is to identify potential targets for the treatment of metastatic breast cancer.

PREVIOUS SUPPORT

(Removed)
Title: Microbiome and TNBC response to immunotherapies.
Houston Methodist Cancer Center
July 2019-June2021
Budget:year

Overlap: None
Effort: 1.2 calendar
Goal: we aim to interrogate the role of the breast and gut microbiome in TNBC patients with the purpose of establishing potential links between them and the patient's response to immunotherapies, and to provide better insight into the relationships between microbiota at different local and remote locations.
Specific Aims:
Aim 1: To establish the microbiome composition from a) nipple aspirate fluid (NAF) and b) fecal samples of TNBC-derived patients.
Aim 2: To evaluate the impact of breast microbiota in the response to immunotherapies in mouse models.

CHEN, SHU-HSIA

ACTIVE:

R01CA208703 (Chen) 09/22/2017– 08/31/2022 3.00 CM NIH/ NCI
Project Title: Modulation of tumor inflammatory factor for immune therapy
Contact: Dianna Bailey; email: baileydianna@mail.nih.gov
Role: PI
Major goals: We will study the mechanisms by which the tumor factor CMTM4 regulates tumor inflammatory microenvironment, which play an important role in the regulation of tumor cells and reprogram of myeloid cell function for cancer immune therapy.
Specific Aims:
Aim 1: CMTM4 is the key driver that controls tumor inflammation through membrane-bound associated proteins and membrane fluidity.
Aim 2: Modulate the function of myeloid cells through CMTM4.
Aim 3: Development of CMTM4 blocking antibodies to target CMTM4 on tumor cells and to modulate myeloid cell function
Overlap: None.

R01CA127483 (Chen) 04/01/2007-07/31/2022 0.6 CM NIH/NCI
Project Title: Intervention of Immune Tolerance by Small Molecules
Contact: Dianna Bailey, email: baileydianna@mail.nih.gov
Role: PI
Major goals: The objective of this proposal is to understand the mechanism by which MDSC biological function is regulated and to devise an optimized protocol for directing the functional activities of MDSC toward suppression of GVHD while allowing sufficient GVL activity to eradicate tumors.
Specific Aims:
Aim 1. Study the regulation of MDSC function and the associated effects on GVHD.
Aim 2. Study the effects of PIR-B ligation on MDSC as related to inhibition of GVHD and the corresponding signaling regulation in an irradiated host.
Aim 3. Study the mechanism and effects of MDSC mediated regulation of GVHD vs. GVL through PIR-B/LILRB engagement in mouse GVHD models and in a human xenograft NSG mouse model.
Overlap: None.

R01CA204191 (Chen) 12/01/2016-11/30/2022 3.00 CM NIH/NCI
Project Title: LILRB Modulates Tumor Microenvironment and Promotes Tumor Progression
Contact: Dianna Bailey, email: baileydianna@mail.nih.gov
Role: PI
Major goals: The goal of our project is to understand the mechanism underlying the regulation of Tumor associate macrophage (TAM)/MDSC pro-tumor and tumor invasion by LILRB. The results from this study will be used to design TAM/MDSC-targeted cancer immune therapies.
Specific Aims:
Aim 1. Modulate the function of myeloid cells through PIRB/LILRB to promote anti-tumor responses.
Aim 2. LILRB controls tumor invasion.
Aim 3. Prevent tumor invasion/progression by fostering M1 macrophage differentiation as an immune checkpoint therapy.
Overlap: None.

U01 OH011328 (Aaronson) 09/01/2016 – 08/31/2022 1.08 CM
NIOSH (Sub only)
Project Title: Impact of WTC dust on immune functions and prostate cancer promotion
Contact: Evelina Berman, email: evelina.berman@mssm.edu
Role: Co-Investigator
Major goals: The goals are to elucidate possible mechanisms by which WTC dust may induce diseases in those at risk, how the inflammatory responses induced by WTC dust may correlate with biomarkers identified in human prostate tumor tissues, and whether prostate tumor progression in mouse models may be ameliorated through control of the inflammatory response and application of cancer immune modulatory therapies.
Overlap: None.

(Change in Role and effort)
R01CA222959-01 (Chen, Liu, Mai) 07/01/2018-11/30/2023 2.4 CM
NIH/NCI
Project Title: Mechanism of intratumoral transport of particulate drugs
Contact: Alley, Michael C, email: alleym@mail.nih.gov
Role: Principal Investigator
Major goals: The goal of this grant application is to understand the process of nanoparticle drug transport inside the tumor tissue.
Specific Aims:
Aim 1. We will examine cell-mediated tumor entry of particulate drugs.
Aim 2. We will analyze the process of intratumoral passage of drug particles.
Aim 3. We will investigate potential impact on tumor microenvironment and anti-tumor immunity as a result of effective intratumoral transport of particulate drugs.
Overlap: None.

BC191397P1 (Grattoni, Partner PI- Chen) 08/01/20 -07/31/23 1.2 CM
DoD Breakthrough level 2
Project Title: Transforming triple negative breast cancer treatment through intratumoral immunotherapy via nanofluidic drug eluting seed
Role: Partner PI
Specific Aims:
Aim 1. To evaluate the effect of NDES-mediated sustained intratumoral delivery kinetics on immunotherapy biodistribution and tumor immune microenvironment modulation.
Aim 2. To evaluate efficacy and toxicity of intratumoral NDES immunotherapy alone or in conjunction with radiotherapy for local and systemic tumor control.
Overlap: None.

W81XWH2110011 (Godin, Frieboes) 03/01/2021 – 02/28/2024 0.24 CM
USAMRAA
Project Title: Nanotechnology-Based Targeting of Breast Cancer Liver Metastases
Role: Co-Investigator
Specific Aims;
Aim 1. Evaluate ability of specific breast tumors to recruit macrophages.
Aim 2. Evaluate proposed nanotherapeutics to deliver and retain drugs to tumor metastatic lesions with high and low macrophage content.
Aim 3. Fine-tune therapy schedules and predict therapeutic responses based on patient tumor-specific quantification of macrophages and other tumor markers.
Overlap: None

(New)
Lupus Research Alliance 07/01/2021 – 06/30/2023 (sub only) 0.24 CM
Project Title: Urinomics as a Guide to the Renal Immune Landscape in SLE
Role: Co-Investigator
Major Goals: Determine if LN-WBC-Panel urine proteins may serve as surrogates of specific renal immune cell infiltrates in LN.
Specific Aims:
Aim 1. To ascertain if urine levels of the 15 proteins in the LN-WBC-Panel can be used to track specific WBC subsets within LN kidneys.
Aim 2. To ascertain if the 15 urine proteins in LN-WBC-Panel are predictive of clinically active LB, in a cross-sectional cohort, or predictive of treatment response to induction therapy of LN.
Overlap: None

COMPLETED:

(Removed)
Master Laboratory Services Agreement 7/2/2020 – 7/1/2021
Ansun BioPharma
Testing the Immunomodulatory effects of DAS181 in SARS-CoV-2 investion
Major Goal: Evaluate the hypotheses for mechanism of action of DAS181 in treating COVID-19
Specific Aims:
Aim 1. Evaluate the DAS181 on the effect of viral entry on human lung cells, macrophages, and 293 cells using SARS-CoV-2 Spike pseudovirus system containg luciferase reporter gene.
Aim 2. Determine the DAS181 on the anti-inflammatory response on M1 vs M2 macrophage lineages, readouts include inflammatory cytokine profiling and cell surface markers.
Aim 3. Test DAS181 on anti-inflammatory response under the condition of Pseudo virus or TLR Ligand or Siglec 14, 15, 16, CD169 (Siglec-1), Ficolin-1, SPP-1, CD33 mediate stimulation on macrophage and lectin complement activation.
Aim 4. Test whether DAS181 can block the inhibitory co-stimulator molecules and promote the T cell proliferation, and HLA-DR expression on monocytes/macrophages, and IFN signaling.

XU, JIAGIONG

Ongoing Research Support

(New)
NIH 1R01NS121405 (Yun) 04/01/21-03/31/26
NCI
Title: S100A4 mediated immune suppression in GBM
The major goal of this project is to elucidate how S100A4 expression in glioma and immune cells generate and maintain the "immune cold" landscape in GBM, through both cell-autonomous and non-autonomous mechanisms.
Specific aims: 1) elucidate mechanisms through which S100A4 expression in glioma cells promotes local immune-suppressive microenvironment in GBM. 2) determine mechanisms through which S100a4 expression in immune cells controls myeloid and T cell trafficking, polarization, and function.
Effort: 5%
Role: Co-Investigator
Point of contact: Jane Fountain, fountai@ninds.nih.gov

W81XWH2110011 (Godin) 2/28/21 – 2/24/24
DoD
Title: Nanomedicine for Advanced Breast Cancer Personalized to the Organ Microenvironment
In this proposal, we aim to deliver and retain nanomedicines to liver metastasis of breast tumors by exploiting innate mechanisms, such as macrophage cell infiltration.
Specific aims: 1) Evaluate the ability of specific breast tumors to recruit macrophages. 2) Evaluate proposed nanotherapeutics to deliver and retain drugs to tumor metastatic lesions with high and low macrophage content. 3) Fine-tune therapy schedules and predict therapeutic responses based on patient tumor-specific quantification of macrophages and other tumor markers.
Effort: 5%
Role: Co-Investigator
Point of contact: Jodi Cardoza, , jodi.l.cardoza.civ@mail.mil

NIRAVATH, POLLY

Ongoing Research Support

Title of Project: A Phase II trial of HKI-272 (neratinib) for patients with HER2-positive breast cancer and brain metastases: TBCRC 22
Name of funding agency: Breast Cancer Research Foundation via HOPKINS
Dates of Funding: 1/1/12-Present
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Title of Project: MONARCH: Randomized, double-blind, placebo-controlled, phase 3study of fulvestrant with or without LY2835219, a CDK4/6 inhibitor, for women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer
Name of funding agency: Lilly
Dates of Funding: 2/1/15-Present
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Title of Project: Phase 2, multicenter, open-label study to assess the efficacy and safety of enzalutamide with trastuzumab in subjects with HER2+ AR+ metastatic or locally advanced breast cancer
Name of funding agency: Astellas
Dates of Funding: 12/1/15-Present
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Title of Project: TBCRC 22: A Phase II trial of HKI-272 (neratinib) for patients with HER2+ breast cancer and brain metastases
Name of funding agency: EISAI/PFIZER (Dana Farber)
Dates of Funding: 6/1/12-Present
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Title of Project: TBCRC 35: Palbociclib in combination with fulvestrant or tamoxifen as treatment for hormone receptor positive metastatic breast cancer previously exposed to inhibitors o the PI3K pathway: A study with pharmacodynamics markers
Name of funding agency: JOHN HOPKINS UNIVERSITY
Dates of Funding: 3/1/14-Present
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Title of Project: NALA (PUMA-NER-1301): A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients HER2+ metastatic breast cancer who have received two or more prior HER2-directed regimens in the metastatic setting
Name of funding agency: PUMA Biotech
Dates of Funding: 3/13/14-ongoing
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Title of Project: SOLAR-1: A Phase III randomized double-blind, placebo controlled study of apelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which has progressed on or after aromatase inhibitor treatment
Name of funding agency: NOVARTIS
Dates of Funding: 12/31/15-Present
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Title of Project: Increasing clinical trial enrollment in underserved patients with metastatic breast cancer
Name of funding agency: NCCN/Pfizer
Dates of Funding: 1/1/16-Present
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Contract
Overlap: None

Each of these clinical trials has a varying need of effort depending on the type of activity currently in progress: protocol development, start-up, patient recruitment, enrollment, follow-up, monitoring, data analysis, publication, and closeout. The cyclic and unpredictable nature of the activities in these trials makes it impossible to assign a precise percent effort for each trial. Dr. Niravath has reviewed her clinical study obligations and confirms that the aggregate effort on all trials listed below does not exceed 10% of institutional effort.

(New)
Title of Project: Texas Southern University Breast Cancer Prevention and Screening Center (TSU BCSPC)
Goal: The goals of this project is to provide low-income medically underserved women with CPRIT funded mammograms.
Role: Co-Investigator
Name of funding agency: CPRIT
Dates of Funding: 9/1/21-8/31/24
Annual Direct cost & Direct cost for overall period:
Specify Grant or Contract: Grant
Overlap: **None**

BC200360 (Godin)
Title of Project: Nanotechnology-Based Targeting of Breast Cancer Liver Metastases

Goal: In this proposal, we aim to deliver and retain nanomedicines to liver metastasis of breast tumors by exploiting innate mechanisms, such as macrophage cell infiltration.
Specific aims: 1) Evaluate the ability of specific breast tumors to recruit macrophages. 2) Evaluate proposed nanotherapeutics to deliver and retain drugs to tumor metastatic lesions with high and low macrophage content. 3) Fine-tune therapy schedules and predict therapeutic responses based on patient tumor-specific quantification of macrophages and other tumor markers.
Name of funding agency: DoD
Dates of Funding: 6/1/2020 – 5/31/2023
Annual Direct cost & Direct cost for overall period:
Effort: 2%, 0.24 calendar months
Role: Co-Investigator
Specify Grant or Contract: Grant
Overlap: None