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TITLE: Transforming Triple-Negative Breast Cancer Treatment Through Intratumoral Immunotherapy via Nanofluidic Drug-Eluting Seed

PRINCIPAL INVESTIGATOR: Shu-Hsia Chen

CONTRACTING ORGANIZATION: Methodist Hospital Research Institute, Houston, TX

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Fort Detrick, Maryland 21702-5012

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

METHODIST HOSPITAL RESEARCH INSTITUTE
6670 BERTNER AVE
HOUSTON TX 77030-2602

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The research addresses the overarching challenge to "revolutionize treatment regimens with ones that are more effective, less toxic, and impact survival." Our approach is to utilize the nanofluidic drug-eluting seed (NDES) for intratumoral immunotherapeutics delivery in a sustained manner. In this report, we showed three major tasks: 1) In addition to determining the biodistribution of PDL1 antibody in the 4T1 and EMT6 via NDES, bolus intratumoral (IT), and intraperitoneal (IP) delivery approach, we performed an extensive investigation of tumor properties, including tumor density, vasculature formation, molecules diffusion coefficient and the percentage of collagen in 4T1 and EMT6 models. We learned that EMT6 tumors showed higher density compared to 4T1 tumors through a series of evaluations. 2) CyTOF analysis revealed the default NDES release rate was insufficient to treat EMT6 tumors. We increased the release rate of NDES. The tumor growth of EMT6 with increased NDES release rate showed effective combinational treatment of radiation therapy and PDL1+CD40 mAbs. Tumor immune microenvironment analysis with optimized NDES rate is currently in progress. 3) We utilized the 4T1 bilateral murine tumor model to assess the systemic treatment effect. 4T1 tumor model is highly metastatic and aggressive, the treatment showed reduced tumor growth on the treated tumor, but no effect on the untreated tumor. An enhanced release of NDES may be required for the bilateral tumor model.

15. SUBJECT TERMS
Intratumoral immunotherapy, sustained release implants, nanofluidics, triple negative breast cancer, controlled drug delivery, local delivery, cancer immunology, drug distribution

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Contents

1. INTRODUCTION:

The objective of the project is to improve the therapeutic efficacy of immunotherapy while mitigating associated toxicities, by replacing current treatment modalities that are ineffective for triple-negative breast cancer (TNBC) patients. Utilizing the nanofluidic drug-eluting seed (NDES) for sustained intratumoral (IT) immunotherapeutics delivery could address the overarching challenge to “revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival” for breast cancer patients.

2. KEYWORDS:

Intratumoral immunotherapy, sustained release implants, nanofluidics, triple negative breast cancer, controlled drug delivery, local delivery, cancer immunology, drug distribution

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1. To evaluate biodistribution of immunotherapeutics delivered through NDES in comparison to systemic and direct IT injection. (months 0-12)
Major Task 2. To compare local and systemic immune landscape of NDES-mediated sustained IT delivery of immunotherapeutics in comparison to systemic and direct intratumoral injection. (months 6-14)
Major Task 3. To assess tumor control achieved through NDES-mediated IT delivery of immunomodulating antibodies in combination with RT. (months 13-23)
Major Task 4. To assess the systemic effect of IT NDES-Ab + Rad on distal (untreated) tumor growth. (months 20-28)
Major Task 5. Analyze impact of treatment on toxicity. (months 29-36)

What was accomplished under these goals?

Specific Aim 1. To evaluate the effect of NDES-mediated sustained IT delivery kinetics on immunotherapy biodistribution and tumor immune microenvironment modulation.

Major Task 1. To evaluate the biodistribution of immunotherapeutics delivered through NDES in comparison to systemic intraperitoneal (IP) and direct intratumoral (IT) injection.
Major Task 1 - 85% complete.
Major activities: *(Site 1 - Grattoni)* We assessed drug biodistribution of PD-L1 antibody (Ab) in two murine breast cancer models, EMT6 and 4T1, in combination with radiation. Additionally, we evaluated 4T1 and EMT6 tumor models to determine whether their intrinsic tumor properties influence drug distribution. (*Site 2 - Chen*) Immunohistology assessment of tumor properties.
Specific objectives: 1) Evaluate tumor properties of 4T1 and EMT6, including the vasculature, tumor density, and drug diffusion. 2) Determine PDL1 Ab biodistribution impact in two different syngeneic triple-negative breast cancer (TNBC) immunocompetent murine models.

Results and discussions: In vivo IVIS live animal imaging showed that NDES maintained fluorescent Alexa Fluor 700 (AF700) labeled PDL1 mAb (AF700-PDL1) signal within both 4T1 and EMT6 tumors throughout the 14-day study duration, compared to IP and IT delivery, indicating sustained intratumoral drug release. The result indicated no significant difference between 4T1 and EMT6 models when AF700-PDL1 was delivered via IP, IT or NDES (Fig 1).

Radiated tumors and non-radiated tumors showed no difference of PDL1-AF700 biodistribution within tumor microenvironment (Fig 2). To further investigate the correlation of biodistribution and tumor properties, we evaluate the tumor density, vasculature, and drug diffusion in two tumor models, 4T1 and EMT6. EMT6 tumors showed significantly higher tumor density and vasculature based on Masson's trichrome staining and imaging analysis via Matlab (Fig 3). Moreover, we performed a fluorescence recovery after photobleaching (FRAP) analysis with FITC-labeled PDL1 mAb and revealed a higher diffusion coefficient of 4T1 than EMT6, which indicated limited mobility of Ab molecules in EMT6 tumor structure. Although there were differences in PDL1-AF700 biodistribution between NDES, IP and IT delivery in both 4T1 and EMT6 models, it was not significant (Fig 3).

The 3D reconstruction imaging analysis demonstrated that tumors in the NDES group displayed relatively homogeneous AF700-PDL1 biodistribution compared to IP and IT (Fig 4). However, the results showed high variation among and between groups, which could be attributable to loss of fluorescence during sample processing, which entailed snap freezing, frozen sectioning and histological procedures involving washing and sample mounting.

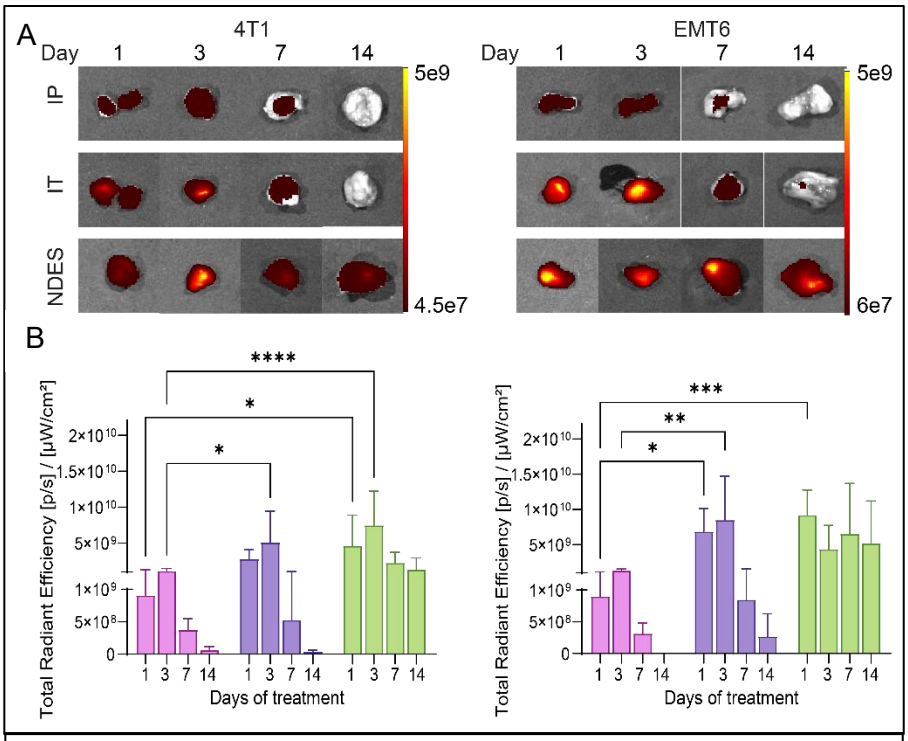

Fig 1. Ex vivo fluorescence imaging analysis of the tumors over 14 days after αPD-L1-AF700. A) representative tumors from each time points. B) Bar graph depicts radiance signal measured. 2way ANOVA was performed for statistical analysis. $p<0.05$, *; $p<0.005$, **; $p<0.001$, ***; $p<0.0001$, ****.

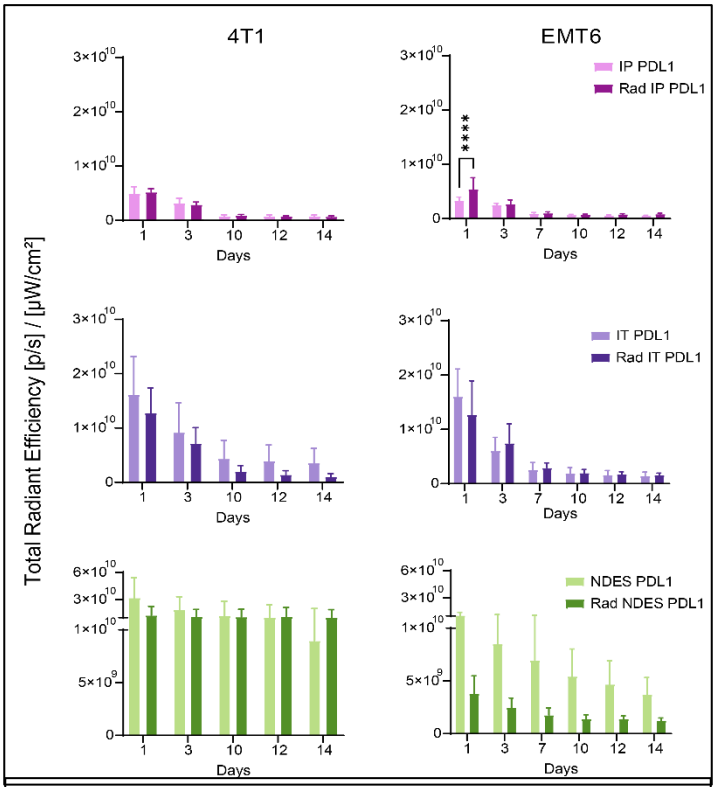

Fig 2. In vivo fluorescence imaging analysis of the tumors over 14 days after αPD-L1-AF700 administration. Bar graphs depict radiance signal (n=5-6 per group).

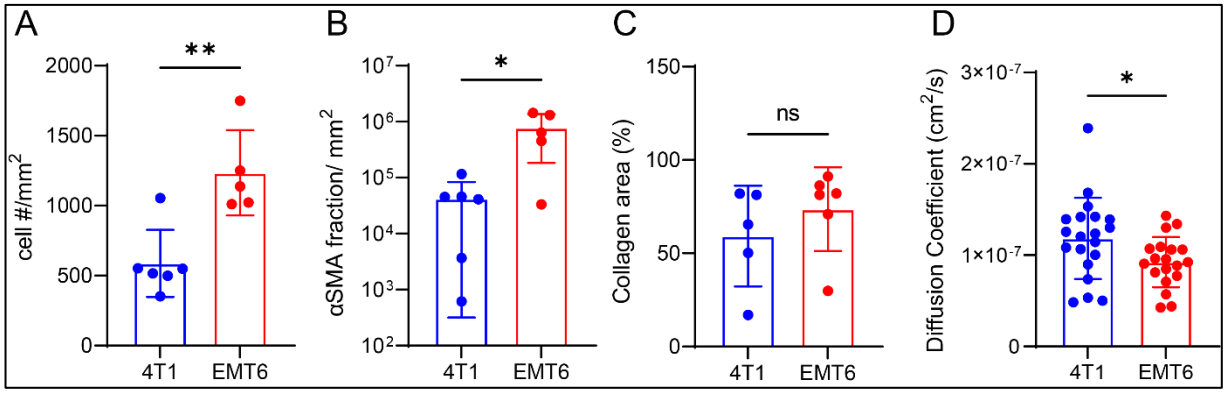

Fig 3. Tumor properties analysis. A) immunohistochemistry image analysis for tumor cell density by measuring the number of nuclei per imaging area. B) Tumor vasculature levels were determined by measuring αSMA fraction per imaging area. C) Masson's trichrome staining selectively stains collagen, which indicates the density of the extracellular matrix. The imaging analysis measured the percentage of collagen area per image. Five to six ROIs were selected from each staining slide, and 4 slides were randomly picked from each tumor model. D) FRAP analysis determined the diffusion coefficient of 4T1 and EMT6. Ten ROIs were analyzed from 3 tumors of each TNBC model. Two-tailed unpaired t-test was performed for statistical analysis. $p<0.05$, *; $p<0.005$, **.

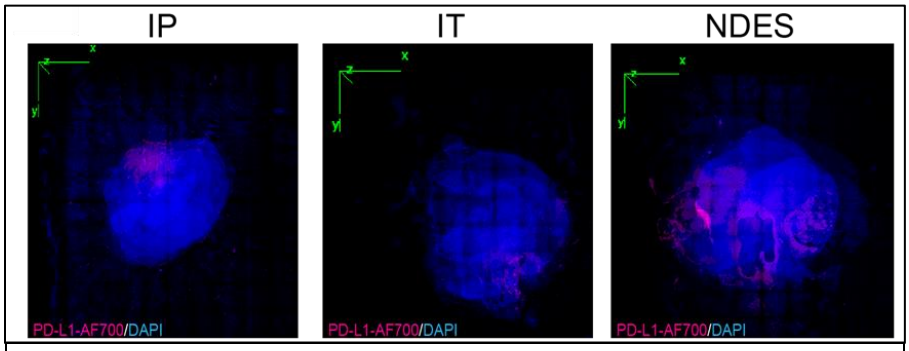

Fig 4. Representative 3D rendering images of antibody distribution within tumor via IP, IT, and NDES delivery methods. n=3/group.

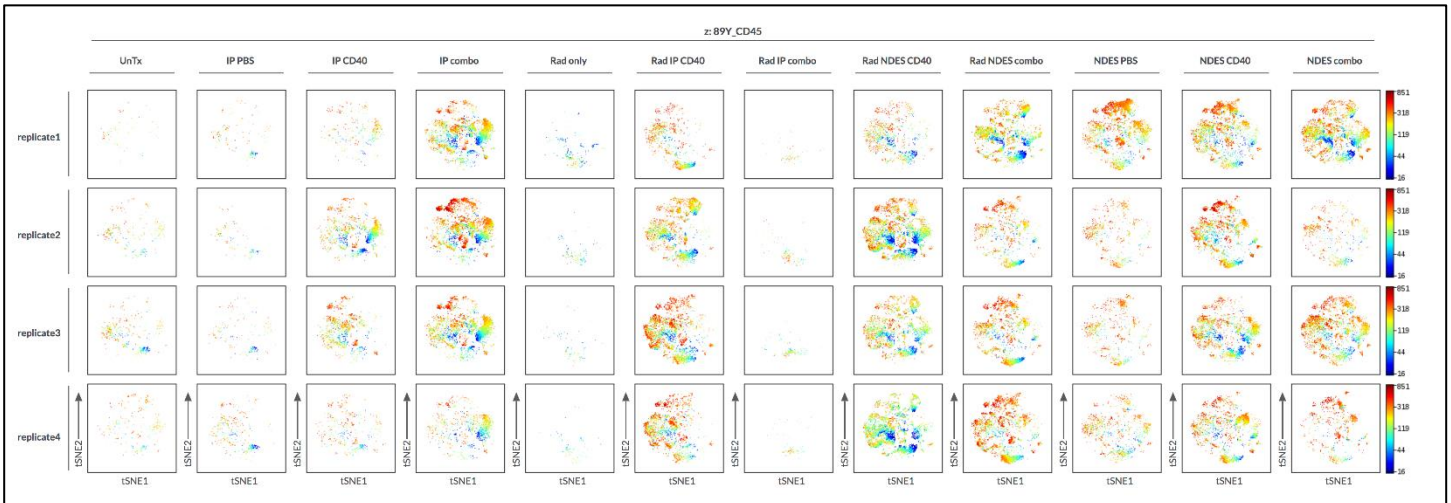

Fig 5. CyTOF analysis of EMT6 treated tumors (n=4 replicate/ group). Poor viable TILs were found in UnTx, IP PBS, Rad only, IP CD40, and Rad IP combo groups. Further improvement in TILs isolation is needed.

Major Task 2. To compare local and systemic immune landscape of NDES-mediated sustained IT delivery of immunotherapeutics in comparison to systemic and direct IT injection.
Major task 2 was completed 40%.
Major activities: *(Site 2 - Chen)* EMT6 tumors treated with CD40 mAb or combo (CD40 mAb + PDL1 mAb) via IP or NDES with and without radiation (8Gy x3) were evaluated by HMRI Immunomonitoring core for immune cell assessment via CyTOF.
Specific objectives: To understand the spatiotemporal dynamics of CD40 or combo within the tumor immune microenvironment (TIME) in response to treatment. CyTOF was performed to understand the immune landscape of tumors.
Results and discussions: EMT6 tumors were treated with either CD40 or combo with or without prior radiation treatment to immunotherapy. Tumor-infiltrated lymphocytes (TILs) (n=4 tumors/ group) were isolated from the tumors and desired markers for CyTOF assessment. The analysis showed that UnTx, IP PBS, Rad only, Rad IP combo, IP CD40 and NDES PBS groups had low number of viable TILs (Fig 5). One possible reason was due to necrosis within the untreated tumors, which is a common occurrence for larger tumors. Another reason is poor TILs isolation from treatment responsive tumors, as little tumor tissue was remaining for harvesting by study endpoint. However, we had sufficient isolated TILs from NDES CD40, NDES combo, Rad NDES CD40 and Rad NDES combo groups for assessment. Based on this experience, we will optimize future TILs isolation protocol. Further analysis is still ongoing.

Specific Aim 2. To evaluate efficacy and toxicity of IT NDES immunotherapy alone or in conjunction with RT for local and systemic tumor control.
Major Task 3. To assess tumor control achieved through NDES-mediated IT delivery of immunomodulating antibodies in combination with RT (months 13-23)
Major task 3: 60% complete.
Major activities: *(Site 1 - Grattoni)* EMT6 tumor bearing mice received 5 Gy radiation dosage over 3 consecutive days, followed by either 4 doses of immunotherapeutics via IP or one-time implantation of NDES. An enhanced local release via NDES membrane was applied in the study. *(Site 2 - Chen)* Ongoing tumor microenvironment analysis via IMC analysis.
Specific objectives: To assess the therapeutic effect of local and systemic immunotherapeutics delivery to EMT6 tumor bearing mice.
Results and discussions:

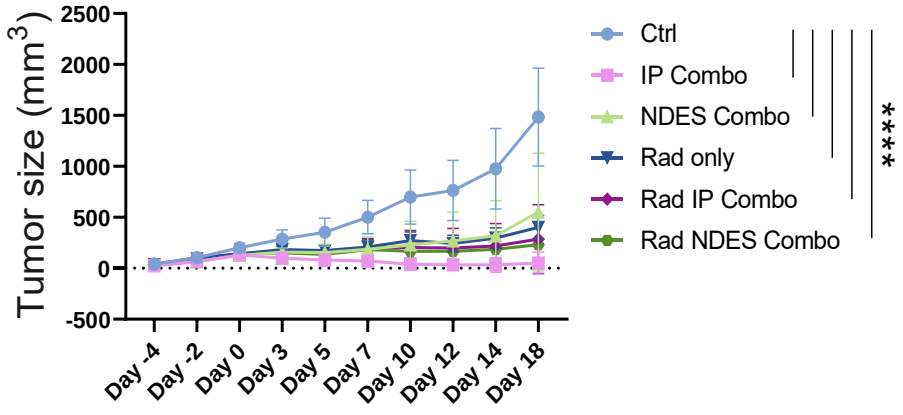

Fig 6. EMT6 model tumor growth curve. Mice were treated with combo immunotherapeutics, which containing CD40 mAb and PDL1 mAb.

We posited that a higher intratumoral dose could be needed to achieve tumor control for EMT6. We enhanced drug release from the NDES using larger membrane sizes to investigate whether the increase dose can effectively inhibit tumor growth and achieve tumor clearance. We observed that tumors treated with IP combo and NDES combo mAbs both showed significant tumor reduction compared to untreated Ctrl (Fig 6). Mice treated with combo either via IP (n=8/10) or NDES (n=3/8) achieved complete clearance in EMT6 model; Fig 7). However, more investigation is needed to achieve a more consistent response among all treated tumors. We also observed that radiation alone or in combination with immunotherapy did not significantly improve tumor response (Fig 6, 7). The results indicated EMT6 required higher dosage to achieve effective tumor inhibition. No metastasis was observed in this model. Ongoing analysis of tumor-infiltrating lymphocytes is being performed at site 2 (Chen) to further understand the impact of local drug delivery to tumor microenvironment.

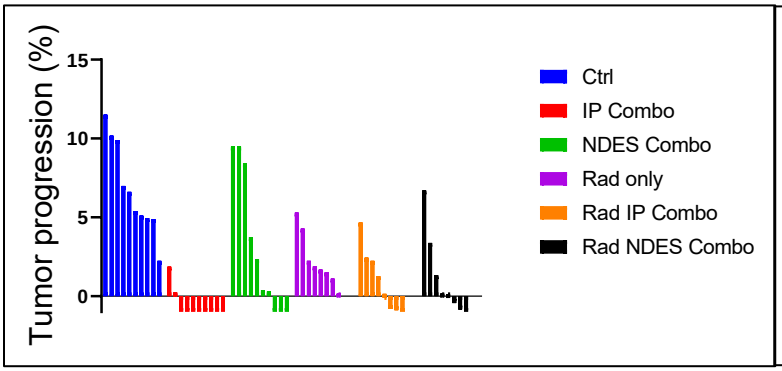

Fig 7. Waterfall plot of tumor growth or inhibition at experimental endpoint. Each bar represents one mouse. NDES combo (n=3 out of 10 mice) and IP combo treated group (n=8 out of 10 mice) were able to achieve tumor clearance (bars with negative value).

Major Task 4. To assess the systemic effect of IT NDES-Ab + Rad on distal (untreated) tumor growth. (months 20-28)

Major task 4 - 50% complete.

Major activities: *(Site 1 - Grattoni)* We generated bilateral tumor-bearing mice. Mice were randomized into designated groups and treated with 8 Gy radiation dosage over 3 consecutive days, followed by locally delivered immunotherapeutics via direct bolus IT injection or one-time NDES implantation, in comparison to IP and untreated controls. Tumor growth was measured every 2 days and euthanized when they reached the humane endpoint of $2cm^3$.

Specific objectives: To assess whether local treatment is able to trigger the abscopal effect and eliminate distal tumors.

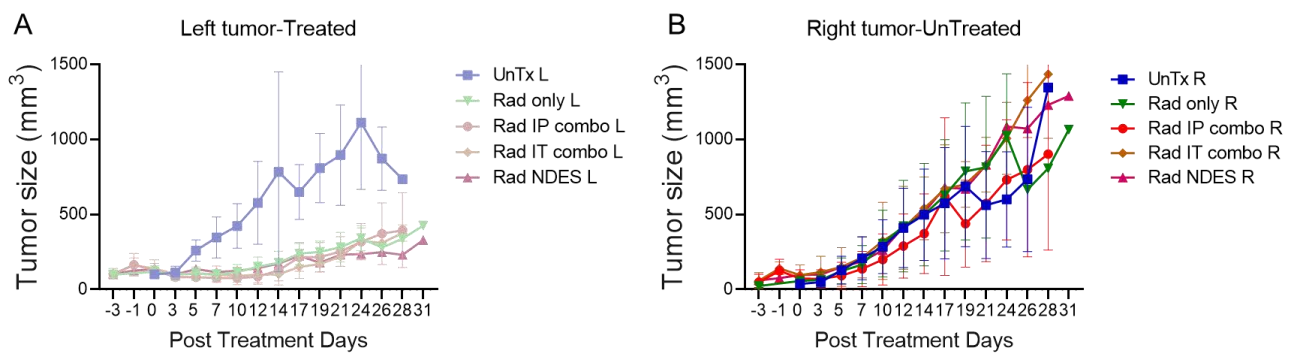

Fig 8. Tumor growth of 4T1 bilateral tumor model. A) Left side tumor received radiation and combo treatment via IP, IT, and NDES. B) Right side tumor received no treatment.

Results and discussion: Mice were inoculated with 3x10^4 4T1 cells on left side of mammary fat pad and 1.5x10^4 4T1 cells on right side of mammary fat pad 3 days later to mimic tumor metastasis to a distant site. In a pilot study, we found that mice were immunogenic toward the inoculated tumor cells and would not grow if the contralateral side (right) was inoculated after the primary tumor (left) volume reached target size of ~150 mm3. Mice were randomized into groups based on the primary (left) tumor size. In a previous study, we learned that the combination of immunotherapeutics and radiation had synergistic effect in 4T1 tumors. Therefore, the treatment groups received radiation and combo mAbs via IP (100µg x 4 doses every other day), IT (20µg x 7 doses every other day) and NDES (7µg / day). The treated primary tumor (left) showed significant tumor reduction compared to the untreated control group (Fig 8A). However, no complete clearance was observed, and tumor growth increased after day 19. This could be due to the drug exhaustion, requiring repeated injections or device refill. No treatment effect was observed on the untreated side (right side) among all the treated group (Fig 8B). We posit that the lack of abscopal effect was attributable to the aggressive nature of 4T1 tumor growth and lung metastasis.

Major Task 5. Analyze the impact of treatment on toxicity (months 29-36)
Major task 5 - 10% completed.

We collected the blood from 4T1 bilateral tumors experiment prior to radiation. Mice were lethargic after the radiation, and thus blood collecting was suspended due to their poor health and body conditioning score. We will increase the support to improve the mice's health and incorporate the procedure in future experiments.

In summary, we are preparing a manuscript for publication of these results in a peer-reviewed journal.

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

Research training and professional development opportunities were provided to post-doctoral fellow and others involved with the project. They were also given opportunities to prepare manuscripts for publication and presentations for scientific conferences. Eight presentations resulted from these studies and one manuscript is pending submission.

How were the results disseminated to communities of interest?

Results of the study has been presented in symposium and workshop as followings.

1. Grattoni A. Biomedical Nanofluidics for Long-Acting Therapeutics. Polytechnic of Turin, Turin, Italy. June 3, 2021. Invited Presentation.
2. Grattoni A. Nanofluidics for Medicine. 16th Annual National Nanomedicine Seminar Series. Nanomedicine Academy at Northeastern University, Boston, Massachusetts, November 10, 2020. Invited virtual presentation.
3. Grattoni A. Local Immunomodulatory Strategies for Cancer Immunotherapy and Cell Transplantation. Houston Methodist Cancer Center Work in Progress Meeting, Houston, Texas, October 8, 2020. Invited Presentation.
4. Grattoni A. Micro-Nanofluidics for Terrestrial and Space Medicine. Texas A&M University, Clinical Science & Translational Research Grand Rounds, College Station, Texas, October 6, 2020. Invited Presentation.
5. Grattoni A. Nanofluidics for Terrestrial and Space Medicine. Cleveland Clinic - UTEC Summit 2020, Cleveland, Ohio, October 2, 2020. Invited Presentation.
6. Grattoni A. Micro-nanofluidics for Medical Applications on-Earth and in Space. Mayo Clinic Center for Regenerative Medicine, Rochester, Minnesota, August 27, 2020. Invited Virtual Presentation.
7. Liu HC, Viswanath DI, Pesaresi F, Xu Y, Zhang L, Di Trani N, Paez-Mayorga J, Hernandez N, Wang Y, Erm DR, Ho J, Susnjar A, Liu X, Demaria S, Chen SH, Teh BS, Butler EB, Chua CYX, Grattoni A. Potentiating anti-tumor efficacy through radiation and sustained intratumoral delivery of α-CD40 and α-PDL1. MAPTA 2020 Summer Science symposium, Houston Methodist Research Institute, 2nd Place Podium; September 2020.
8. Liu HC, Viswanath DI, Pesaresi F, Xu Y, Zhang L, Di Trani N, Paez-Mayorga J, Hernandez N, Wang Y, Erm DR, Ho J, Susnjar A, Liu X, Demaria S, Chen SH, Teh BS, Butler EB, Chua CYX, Grattoni A. Intratumoral nanofluidic implant for sustained in situ immunotherapy delivery to potentiate antitumor efficacy. Controlled Release Society Virtual Annual Meeting. July 25-29, 2021.

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

During the next reporting period, we will complete the biodistribution analysis in Major task 1 and continue Major tasks 2 and 3 evaluation. We will also start Major task 3 and 4.

We anticipate achieving: Major task 1 - 85% completion; Major task 2 - 40% completion; Major task 3 - 60% completion; Major task 4 - 50% completion; Major task 5 - 10% completion.

4. IMPACT:

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

Immunotherapy elution directly into the tumor using an intratumoral drug delivery device can improve drug distribution within the tumor and limit unnecessary exposure to other healthy tissues. This could translate to less adverse side effects and improved quality of lives on patients who receive immunotherapy treatment. However, the cancer subtype or patient population which stand to benefit from intratumoral treatment have yet to be elucidated. Our study could elucidate the immune landscape in response to immunotherapy treatment and inform on therapeutic efficacy. If successful, we will be able to tailor treatment specific to each patient for personalized therapy.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

To further understand the relationship of drug biodistribution and tumor microenvironment, we added studies for tumor properties evaluation including assessing tumor density, vascular leakage, and determining molecule diffusion coefficient between 4T1 and EMT6 models.

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

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.

Nothing to report

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

Nothing to report

Other publications, conference papers, and presentations.

Presentations:

1. Grattoni A. Biomedical Nanofluidics for Long-Acting Therapeutics. Polytechnic of Turin, Turin, Italy. June 3, 2021. Invited Presentation.
2. Grattoni A. Nanofluidics for Medicine. 16th Annual National Nanomedicine Seminar Series. Nanomedicine Academy at Northeastern University, Boston, Massachusetts, November 10, 2020. Invited virtual presentation.
3. Grattoni A. Local Immunomodulatory Strategies for Cancer Immunotherapy and Cell Transplantation. Houston Methodist Cancer Center Work in Progress Meeting, Houston, Texas, October 8, 2020. Invited Presentation.
4. Grattoni A. Micro-Nanofluidics for Terrestrial and Space Medicine. Texas A&M University, Clinical Science & Translational Research Grand Rounds, College Station, Texas, October 6, 2020. Invited Presentation.
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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?

Site 1 Personnel

Houston Methodist Research Institute

Name:	Alessandro Grattoni
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-7888-422X
Nearest person month worked:	1.8
Contribution to Project:	Responsible for the overall project coordination and leadership. He provides guidance and supervision to the research team leadership for design and fabrication of the intratumoral nanofluidic drug-eluting seed, in vitro and in vivo testing.

Name:	Ying Xuan Chua
Project Role:	Research Faculty
Researcher Identifier (e.g. ORCID ID):	0000-0002-5724-8715
Nearest person month worked:	8.2
Contribution to Project:	Responsible for the coordination of the project, in vivo studies, data collection and analysis

Name:	Hsuan-Chen Liu
Project Role:	Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):	0000-0001-7857-0204
Nearest person month worked:	5.9
Contribution to Project:	Responsible for the coordination of the day to day activity and in vivo studies, data collection and analysis

Name:	Robin Vander Pol
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	NA
Nearest person month worked:	6.0
Contribution to Project:	Assist Dr. Liu with the in vivo experiments, sample collection and processing

Mayo Clinic

Name:	Sunil Krishnan
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-1340-4771
Nearest person month worked:	.06
Contribution to Project:	Oversight of radiation dosing during experiment execution

University of Washington

Name:	Elizabeth Nance
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-7167-7068
Nearest person month worked:	0.88
Contribution to Project:	UW site supervisor, oversight of personnel, data analysis and validation.

Name:	Phuong Huynh N Nguyen
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-8088-8665
Nearest person month worked:	1.04
Contribution to Project:	Methodology optimization, imaging and image analysis

Name:	Ana Rios
Project Role:	Undergraduate Research Assistant
Researcher Identifier (e.g. ORCID ID):	NA
Nearest person month worked:	2.64
Contribution to Project:	Tissue processing

Name:	Eleanor Wu
Project Role:	Undergraduate Research Assistant
Researcher Identifier (e.g. ORCID ID):	NA
Nearest person month worked:	0.22
Contribution to Project:	Tissue processing and imaging

Site 2 Personnel
Houston Methodist Research Institute

Name:	Shu-hsia Chen
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-9168-5775
Nearest person month worked:	1.2
Contribution to Project:	Dr. Chen is responsible for reviewing experimental design and results, troubleshooting experiments, and providing guidance on animal studies. She supervises the work done by Research Scientist Jilu Zhang

Name:	Jenny Chang
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-0890-9302
Nearest person month worked:	0.3
Contribution to Project:	Dr. Chang provides guidance on IT device deployment and immunotherapy dosing in breast cancer tumor models for clinical translation.

Name:	Sumaira Ali
Project Role:	Research Assistant II
Researcher Identifier (e.g. ORCID ID):	0000-0001-9756-6526
Nearest person month worked:	4.8
Contribution to Project:	Performed the CyTOF and imaging mass cytometry experiments.

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 for change in active support.

What other organizations were involved as partners?

University of Washington
Seattle, Washington
Contribution: Dr. Nance's team is located at University of Washington and currently use the facilities there.

Mayo Clinic – Jacksonville
Jacksonville, Florida
Contribution: Dr. Krishnan is located at Mayo Clinic.

8. SPECIAL REPORTING REQUIREMENTS:

Award chart is attached.

9. APPENDICES:

GRATTONI, ALESSANDRO

ACTIVE

(This grant)
W81XWH-20-1-0600 (Grattoni) 08/01/2020 – 07/31/2023 1.8 calendar
Department of Defense
Transforming triple negative breast cancer treatment through intratumoral immunotherapy via nanofluidic drug eluting seed
The goal is to evaluate an intratumoral nanofluidic technology for the sustained delivery of immunotherapeutics to enhance efficacy of radio-immunotherapy in triple negative breast cancer murine models.
Specific Aims: 1) To evaluate the effect of NDES-mediated sustained intratumoral delivery kinetics on immunotherapy biodistribution and tumor immune microenvironment modulation. 2) To evaluate efficacy and toxicity of intratumoral NDES immunotherapy alone or in conjunction with RT for local and systemic tumor control.
Role: Principal Investigator
Contact: Jamie A. Shortall
No Overlap

(New)
R01DK132104 07/01/2022 – 4/30/2026 2.4 calendar
NIH/NIDDK
Vascularized Islet transplantation NICHE with local immunosuppression for the treatment of type 1 diabetes
The goal is to develop a clinically translatable subcutaneous encapsulation platform integrating vascularization and sustained local immunosuppressant elution for in situ immunoprotection of transplanted cells
Specific Aims: 1) To evaluate effects of mesenchymal stem cells (MSC) on prevascularization and immunomodulation of NICHE for islet engraftment in diabetic rats. 2) To evaluate biodistribution of immunosuppressants locally eluted within NICHE and assess immunomodulation and pharmacokinetics in diabetic rats. 3) To evaluate efficacy of NICHE with allotransplanted islets to restore and maintain euglycemia in diabetic rats for one year.
Role: Principal Investigator
Contact: Guillermo Arreaza-Rubin, arreaza-rubing@niddk.nih.gov
No Overlap

(New)
R01AI165372 (Grattoni) 06/01/2022 – 5/31/2027 3.6 calendar
NIH/NIAID
Ultra-long Acting Transcutaneously Refillable Islatravir Nanofluidic Implant for HIV Pre-Exposure
The goal is to show that constant and sustained ISL delivery from NanoDDI will effectively prevent simian-human immunodeficiency virus (SHIV) infection in non-human primates (NHP) for a 2-year duration.
Specific Aims: 1) to develop and optimize NanoDDI and ISL formulation for sustained and constant release; 2) to assess pharmacokinetics (PK), tolerability, and safety of NanoDDI-ISL for 2 years in NHP and evaluate effectiveness of transcutaneous drug refilling; and 3) to comprehensively evaluate PrEP efficacy of NanoDDI-ISL in NHPs using 4 routes of simian HIV transmission, namely rectal, penile, vaginal and intravenous.
Role: Principal Investigator
Contact: Thomas Houze, thomas.houze@nih.gov
No Overlap

(New)
2-SRA-2022-1224-S-B (Grattoni) 06/01/2022 – 5/31/2024 0.96 calendar
JDRF
Investigation of novel local immunomodulating strategies to enhance islet transplantation for T1D

The objective of this proposal is to study various IS that hold promise
to improve transplant outcome and determine the immunosuppressive effects of each drug when used in a local setting.
Specific Aims: Aim 1. Study safety and mechanisms of local immunosuppression of 5 IS drugs for allogeneic islet rejection prophylaxis. Aim 2. Evaluate biodistribution of local IS delivery.
Role: Principal Investigator
Contact: Jaime Giraldo, JGiraldo@jdrf.org
No Overlap

2-SRA-2021-1078-S-B (Grattoni/Gaber) 08/01/2021-07/31/2023 0.96 calendar
JDRF
Prevascularized encapsulation platform with local immunosuppression for Islet transplantation
The goal of this proposal is to optimize key parameters of NICHE necessary for achieving long-term islet engraftment.
Specific aims: 1) Ooptimization of NICHE microenvironment for islet engraftment by determining transplant window. 2) Elucidate the optimal islet transplant dose in the NICHE to achieve euglycemia. 3) Optimization of the local IS dose needed for islet engraftment in NICHE.
Role: Principal Investigator
Contact: Jaime Giraldo, JGiraldo@jdrf.org
No Overlap

R01GM127558 (Grattoni/Liu) 04/15/2018 – 01/31/2023 NCE 0.6 calendar
NIH/NIGMS
A nanofluidic platform for tunable drug delivery
Our goal is to demonstrate in small and large animal models an implantable drug delivery systems based on electrostatic gating for the remotely controlled delivery of therapeutics.
Our specific aim includes: 1) To design and assemble remotely controlled delivery implants. 2) To investigate the tunable and remote controlled release of drugs in vitro. 3) To test the RF-controlled implant for the tunable delivery of drugs in small and large animals.
Role: Principal Investigator
Point of Contact: Richard Okita
No Overlap

Gilead (Grattoni) 04/19/2021 – 12/31/2022 NCE 0.06 calendar Gilead
Safety and tolerability of sustained TAF release from a subcutaneous nanofluidic Implant
The goal is to perform the comparative assessment of the safety, tolerability, and tissue response of sustained subcutaneous administration of three forms of tenofovir alafenamide (TAF) released from a nanofluidic implant.
Role: Principal Investigator
Contact: Celestine Navarro, celestine.navarro1@gilead.com
No Overlap

GA-2020-145 Renewal (Grattoni) 07/01/2020 – 06/01/2023 NCE 0.06 calendar
CASIS
Remote controlled nanochannel implant for tunable drug delivery: Development and Demonstration on the International Space Station.
The objective of this proposal is to develop a miniature drug delivery system for telemedicine application for Space exploration. As a proof of concept, the system is developed to enable drug delivery in mice housed on the International Space Station (ISS).
Role: Principal Investigator
Point of Contact: Kenneth Shields
No Overlap

GA-2019-003 (Grattoni) 08/01/2014 – 10/30/2022 NCE 0.06 calendar
CASIS
Study of Lamborghini's carbon fiber composites for aerospace applications
Our goal is to investigate the effect of extreme environmental conditions such as high level of radiation exposure, atomic oxygen, vacuum, and abrupt temperature fluctuations on the physicochemical properties of carbon fiber composites fabricated via additive manufacturing, forging, and conventional technology.
Our specific aim includes: To investigate the performances of 5 selected carbon fiber materials developed by Automobili Lamborghini for aerospace applications.
Role: Principal Investigator
Point of Contact: Kenneth Shields
No Overlap

COMPLETED

(Completed)
R01AI120749 (Grattoni) 09/01/2016-05/31/2022 3.0 calendar
NIH/NIAID
A novel nanochannel system for sustained delivery of Tenofovir Alafenamide Fumarate and Emtricitabine for HIV pre-exposure prophylaxis.
Our goal is to develop a transcutaneously refillable drug delivery implant of TAF and FTC and evaluate the PK and preventive efficacy in the context of HIV pre-exposure prophylaxis.
Our specific aim includes: 1) To develop nDS implants capable of sustained and constant release of TAF/FTC in rats and NHP. 2) To assess the pharmacokinetics of constant delivery of TAF/FTC from nDS implants at target release rates for 60 days in NHP. 3) To evaluate prevention of SHIV infection through rectal challenge by release of TAF/FTC from nDS implants in NHP.
Role: Principal Investigator
Point of Contact: Jim Turpin
No Overlap

(Completed)
U54CA210181 Pilot (Grattoni) 8/1/2020 – 7/31/2022 0.6 calendar
NIH/NCI
Implantable therapeutic cancer vaccine for triple negative breast cancer treatment
The goal is to develop an implantable therapeutic vaccine by way of a tunable immunostimulatory niche for continuous activation of antitumor immune cascade for long term cancer eradication.
Specific aims: 1) Evaluate the efficacy of NanoLymph for dendritic cell recruitment and activation. 2) Evaluate efficacy of NanoLymph for tumor control and metastasis prevention.
Role: PI on Pilot Project
Contact: Dianna N Bailey, baileydianna@mail.nih.gov
No Overlap

(Completed)
Grattoni 03/01/2018 – 02/28/2022 0.12 calendar Wilfred
Masterson Burke Medical Research Institute
Controlled delivery of butyrate from a nanofluidic implant
Our goal is to develop a sustained delivery system for the administration of butyrate.
Our specific aim includes: 1) to develop HPLC methods for the quantification of butyrate in vitro. 2) To test the release of butyrate from nanofluidic membranes and determine release rates adequate for in vivo testing.
Role: Principal Investigator
Point of Contact: Rajiv Ratan
This project relates to assessing the sustained release of butyrate in vitro. No Overlap

(Inactive)
Grattoni 1/01/2019-12/31/2021 0.12 calendar
Nancy Owens Memorial Foundation
Intratumoral Implant for Breast Cancer Immunotherapy.
Specific Aim: To evaluate efficacy of nanofluidic implant in murine and rodent models of breast cancer.
Role: Principal Investigator
Overlap: None

(Transferred)
Gaber/Grattoni 11/01/2011 – 12/31/2023 0.12calendar
Vivian Smith Foundation
Examining the potential of human Mesenchymal stem cells and osteocalcin in augmenting human islet mass and improving islet engraftment and long-term function.
Our goal is to develop a protocol for the differentiation of stem cells into islet like insulin producing cells and assess their ability to secrete insulin in vivo in a polymeric encapsulation system.
Our specific aim includes: 1) to develop and optimize MSC differentiation protocol to achieve islet like insulin producing aggregates (ILIPA) of cells. 2) To develop a 3D printed encapsulation for the delivery of cells and assess its degradation and biocompatibility in vitro. 3) To test the ILIPA in the encapsulation system in vivo in rodents.
Role: Co-Principal Investigator
Point of Contact: Jackie Callies
No Overlap

(Transferred)
Grattoni 08/01/2019-07/31/2021 0.12calendar
Men of Distinction
Overcoming the epidemic of pediatric obesity and prediabetes via a nanofluidic technology
The project objective is to assess the efficacy of a new co-form of the thyromimetic molecule sobetirome in the treatment of obesity and metabolic syndrome in an advanced preclinical model in non-human primates.
Specific Aim: To evaluate anti-obesity efficacy of sustained delivery of GC-1 in non-human primates
Role: Principal Investigator
Point of Contact: Tiffany Polk
No Overlap

(Transferred)
Grattoni/Chen 08/01/2018-12/31/2021 0.12 calendar Golfers Against Cancer
Leveraging synergistic effects of local radio-immunotherapy to eradicate breast cancer.
Our goal is: To combine intratumoral immunotherapy delivery with radiation to induce a potent systemic anti-tumor immune response to eliminate primary and metastatic tumors. If successful, the potential to revolutionize treatment extends beyond breast cancer.
Our specific aim includes: 1) Evaluate effects of intratumoral release of monoclonal antibody, 4-1BB, alone or in combination with radiation on tumor growth and immune response. 2) Compare conventional systemic 4-1BB delivery with sustained intratumoral delivery to examine efficacy and effects on toxicity. 3) Assess efficacy of 4-1BB antibody alone or in combination with radiation to prevent tumor recurrence and metastasis.
Role: Principal Investigator
Point of Contact: Tiffany Polk
No Overlap

(Transferred)
Grattoni/Shen 08/01/2018-12/31/2021 0.12 calendar

Golfers Against Cancer
Triggering the abscopal effect in triple negative breast cancer with nDSmini.
Our goal is: To reproducibly trigger a systemic immunological response that could eradicate both primary tumor and metastasis.
Our specific aim includes: 1) Demonstrate release of chemoimmunotherapeutic drugs (doxorobicin, CD40 and PD-1 antibodies) directly into the tumor via intratumoral drug delivery implant, towards achieving tumor regression. 2) Establish that prolonged tumor exposure to chemoimmunotherapeutic drugs will maximize drug uptake and induce systemic anti-tumor immune response, and thereby enhance treatment efficacy. 3) Treat primary tumor and prevent cancer recurrence and metastasis.
Role: Principal Investigator
Point of Contact: Tiffany Polk
No Overlap

CURRENT & PENDING SUPPORT FOR DOD

KRISHNAN, SUNIL

ACTIVE

(New)

Title/PI/Grant No:	In situ cancer cell specific biomineralization to overcome nanoparticle delivery barriers and sensitize pancreatic cancer to radiotherapy/Sokolov, Krishnan/R01CA274415
Effort:	0.18
Supporting Agency:	NIH/NCI
Grants Officer:	Pat Prasanna, patajeprasanna@mail.nih.gov
Performance Period:	08/02/2022 – 07/31/2027
Funding Amount:	
Project Goals:	Our goal is to show that small gold ions (i) will uniformly distribute throughout the tumor as their diffusion is not likely to be impeded by the stroma, (ii) will be reduced to GNPs via the process of in situ biomineralization after specific uptake by cancer cells, and (iii) will radiosensitize the tumor while sparing adjacent normal tissue.
Specific Aims:	1) to determine the mechanism of and to optimize conditions for intracellular synthesis of GNPs by PDAC cells; 2) to evaluate the determinants of radiosensitization efficacy in vitro and in vivo; and 3) to develop a predictive biological effect computational model of radiosensitization by in situ synthetized GNPs.
Overlap:	None

Title/PI/Grant No:	Mayo Comprehensive Cancer Center Grant (PS on Dr. Diasio's CA15083 grant renewal at MCR)/Dronca/ P30CA15083-46
Effort:	1.20
Supporting Agency:	NCI
Grants Officer:	Min He
Performance Period:	06/01/2019-02/29/2024
Funding Amount:	
Project Goals:	To steer and harmonize clinical, translational and basic science research efforts across all thee Mayo sites in GI cancer space
Specific Aims:	1) To investigate novel approaches for early detection of gastrointestinal malignancies with a focus on luminal cancers. 2) To identify and evaluate novel biomarkers for prognostic stratification and prediction of therapeutic outcomes. 3) To examine the role of the tumor microenvironment, including the role of the gut microbiome in the initiation and progression of GI malignancies. 4) To develop and test individualized treatment approaches against novel therapeutic targets.
Overlap:	None

Title/PI/Grant No:	Enhancing immune mediated head and neck cancer anti-tumor activity using nanoparticles/Krishnan/R01DE028105
Effort:	2.40
Supporting Agency:	NIH
Grants Officer:	Chiayeng Wang
Performance Period:	01/01/2019-12/31/2023

Funding Amount:	
Project Goals:	To evaluate strategies to target radioresistance mediated by PD-L1 using targeted nanoparticles, enhancement of PDL1 expression, and interrogation of exhaustion mechanisms.
Specific Aims:	1) Can we use PD-L1 to home gold nanoparticles and en-hance radiation specifically within tumor cells? 2) By what mechanism is PD-L1 blocking the activity of infiltrating cytotoxic T cells and does this drive therapeutic resistance in HNSCC? 3) Can high linear energy transfer (LET) radiation increase immunogenicity of dying tu-mor cells as a part of an immune driven paradigm to improve radiation response in HNSCC?
Overlap:	None

Title/PI/Grant No:	Enhancing Chemoradiation Efficacy through Unbiased Drug Discovery Approaches/Krishnan/U01CA216468
Effort:	1.80
Supporting Agency:	NIH
Grants Officer:	Jeffrey Buchsbaum
Performance Period:	09/01/2019-08/31/2023
Funding Amount:	
Project Goals:	Screen the entire CTEP portfolio of drugs for radiosensitization potential in lung and pancreatic cancer models and evaluate the effect of tumor heterogeneity.
Specific Aims:	1) Identify candidate molecular targeted agents that enhance both radiotherapy and CRT using the HCS system. 2) Evaluate the enhancement of CRT by candidate agents in representative in vivo models. 3) Unravel tumor heterogeneity and molecular pathways that are associated with adaptive response to targeted therapies and chemotherapy
Overlap:	None

Title/PI/Grant No:	In situ cancer cell specific synthesis of gold nanoclusters for radiosensitization of pancreatic cancer/Krishnan/R21CA252156
Effort:	0.60
Supporting Agency:	NIH
Grants Officer:	Christopher Hartshorn
Performance Period:	07/01/2020-12/31/2022
Funding Amount:	
Project Goals:	To synthesize gold nanoparticle clusters that self aggregate in cancer cells and permit radiosensitization
Specific Aims:	1) Optimization and characterization of intracellular synthesis of GNPs by pancreatic cancer cells. 2) Evaluate radiosensitization efficacy of in situ synthetized GNPs in models of pancreatic cancer
Overlap:	None

(This grant)

Title/PI/Grant No:	Nanofluidic platform to modulate tumor microenvironment via intratumoral radioimmunotherapy/Krishnan/NA
Effort:	0.48
Supporting Agency:	DoD
Grants Officer:	Jamie A. Shortall
Performance Period:	08/01/2020-07/31/2023

Funding Amount:	
Project Goals:	To use a nanofluidic device to instill agents into tumors to synergize with radiotherapy
Specific Aims:	1) To evaluate the effect of NDES-mediated sustained intratumoral delivery kinetics on immunotherapy biodistribution and tumor immune microenvironment modulation. 2) To evaluate efficacy and toxicity of intratumoral NDES immunotherapy alone or in conjunction with RT for local and systemic tumor control.
Overlap:	None

Title/PI/Grant No:	Rational translation of gold nanoparticle mediated radiosensitization to the clinic/Krishnan/ R01CA257241-1
Effort:	1.80
Supporting Agency:	NCI
Grants Officer:	Pataje Prasanna
Performance Period:	1/13/2021-12/31/2025
Funding Amount:	
Project Goals:	The goal is to test gold nanoparticles (GNPs) as radiation sensitizers in colorectal cancer
Specific Aims:	1) Assessment of determinants of radiosensitization efficacy in vitro and in vivo. 2) Computational modeling of GNP-mediated dose enhancement/radiosensitization 3) Pilot trial of GNP-enhanced RT of colorectal cancers with actively targeted GNPs
Overlap:	None

COMPLETED

Title/PI/Grant No:	I-PARTS Integrated Platform for Anti-Cancer Radiation Therapeutic Screening/Krishnan/N/A
Effort:	1.20
Supporting Agency:	NCI
Grants Officer:	Ming Zhao
Performance Period:	09/16/2019-09/15/2021
Funding Amount:	
Project Goals:	To develop a high throughput system for screening anti-cancer compounds as radiosensitizers
Specific Aims:	1) To develop and design engineered cell arrays for HTS clonogenic system. 2) Design and develop cellular dosimetry and characterize in high-throughput (HTS) irradiation system that can irradiate 6-well plates with varied amounts of doses and in real time monitor the absorbed dose through NIST traceable dosimetry. 3) Develop a prototype system by integrating tissue culture incubation system, along with irradiation system and microscopy
Overlap:	None

Title/PI/Grant No:	A Prognostic Blood Test to Monitor Pancreatic Cancer Treatment by MiRNA Profiling/Krishnan/R44CA199058-1
Effort:	0.12
Supporting Agency:	NIH
Grants Officer:	Ming Zhao
Performance Period:	05/01/2020-04/30/2022

Funding Amount:	
Project Goals:	To identify circulating miRNA markers of treatment response in pancreatic cancer.
Specific Aims:	1) Direct miRNA Analysis. 2) Chemotherapy Clinical Study. 3) Radiotherapy Clinical Study.
Overlap:	None

Title/PI/Grant No:	A versatile radiation-triggered phosphor platform for localized anti-cancer therapy /Papineni/75N91019C00016
Effort:	0.6
Supporting Agency:	NIH/NCI
Grants Officer:	Ming Zhao
Performance Period:	09/16/2019 - 12/15/2020
Funding Amount:	
Project Goals:	To develop nanoscintillators that are triggered by radiation for x-ray induced photodynamic therapy of pancreatic cancer
Specific Aims:	1) Fabricate and characterize scintillator-photosensitizer complexes that can generate cytotoxic ROS concentrations below 1 Gy
Overlap:	2) Demonstrate cellular uptake and tumor cytotoxicity of the nanocomplexes upon low dose X-ray excitation in vitro

NANCE, ELIZABETH

ACTIVE

(New)
Title: Support for the 13th Hershey Conference on Developmental Brain Injury
Effort: 0.01 calendar months
Supporting agency: Request ID#1022434 (PI: Nance)
Contact: Kelly Rose, krose@bwfund.org
Performance period: 5/15/2022 – 9/30/2022
Funding amount:
Project Goal: The overall goals of the proposed meeting are to bring together internationally known clinical and basic scientists involved in research pertaining to brain injury and regeneration in developing animals and humans.
Specific aims: (1) identify clinical paradigms that inform basic science concepts and translate those new basic concepts into more refined clinical application; (2) explore areas of gaps in our current knowledge, and to include experts in tangential fields to provide new perspectives on these gaps; (3) promote novel collaborations; (4) promote trainee and junior faculty participation and to identify trainees/junior faculty from racial/ethnic minorities and underrepresented institutions to attend this conference.
Role: PI
Overlap: None

Title: Repurposing azithromycin for premature brain injury
Effort: 0.6 calendar months
Supporting agency: NINDS 1R01HD101422 (PI: Wood)
Contact: Antonello Pileggi, antonello.pileggi@nih.gov
Performance period: 3/19/2021 – 2/28/2026
Funding amount:
Project Goal: To examine the short-term in vitro and long-term in vivo neuroprotective effects of azithromycin in a late-preterm brain injury model in the developing ferret, including effects on microglial phenotype and brain connectivity on MRI.
Specific aims: This project aims to (1) evaluate how AZ alters mechanisms of in vitro brain injury using cultured ferret organotypic brain slices; (2) determine the optimal dosing strategy for neuroprotection in the ferret HIH model; and (3) evaluate the long-term effects of AZ treatment after LPS-sensitized HIH premature brain injury
Role: Co-I
Overlap: None

Title: The role of semen in induction of paternal-specific tolerance during pregnancy
Effort: 1.2 calendar months
Supporting agency: NIH 1R01AI153342 (PI: Vojtech)
Contact: Mercy Prabhudas, mprabhudas@niaid.nih.gov
Performance period: 02/25/2021 – 01/31/2026
Funding amount:
Project Goals: The major goal of this project is to investigate how factors in semen educate the immune system to tolerate fetuses, and to compare these tolerance mechanisms between healthy pregnancies and those complicated by preeclampsia.
Specific aims: 1) We will investigate how components of semen induce tolerance in APCs from vaginal and cervical tissues. 2) we will examine where semen EV distribute in the mucosa after vaginal exposure. 3)

we will determine how paternal antigen specific Tregs in the decidua and blood following delivery differ between healthy pregnancies and PE.
Role: Co-I
Overlap: None

Title: Enzyme-loaded nanoparticles for treatment of neonatal HIE
Effort: 1.02 calendar months
Supporting agency: NIH/ NICHD 5R21HD100639 (PI: Nance)
Contact: Andrew Bremer, andrew.bremer@nih.gov
Performance period: 06/16/2020 – 05/31/2022 (no-cost extension to 5/31/2023)
Funding amount:
Project Goals: The major goal of this project is to investigate the pharmacokinetics, biodistribution, and neuroprotective potential of SOD- and catalase-loaded polymeric nanoparticles in a rat model of term HIE.
Specific aims: 1) Will focus on determining the biodistribution and effective dose of SOD-loaded and catalase-loaded poly(lactic-co-glycolic)-poly(ethylene glycol) (PLGA-PEG) nanoparticles. 2) Will evaluate the efficacy of a combined delivery of SOD-loaded and catalase-loaded PLGA-PEG nanoparticles to determine the neuroprotective effects in newborn rats with HI in comparison to free drug and saline treated controls.
Role: PI
Overlap: None

(This grant)
Title: Transforming triple negative breast cancer treatment through intratumoral immunotherapy via nanofluidic drug eluting seed
Effort: 0.96 calendar months
Supporting Agency: DoD W81XWH-20-1-0600 (PI: Grattoni)
Performance period: 8/1/2020 – 7/31/2022 (no-cost extension to 7/31/2023)
UW Subcontract amount: (Direct)
Project Goals: The goal is to evaluate an intratumoral nanofluidic technology for the sustained delivery of immunotherapeutics to enhance efficacy of radio-immunotherapy in triple negative breast cancer murine models.
Specific Aims: 1) To evaluate the effect of NDES-mediated sustained intratumoral delivery kinetics on immunotherapy biodistribution and tumor immune microenvironment modulation. 2) To evaluate efficacy and toxicity of intratumoral NDES immunotherapy alone or in conjunction with RT for local and systemic tumor control.
Role: Co-I
Point of Contact: Jamie A. Shortall *Overlap*:
None.

Title: HDR: I-DIRSE-FW: Accelerating the Engineering Design and Manufacturing Life-Cycle with
Data Science
Effort: 0.25 calendar months
Supporting agency: NSF HDR: I-DIRSE-FW
Performance period: 09/01/2019 – 08/31/2021 (no-cost extension to 8/31/2023)
Funding amount: (Direct)

Project Goals: To form a new Engineering Data Science Institute (EDSI) to develop data science approaches to accelerate the engineering life cycle for design, characterization, manufacturing, and operation
Specific aims: The thrusts of this proposal are (1) reduction of experimental design space with data science tools; (2) advancing characterization and analysis with data science; and (3) improving manufacturing, optimization, and control.
Role: Co-I
Overlap: None

Title: Quantitative 3D imaging of *in situ* nanoparticle movement and cellular behavior during neuroinflammation
Effort: 2.4 calendar
Supporting Agency: NIH NIGMS 1 R35 GM124677-01
Contact: Paul Sammack, paul.sammak@nih.gov,
Performance period: 08/01/2017- 07/31/2023
Funding amount: (Direct)
Project goals: The major goals of this project are to develop a quantitative 3D imaging methodology and platform to evaluate in situ nanoparticle movement and behavior during neuroinflammation
Specific Aims: The project thrusts of this award are (1) in vitro evaluation of nanoparticle behavior in complex biological media; (2) multiple particle tracking to evaluate tissue compartmentalization using organotypic tissue slice models and high-resolution spatiotemporal imaging; (3) evaluation of biological variables, including region and disease, on nanoparticle tissue compartmentalization in organotypic brain slices
Role: PI
Overlap: None

COMPLETED

(Completed)
Title: Combined molecular simulation and experimental study to discover, predict and control enzyme immobilization in polymeric nanoparticles
Effort: 0.5 summer
Supporting Agency: NSF CBET 1703438
Contact: Nora Savage, nosavage@nsf.gov
Performance period: 09/01/2017- 08/31/2020
Funding amount: (Direct)
Project goals: To combine molecular simulation and experimental study to discover, predict and control enzyme immobilization in polymeric nanoparticles
Specific Aims: The project aims are (1) use molecular dynamics screening for monomer and oligomer/enzyme surface binding; (2) synthesize and characterize particles; (3) reconcile experiments and simulations with supervised machine learning modeling; and (4) rationally design a dual enzyme-polymer nanoparticle system with a controlled release profile. *Role*: Co-I
Overlap: None

(Completed)
Title: Institutional start-up funds (Nance)
Effort: 0.01 calendar
Supporting Agency: University of Washington

Contact: Mesgana Teklegiorgis, teklem2@uw.edu
Performance period: 09/16/15-9/15/2021
Funding Amount: remaining)
Program goals: To establish a sustainable research program that integrates engineering, neurobiology, data sciences, and clinically relevant animal models of brain injury/brain disease
Specific Aims: To (1) better understand the developing brain in response to injury and (2) engineer more effective therapies to protect or treat the injured perinatal or neonatal brain.
Role: PI
Overlap: The start-up funds cover personnel and general lab supplies not covered by a grant proposal.

(Completed)
Title: Experimental diffusion analysis to extract changes in tissue-structure function in the diseased brain
Effort: 0.01 calendar
Supporting Agency: University of Washington Chemical Engineering Data Science Incubator
Contact: Debbie Carnes, drae@uw.edu
Performance period: 03/01/2018 – 08/31/2019
Funding amount (Direct)
Project goals: To develop data science software packages that extract statistical information from multiple particle tracking videos and can be aligned with histology and immunohistochemistry imaging.
Specific aims: The project aims are (1) map region specific nanoparticle diffusion data obtained from the living brain, using a novel Python-Image J analytics package; and (2) extract tissue-structure function using nanoparticle diffusion data that demonstrate regional differences in the living brain, through application of image registration packages.
Role: PI
Overlap: None

CHEN, SHU-HSIA

CURRENT:

(This grant)
Project Title: Transforming triple negative breast cancer treatment through intratumoral immunotherapy via nanofluidic drug eluting seed
Time Commitments: 1.2 CM
Supporting Agency: DoD Breakthrough level 2
Performance Period: 08/01/20 -07/31/23
Level of funding:
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.

Project Title: Modulation of tumor inflammatory factor for immune therapy
Time Commitments: 3.00 CM
Supporting Agency: NIH/NCI
Contact: Dianna Bailey; email: baileydianna@mail.nih.gov
Performance Period: 09/22/2017– 08/31/2022
Level of funding:
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.

Project Title: LILRB Modulates Tumor Microenvironment and Promotes Tumor Progression
Time Commitments: 3.00 CM
Supporting Agency: NIH/NCI
Contact: Dianna Bailey; email: baileydianna@mail.nih.gov
Performance Period: 12/01/2016-11/30/2022
Level of funding:
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.

Project Title: Impact of WTC dust on immune functions and prostate cancer promotion
Time Commitments: 0 CM
Supporting Agency: NIOSH
Contact: Evelina Berman, email: evelina.berman@mssm.edu
Performance Period: 09/01/2016 – 08/31/2022
Level of funding:
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.

Project Title: Mechanism of intratumoral transport of particulate drugs
Time Commitments: 1.2 CM
Supporting Agency: NIH/NCI
Contact: Alley, Michael C, email: alleym@mail.nih.gov
Performance Period: 07/01/2018-11/30/2023
Level of funding:
Role: PI
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.

Project Title: Nanotechnology-Based Targeting of Breast Cancer Liver Metastases
Time Commitments: 0.24 CM
Supporting Agency: DoD Breakthrough level 2
Performance Period: 03/01/2021 – 02/28/2024
Level of funding:
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

Project Title: Urinomics as a Guide to the Renal Immune Landscape in SLE
Time Commitments: 0.12 CM
Supporting Agency: Lupus Research Alliance
Contact: Alley, Michael C, email: alleym@mail.nih.gov

Performance Period: 07/01/2021 – 06/30/2023
Level of funding:(sub only)
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

(New)
Project Title: XBP1 Inhibition and STING activation for the treatment of cancer
Time Commitments: 0.6 CM
Supporting Agency: NIH/NCI
Contact: Singh, Anju, email: anju.singh@nih.gov
Performance Period: 04/08/2022 – 03/31/2027
Level of funding:
Role: Co-Investigator
Major goals: We have developed inhibitors of a cancer-promoting protein called spliced X box-binding protein-1 (XBP-1s) and shown that these inhibitors are effective in killing chronic lymphocytic leukemia (CLL). In addition, we have shown that activation of a protein called the stimulator of interferon genes (STING) can also cause CLL cell death. Because both inhibition of XBP-1s and activation of STING can suppress a critical survival mechanism called B cell receptor signaling, we propose to treat CLL through a combination of these approaches and believe that results emanating from this study will inform new treatment strategies to combat CLL.
Overlap: None.

PREVIOUS:

(Completed)
Project Title: Intervention of Immune Tolerance by Small Molecules
Supporting Agency: NIH/NCI
Contact: Dianna Bailey; email: baileydianna@mail.nih.gov
Performance Period: 04/01/2007-07/31/2022
Level of funding:
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.

(Completed)
Project Title: Testing the Immunomodulatory effects of DAS181 in SARS-CoV-2 infection
Supporting Agency: Ansun BioPharma

Performance Period: 7/2/2020 – 7/1/2021
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.
Overlap: None.

(Completed)
Project Title: Harnessing Transport Properties of PMN-MDSC for Enhancement of Anti-Tumor Immunity
Supporting Agency: NIH/NCI
Contact: Dianna Bailey; email: baileydianna@mail.nih.gov
Performance Period: 8/1/2020-7/31/2022
Level of funding:
Role: Co-I on Administrative Supplement
Major Goal: The goal is to show that PMN-MDSC can serve as a unique vehicle for tumor tissue-targeted drug transport.
Specific Aims:
Aim 1: Examine modification of tumor microenvironment upon T1-Dox treatment in murine model of HER2-positive breast cancer.
Aim 2: Evaluate synergy between T1-Dox and therapeutic cancer vaccine on anti-tumor efficacy.
Overlap: None.

CHANG, J.C.

ACTIVE

W81XWH-16-0418 (Wang, Partner PI - Chang) 09/30/16-9/29/23 1.20 CM
DOD Breakthrough Award Levels 3 and 4
Role: Partnering PI
Title: NY-ESO-1-specific TCR-Engineered T cell Immunotherapy for Triple Negative Breast Cancer
Major goals: The goal of this study is to conduct a phase 1 clinical study with NY-ESO-1 TCR T-cells in metastatic breast cancer patients.
Overlap: None

Breast Cancer Research Foundation (Chang) 10/01/15-09/30/23 0.6 CM
BCRF
Title: Novel Potential drug targets for treatment of triple negative breast cancer
Role: PI
Major goals: The goal of this study is to identify potential targets for the treatment of metastatic breast cancer.
Overlap: None

W81XWH-20-1-0601 (Grattoni, Partner PI- Chen) 06/01/20 -05/31/23 0.36 CM
DoD Breakthrough level 2
Project Title: Transforming triple negative breast cancer treatment through intratumoral immunotherapy via nanofluidic drug eluting seed
Role: Co-I
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.

R01 CA251710 (Wong) 06/01/20-05/31/25 0.48 CM
National Institute of Health (NIH)
Project Title: Convergent AI for Precise Breast Cancer Risk Assessment
Role: Co-I
Specific Aims:
Aim 1) Development of the integrative multimodality database consisting of selected breast images, clinical report features, pathological molecular variables, and demographic signatures in BI-RADS 4 breast cancer suspicious patients.
Aim 2) Development of an improved cancer risk assessment model for BI-RADS 4 patients using deep learning algorithms on the breast multimodality database.
Aim 3) Multi-center evaluation and prospective clinical study to validate iBRISK by comparing its predictive accuracy of biopsy recommendations with BI-RADS recommendations.
Overlap: None.

U01 CA253553 (Wong) 09/15/2020-08/31/2025 0.3 CM
National Institute of Health (NIH)
Project Title: Spatiotemporal modeling of cancer-niche interactions in breast cancer bone metastasis

Role: Co-I
Major goals: The goal of this project is to investigate the spatiotemporal dynamics, molecular crosstalk, and therapeutic targets underling the interaction between breast cancer cells and their microenvironment niches in bone.
Overlap: None.

CHEST: Cytostorm Study (Chang) 09/15/2020-09/15/2023 0.12 CM
CHEST Foundation
Project Title: Cytokine release in SARS CO-V2 viral illness and Trends of inflammasome expression in Acute Respiratory Distress Syndrome manifestations and Management
Role: PI
Major goals: This prospective study aims to understand the ongoing processes related to both the immunological response in patients affected with the COVID-19 viral infection and how the severity of ARDS and management of the disease affect that response.
Overlap: None.

(New)
U01 (MPI: Chang, Meric, Lipkwitz, Wink, Wong) 06/10/2022-05/31/2027 1.2 CM
National Institute of Health (NIH)
Title: A phase II multi-center trial evaluating dual targeting of the PI3K/AKT and NOS pathways for treating metaplastic breast cancer (MpBC)
Role: MPI
Major goals: 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.
Overlap: None.

COMPELTED

(Completed)
U54 CA210181 (Shen, Chang) 08/29/16-07/31/22 0.6 CM
National Institute of Health (NCI)
Title: Center for Immunotherapeutic Transport Oncophysics
Role: MPI
Major goals: The goal of this Center is to understand transport limitation of immune cells and immunotherapeutics; establish a precision immunotherapeutics framework on the basis of transport oncophysics; and exploit oncophysical transport-based cues for the development of successful personalized immunotherapeutics strategies based on transport phenotypes.
Overlap: None

Award Log Number: W81XWH-20-1-0601

PI: Shu-Hsia Chen, HMRI, TX
Budget: $899,619
Topic Area: Breast Cancer
Mechanism: BCRP Breakthrough Award Level 1 and 2

Research Area(s): 1602 Device Validation/0807 Immunotherapies
Award Status: 8/1/2020 – 7/31/2023

Study Goals: **Our goal is to address one of the overarching challenges of breast cancer described in the FY19 BCRP Breakthrough Award: to revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival.**

Specific Aims: **Specific Aims. To test this hypothesis, we propose the following specific aims to be performed in the span of 3 years: 1) To evaluate the effect of NDES-mediated sustained intratumoral delivery kinetics on immunotherapy biodistribution and tumor immune microenvironment modulation. 2) To evaluate efficacy and toxicity of intratumoral NDES immunotherapy alone or in conjunction with RT for local and systemic tumor control.**

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date