AWARD NUMBER: W81XWH-20-1-0601

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

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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 progress in three tasks: 1) We investigated the biodistribution of PDL1 antibody delivered via NDES in 4T1 and EMT triple-negative breast cancer murine models. NDES demonstrated high drug retention within the tumor with minimal systemic dissemination, compared to bolus intratumoral (IT) or intraperitoneal (IP) delivery approaches. IP groups showed high levels of PDL1 antibody accumulation in liver indicative of potential systemic toxicity. We further demonstrated that the addition of radiotherapy had no effect in PDL1 antibody biodistribution. 2) The immune cell landscape associated with IP, IT and NDES drug delivery methods were examined by imaging mass cytometry. NDES delivery enhanced myeloid cell infiltration at early time points of day 3 and 7. However, our result on day 14 time point indicated that PDL1 antibody alone may be insufficient to maintain anti-tumor immune response. 3) Treatment efficacy of CD40 antibody as well as combination of CD40 and PDL1 antibodies were evaluated in EMT6 model with and without radiation treatment. IP, IT, and NDES drug delivery approaches were investigated. IP administration of combination CD40 and PDL1 antibodies achieved the highest tumor reduction whereby the addition of radiation did not improve growth inhibition. We postulate that a higher drug release rate from NDES is needed to effectively target EMT6.

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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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?

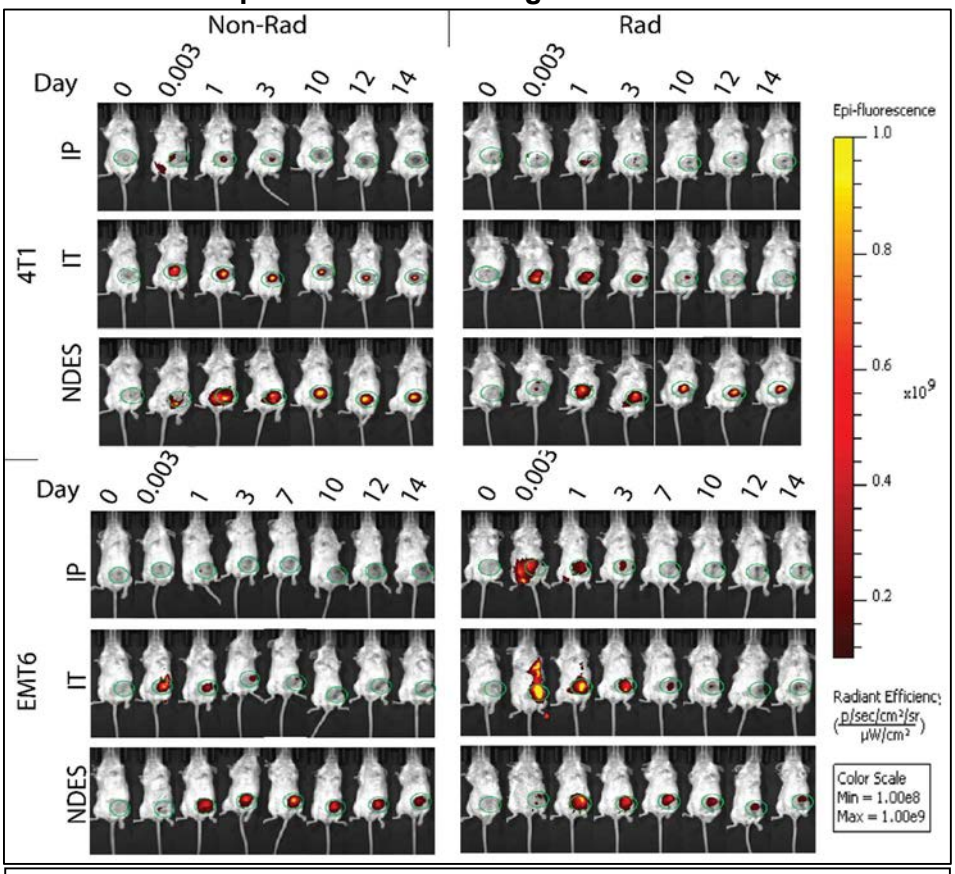


Fig 1. In vivo analysis of PDL1-AF700 in 4T1 and EMT6 mice treated with PDL1 antibody via IP, IT or NDES delivery w/ or w/o radiation.

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 biodistribution of immunotherapeutics delivered through NDES in comparison to systemic intraperitoneal (IP) and direct intratumoral (IT) injection.
Major Task 1 was 45% completed.
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.
Specific objectives: 1) Investigate PDL1 Ab biodistribution in two different syngeneic triple negative breast cancer (TNBC) immunocompetent murine models, EMT6 and 4T1. 2) Evaluate the

impact of PDL1 Ab biodistribution in combination with radiation.

Results and discussions: 4T1- or EMT6- tumor bearing mice were administered PDL1 conjugated to Alexa Fluor 700 (AF700) via IP, IT or NDES administration when tumor volume reached 100mm^3. Specifically, IP or IT cohorts received one bolus injection of 100 µg PDL1, whereas a one-time intratumoral device implantation was performed for NDES, which released 7 µg/day. Tumors in the radiation experimental arm were irradiated prior to immunotherapy treatment, where 4T1 tumors were irradiated with 8 Gy over 3 consecutive days (8 Gy x 3), while EMT6 tumors received 5 Gy x 3. We monitored drug retention in mice using in vivo imaging system (IVIS) to detect AF700 fluorescence signal. We collected blood, spleen, tumor, lymph node, kidney, liver and lung for ex vivo imaging analysis and ELISA analysis to quantify PDL1 Ab. Tumors were preserved with OCT for 3D reconstruction of the fluorescent distribution of Ab within the tumor.

In vivo IVIS live animal imaging showed that NDES maintained fluorescent Ab signal within both 4T1 and EMT6 tumors throughout the 14-day study duration, compared to IP and IT delivery, indicating sustained intratumoral drug release (Fig 1). IT group showed rapidly declining AF700 signal, suggesting tumor clearance. In contrast,

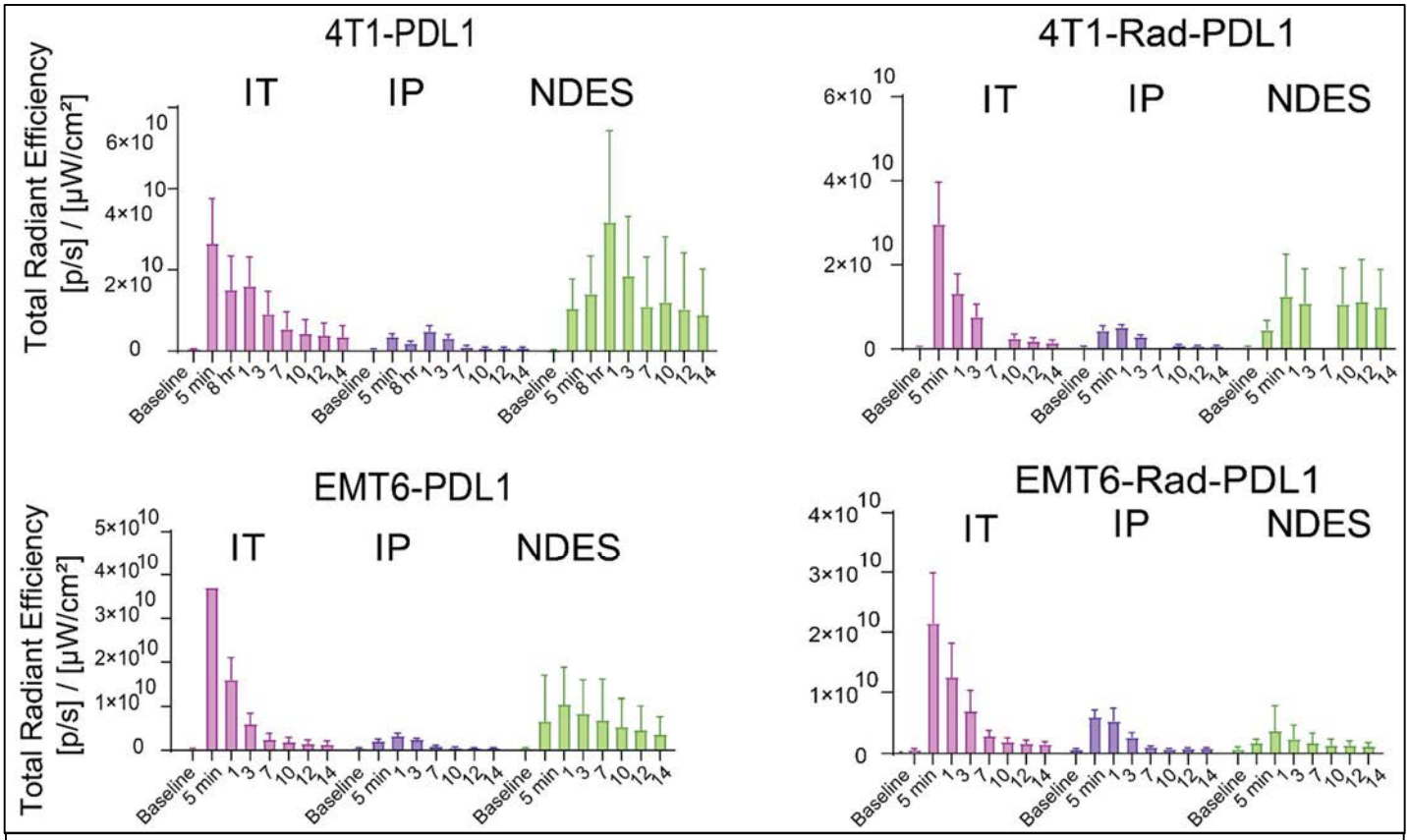


Fig 2. In vivo assessment of total radiance signal of PDL1 Ab in 4T1 and EMT6 tumor comparing IT, IP or NDES delivered PDL1.

IP had minimal AF700 signal in the tumor, indicative of poor tumor penetrance. The total radiance analysis from the IVIS imaging demonstrated relatively sustained PDL1-AF700 signal within the NDES treated tumors (Fig 2) compared to IT and IP groups. There was no significant impact of radiotherapy on PDL1 Ab distribution in 4T1 or EMT6 tumors. Ex vivo organ imaging assessment showed NDES achieved sustained and high drug localization in the tumor (Fig 3) with minimal dispersion to other organs throughout the study (Fig 4). For IT and IP cohort, there was a decline of PDL1 Ab from the tumor after day 3 (Fig 3). IP group showed systemic drug exposure with higher signal in liver and other organs such as lung, spleen and kidney compared to NDES and IT at early time points (Fig 4). Data for EMT6 not shown.

Tumors (n=3) were preserved in OCT after ex vivo IVIS imaging and assessed via 3D fluorescence scanning transillumination to detect PDL1-AF700 antibody (Fig 5). Quantification of PDL1 Ab per mm^3 of tumor via 3D fluorescence transillumination imaging analysis is currently ongoing. The results will be provided and discussed in the following report.

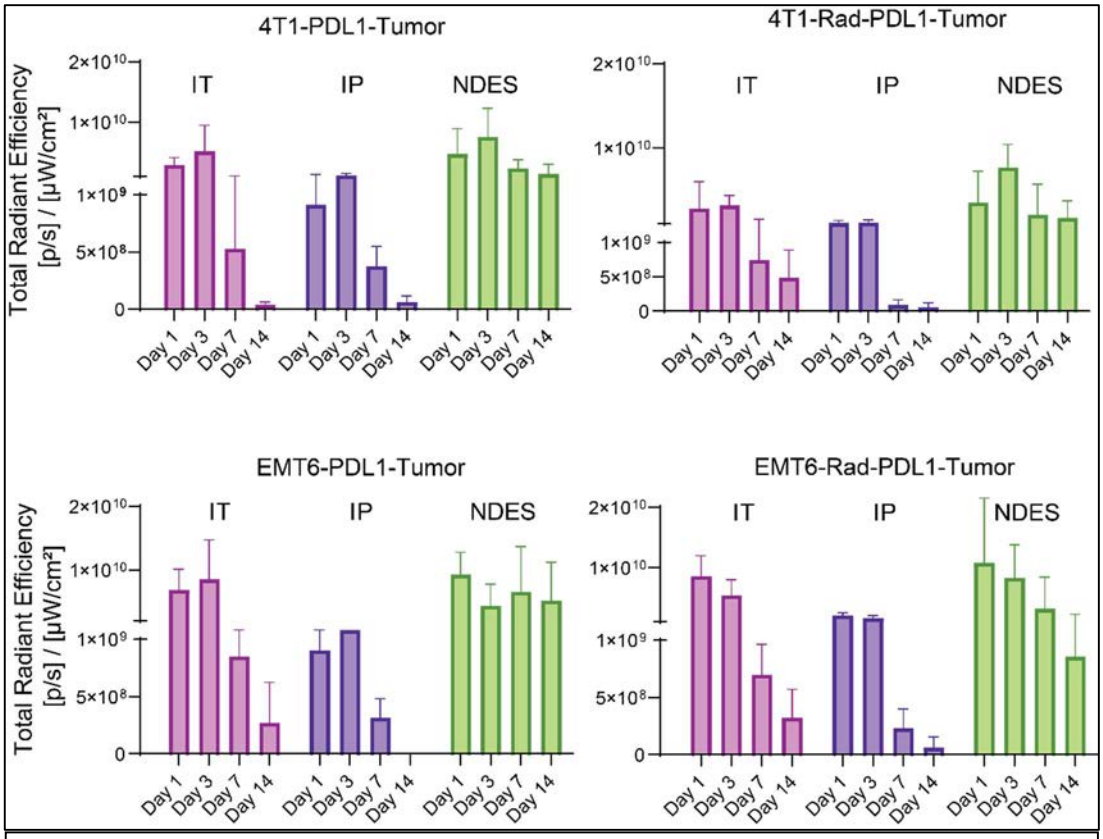


Fig 3. Ex vivo assessment of fluorescence PDL1 antibody signal within tumor in IT, IP and NDES at different time points.

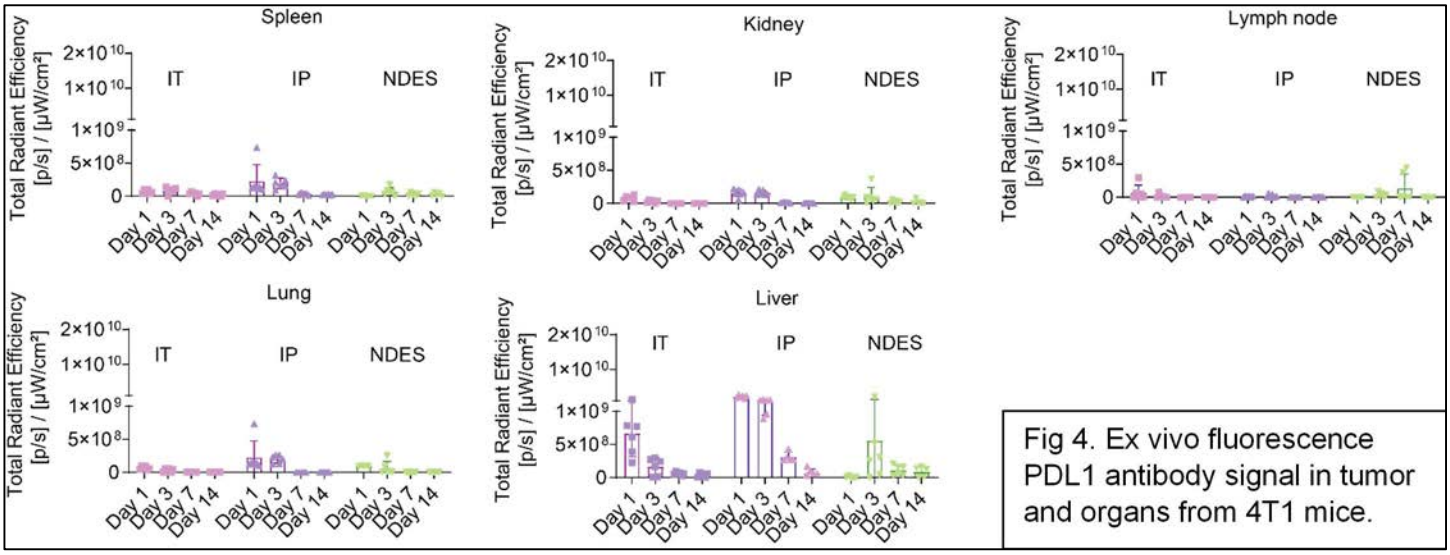


Fig 4. Ex vivo fluorescence PDL1 antibody signal in tumor and organs from 4T1 mice.

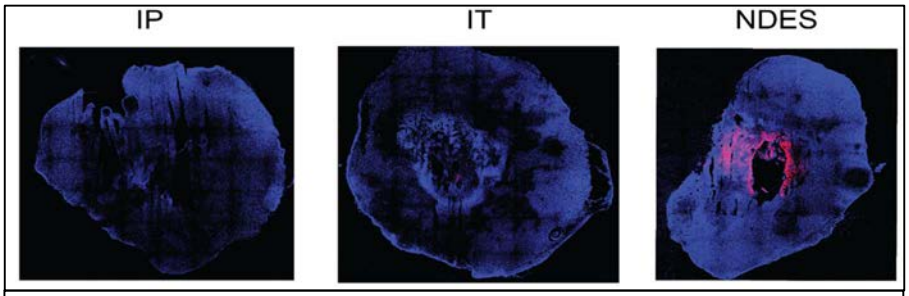
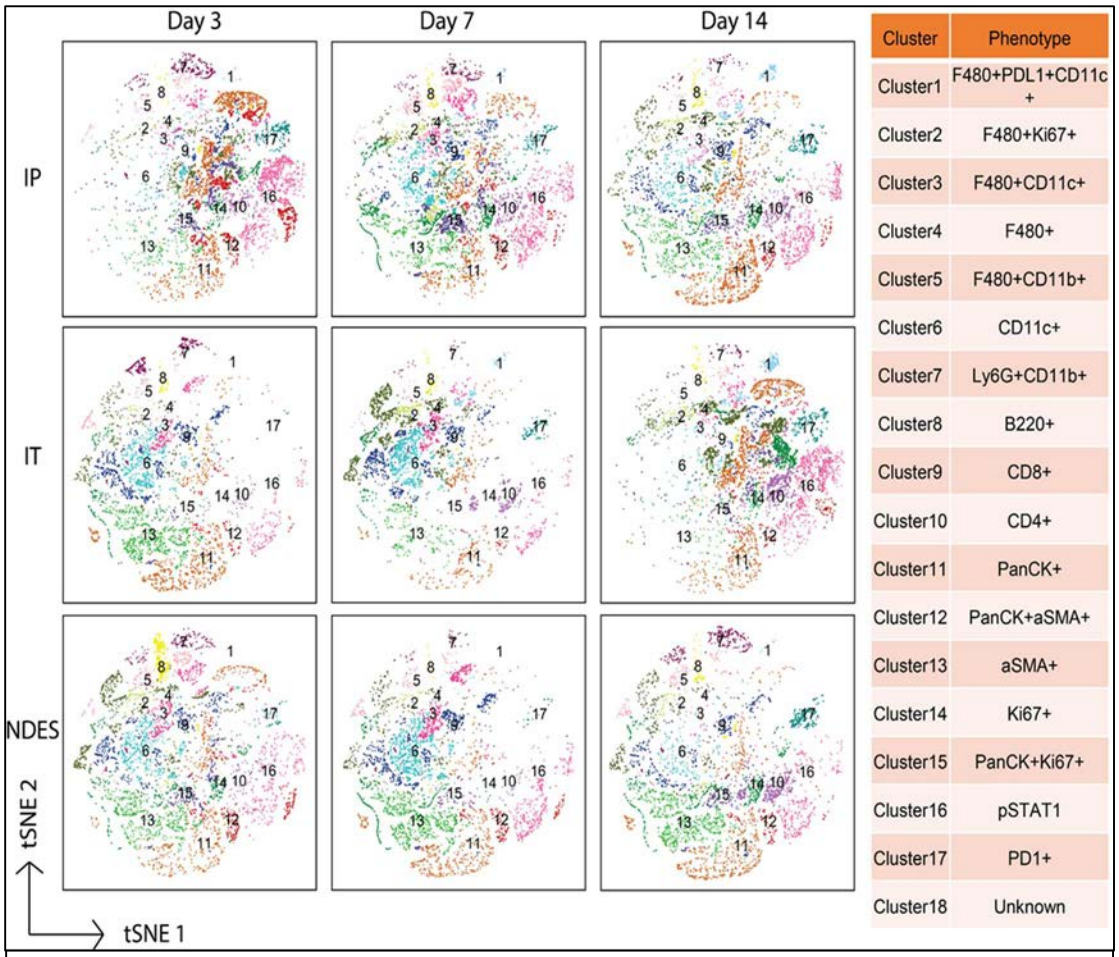


Fig 5. 3D reconstruction scanning showed PDL1-AF700 Ab localization within tumors between different delivery approaches.

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 12%.
Major activities: (Site 2 - Chen) Non-radiated PDL1 Ab treated 4T1 tumors (IP, IT and NDES) were evaluated by HMRI Immunomonitoring core for immune cell assessment via imaging mass cytometry (IMC).
Specific objectives: To understand the spatiotemporal dynamics of PDL1 within the tumor immune microenvironment (TIME) in response to treatment. Imaging mass cytometry was performed to assess immune cells network in TIME.
Results and discussions: IMC analysis showed immune cell density and population in TIME of IT, IP and NDES-PDL1 groups on days 3, 7 and 14. Cell types enrichment and unsupervised clustering analysis was performed (Fig 6). We further investigated the cell type density based on the expression markers of each clusters. In cluster 1, NDES groups showed low expression of PDL1+ myeloid cells population within TIME at all 3 time points (Fig 7), indicating effective and sustained PDL1 antibody release within tumor. Further demonstrating the effect of continuous drug release, we observed sustained levels of intratumoral macrophages in NDES across all time points in cluster 5, compared to IT and IP cohorts. In cluster 6, IT and NDES showed higher tumor-infiltrating dendritic cells (DCs) on days 3 and 7, suggesting effective DC recruitment to TIME (Fig 6). Thereafter, the decreased intratumoral levels on day 14 indicated DCs in circulation, though systemic analysis is required for confirmation. In cluster 10, CD4+ cells were increased in IT and NDES on day 14; further clarification of the specific CD4+ subtype is needed. In cluster 15, NDES groups showed lower levels of proliferating cancer cells on days 3, 7 and 14, whereas IT groups showed an increase on day 14. As only 1 bolus PDL1 Ab was administered for IP and IT to track immune cell changes across time points, we did not expect tumor control; therefore, by day 14, we did not observe sustained anti-tumor immune response. On the contrary, results from NDES suggested the effect of sustained drug release on intratumoral immune landscape. More in-depth cell clusters and neighborhood analysis are still ongoing.



Cluster	Phenotype
Cluster1	F480+PDL1+CD11c+
Cluster2	F480+Ki67+
Cluster3	F480+CD11c+
Cluster4	F480+
Cluster5	F480+CD11b+
Cluster6	CD11c+
Cluster7	Ly6G+CD11b+
Cluster8	B220+
Cluster9	CD8+
Cluster10	CD4+
Cluster11	PanCK+
Cluster12	PanCK+aSMA+
Cluster13	aSMA+
Cluster14	Ki67+
Cluster15	PanCK+Ki67+
Cluster16	pSTAT1
Cluster17	PD1+
Cluster18	Unknown

Fig 6. Cell clusters of TIME of each group displayed via viSNE.

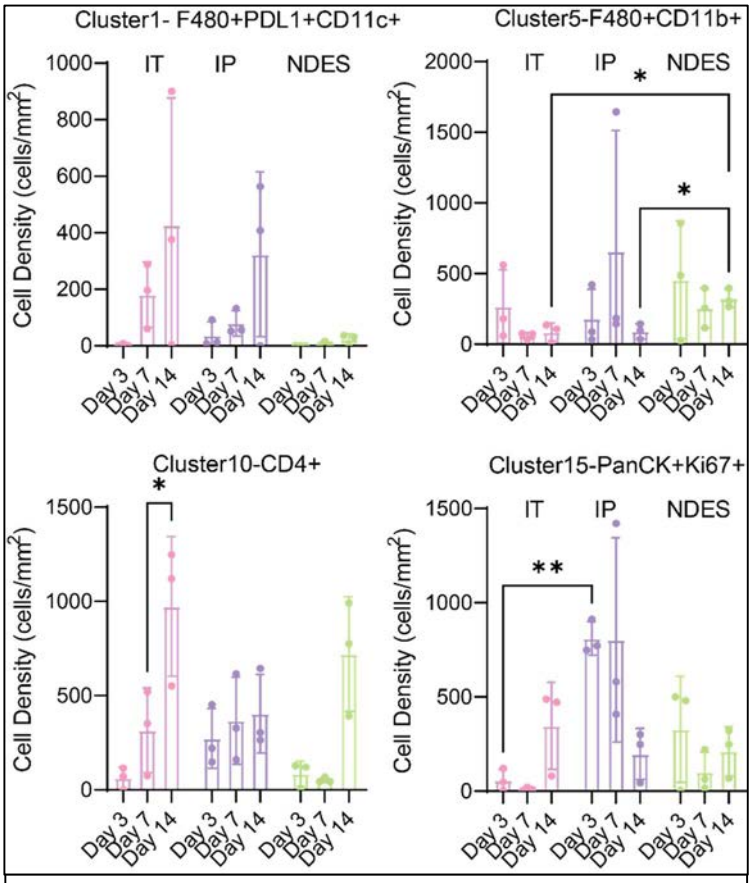


Fig 7. IMC analysis of cell density of selected cluster.

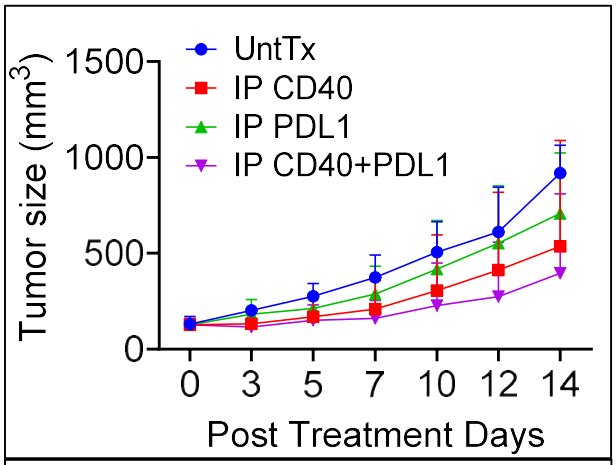


Fig 8. Tumor growth rate of EMT6 treated with CD40, PDL1 or CD40+PDL1 via IP delivery.

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 - 23% complete.

Major activities: (Site 1) EMT6 tumor bearing mice received 5 Gy radiation dosage over 3 consecutive days, followed by either 4 doses of immunotherapeutics via IT or IP or one-time implantation of NDES. Fourteen days after immunotherapy administration, mice were euthanized. **(Site 2)** Four tumors (n=4) were allocated for CyTOF analysis, and the other half of tumors (n=3 or 4) were formalin fixed and paraffin embedded for IMC analysis. **(Site 1)** Blood was collected for cytokine analysis. Lung and liver were collected for metastasis and toxicity, respectively.

Specific objectives: To assess the therapeutic effect of local and systemic immunotherapeutics delivery to EMT6 tumor bearing mice.

Results and discussions: Pilot experiments were performed where 5 Gy x 3 radiation dosage was selected for EMT6. We assessed EMT6 tumor response to single drug, CD40 or PDL1 Ab, as well as the combination of both antibodies. Mice received either 100 µg PDL1 Ab, 100 µg CD40 Ab or combination (50 µg CD40 Ab + 50µg PDL1 Ab) via IP for a total of 4 doses. Tumor growth rate indicated monotherapy with CD40 or the combination of CD40 Ab and PDL1 Ab improved tumor control compared to PDL1 Ab alone (Fig 8). Therefore, CD40 Ab and combination of CD40 and PDL1 Ab was used for EMT6 treatment.

We treated EMT6 tumors with 3 daily consecutive doses of 5 Gy radiation, followed by either 4 doses of CD40 or combo (CD40+PDL1) delivered by IP injection or a one-time intratumoral implantation of NDES, which released 7 µg of CD40 or combination Ab per day. IP combination Ab had the most effective tumor growth inhibition, followed by IP CD40, in comparison to control groups. The addition of radiation did not improve tumor outcomes. NDES showed no effect on tumor growth compared to control groups (Fig 9). We posit that a higher intratumoral dose could be needed to achieve tumor control for EMT6; we are currently investigating this hypothesis. No visible metastatic nodules were observed in the lungs; further histological analysis is ongoing.

Four tumors from each group were processed with Lymphoprep to isolate tumor infiltrating lymphocytes (TIL) for CyTOF analysis. Data analysis is ongoing. Overall, we posit that the lack of treatment response in NDES group could be due to insufficient dosage of CD40 in EMT6 model. The total delivered dosage for the IP groups was 400µg, and the total dosage from NDES was 98µg. EMT6 is an immunogenic tumor model; we postulate that

enhanced response could be achieved with a higher intratumoral dosage. We will increase the Ab release rate in the NDES through modifying nanochannel size on the nanofluidic membrane.

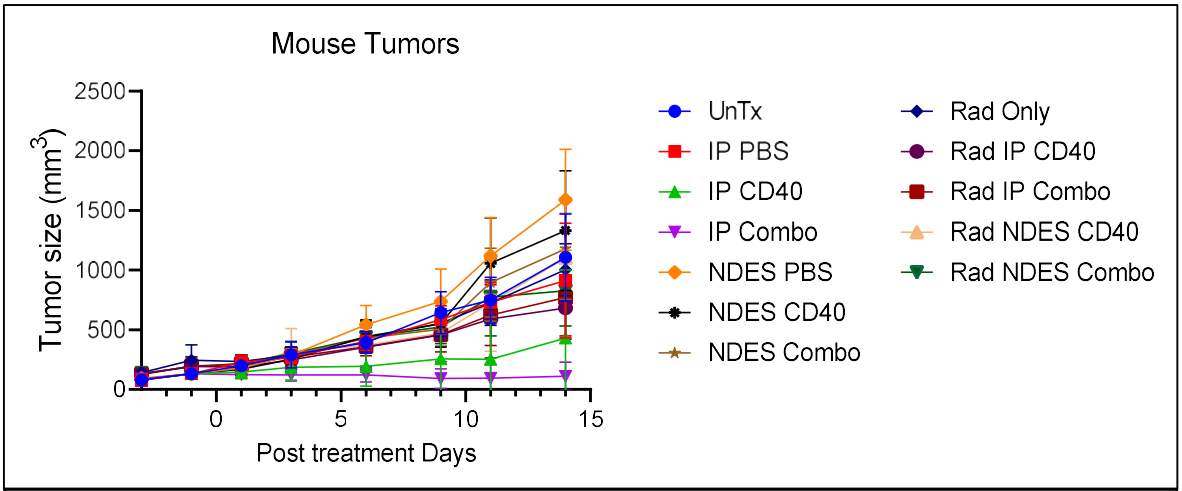


Fig 9. EMT6 tumor growth. Mice received radiation (5Gy x3) and/or CD40 or combo via IP or NDES delivery.

Major Task 4. To assess the systemic effect of IT NDES-Ab + Rad on distal (untreated) tumor growth. (months 20-28)
Major task 4 has not been completed, 0% complete.

Major Task 5. Analyze impact of treatment on toxicity. (months 29-36)
Major task 5 has not been completed, 0% complete.

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. Two presentations resulted from these studies.

How were the results disseminated to communities of interest?

Results of the study was presented at the Houston Methodist Research Institute Summer Science symposium where attendees included undergraduate interns from all backgrounds who are interested in pursuing science as a career.

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 - 100% completion; Major task 2 - 50% completion; Major task 3 - 60% completion; Major task 4 - 10% 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

In Aim 2, our experimental design evaluated efficacy of CD40 and PDL1 Ab, either alone or in combination. Our results showed that the combination of CD40 and PDL1 Ab effectively reduced tumor burden. Therefore, our future studies will be performed with combination CD40 and PDL1 Ab.

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:

Grattoni A. Biomedical Nanofluidics for Long-Acting Therapeutics. Polytechnic of Turin, Turin, Italy. June 3, 2021. Invited Presentation.

Grattoni A. Nanofluidics for Medicine. 16th Annual National Nanomedicine Seminar Series. Nanomedicine Academy at Northeastern University, Boston, Massachusetts, November 10, 2020. Invited virtual presentation.

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.

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.

Grattoni A. Nanofluidics for Terrestrial and Space Medicine. Cleveland Clinic - UTEC Summit 2020, Cleveland, Ohio, October 2, 2020. Invited Presentation.

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.

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.

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

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:	1.7
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:	4.2
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:	5.1
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:	5.1
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:	.05
Contribution to Project:	Oversight of radiation dosing during experiment execution

Univeristy of Washington

Name:	Elizabeth Nance
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-7167-7068
Nearest person month worked:	0.4
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:	2.4
Contribution to Project:	Methodology optimization, imaging and image analysis

Name:	Mengying Zhang
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0003-0674-9437
Nearest person month worked:	1.75
Contribution to Project:	Methodology development, imaging and image analysis

Name:	Ana Rios
Project Role:	Undergraduate Research Assistant
Researcher Identifier (e.g. ORCID ID):	NA
Nearest person month worked:	1.5
Contribution to Project:	Tissue processing

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:	0.36
Contribution to Project:	Dr. Chang provides guidance on IT device deployment and immunotherapy dosing in breast cancer tumor models for clinical translation.

Name:	Jilu Zhang
Project Role:	Research Scientist
Researcher Identifier (e.g. ORCID ID):	0000-0001-9756-6526
Nearest person month worked:	6
Contribution to Project:	Dr. Zhang has 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 (PI: 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
There is no scientific or budgetary overlap.

(New)
2-SRA-2021-1078-S-B (PI: Grattoni/Gaber) 08/01/2021-07/31/2022 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: Kristin McGowen, KMcgowan@jdrf.org
There is no scientific or budgetary overlap.

(New)
U54CA210181 Pilot (PI: 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
There is no scientific or budgetary overlap.

(New)
Gilead (PI: Grattoni) 04/19/2021 – 04/18/2022 0.36 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
There is no scientific or budgetary overlap.

(New)
GA-2020-145 Renewal (PI: Grattoni) 07/01/2020 – 10/01/2021 1.2 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
There is no scientific or budgetary overlap.

GA-2019-003 (PI: Grattoni) 08/01/2014 – 10/30/2022 0.6 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
There is no scientific or budgetary overlap.

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. There is no scientific or budgetary overlap.

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
There is no scientific or budgetary overlap.

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
There is no scientific or budgetary overlap.

R01GM127558 (PI: Grattoni/Liu) 04/15/2018 – 01/31/2022 3.0 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
This project relates to the development of a remotely controlled gated drug delivery system. There is no scientific or budgetary overlap.

R01AI120749 (PI: 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
This project relates to the demonstration of an implant for HIV PrEP. There is no scientific or budgetary overlap.

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
This project relates to cell transplantation for the treatment of diabetes. There is no scientific or budgetary overlap.

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 (2% effort)
Overlap: None

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
There is no scientific or budgetary overlap.

COMPLETED

(Completed)
Grattoni/Butler/Filgueira 09/01/2016-12/31/2020 0.24 calendar
Golfer's Against Cancer total
From Local Delivery to Systemic Immune Activation: One-Two Punch to Cancer
Our goal is to intratumorally deliver gold nanoparticles through an innovative device and use a one-two punch of photothermal and radiation therapies to eradicate solid tumors and trigger an anti-tumor immune response to eliminate metastases around the body.
Our Aims are to 1) accurately quantitate the amount of gold nanoparticles released from our device into the tumor and demonstrate a higher yield when compared with intravenously injected nanoparticles, 2) excite the particles through both the photothermal effect and radiotherapy and show cancer cell death by measuring tumor size, and 3) monitor the immune response induced by both photothermal and radiation therapy destruction of the tumor and assess the abscopal effect of distal metastasis.
Role: Co-Principal Investigator
Point of Contact: Tiffany Polk
This project relates to lung cancer and gold nanoparticle radiotherapy. There is no scientific or budgetary overlap.

(Completed)
Grattoni 07/01/2017-06/30/2020 0.6 calendar
Lamborghini Auto
Investigation of the biocompatibility of carbon fibers composites for implantable medical devices.
Our goal is to assess the biocompatibility of 16 carbon fiber materials for potential biomedical implantable applications.
Our specific aim includes: 1) To test in vitro the cytotoxicity and genotoxicity of CFRPs and assess their effects on osteoblast and macrophages. 2) To evaluate acute systemic toxicity and sub-chronic toxicity of CFRPs after

subcutaneous implantation. 3) To investigate chronic toxicity and foreign body response to CFRP implants during 6 month implantation in a domestic pig model.
Role: Principal Investigator
Point of Contact: Luciano De Oto
This project relates to the evaluation of the biocompatibility of new materials. There is no scientific or budgetary overlap.

(Completed)
Filgueira 01/01/2019-6/30/2020 0.18 calendar
Department of Defense PRMRP Discovery Award total
Implantable Nanochannel System for the Controlled Delivery of Osteogenic Growth Peptide
Our objective is to design a spinal implant permitting sustained release of Osteogenic Growth Peptide (OGP) and to perform in vivo efficacy testing in a large animal (rabbit) model.
Specific Aim 1: Design a spinal fusion implant that allows for sustained release of OGP and Specific Aim 2: Release of OGP in an established large animal (rabbit) model.
Role: Co-Investigator
Point of Contact: Allison Milutinovich, Ph.D. Program Manager
This project involves use of an implantable nanofluidic membrane for the controlled administration of OGP and there is no scientific or budgetary overlap with any of the previous, current, or pending funding support.

(Completed)
Grattoni 09/24/2018-03/31/2020 1.2 calendar
Gilead
Nanochannel implant for sustained delivery of TAF for HIV PrEP
Specific Aim: To assess the preventive efficacy of TAF monotherapy delivered via a nanochannel implant in non-human primates for HIV PrEP.
Role: Principal Investigator
Point of Contact: Celestine Navarro, celestine.navarro1@gilead.com
There is no scientific or budgetary overlap.

(Completed)
GA-2019-953 (PI: Chua/Grattoni) 11/16/2019-07/31/2019 0.24calendar
CASIS
Sustained delivery of a bisphosphonate-prostaglandin analog complex (C3) for the prevention and treatment of osteopenia
Our goal is to study our nanofluidic implant for zero-order and sustained delivery of C3 for effective and safe prevention of osteoporosis in microgravity.
Specific Aims: 1) To optimize the nanofluidic implants for constant and sustained delivery of C3 in preparation for the microgravity flight experiment. 2) To test the efficacy of sustained subcutaneous delivery of C3 released from nanofluidic implants in microgravity-induced spontaneous mouse model of osteoporosis.
Role: Co-Principal Investigator
Point of Contact: Kenneth Shields
There is no scientific or budgetary overlap.

NANCE, ELIZABETH

ACTIVE

(New)
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

(New)
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

(New)
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
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: 6/1/2020-5/31/2023
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 – 08/31/2020
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- 07/31/2022

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

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

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

(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

CURRENT & PENDING SUPPORT FOR DOD

KRISHNAN, SUNIL

ACTIVE

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/DE028105
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/NA
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/CA252156
Effort:	0.60
Supporting Agency:	NIH
Grants Officer:	Christopher Hartshorn
Performance Period:	07/01/2020-06/30/2022
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

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

(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:	04/01/2021-03/31/2026
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

(New)

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

(Completed)

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 2) Demonstrate cellular uptake and tumor cytotoxicity of the nanocomplexes upon low dose X-ray excitation in vitro 3) Perform in vivo pharmacokinetic/biodistribution analyses followed by tumor regrowth studies in murine pancreatic cancer models
Overlap:	None

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.

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 – 08/31/2021 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.

R01CA222959-01 (Shen) 1.2 CM
NIH/NCI 07/01/2018-06/30/2023
Project Title: Mechanism of intratumoral transport of particulate drugs
Contact: Alley, Michael C, email: alleym@mail.nih.gov
Role: Co-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.

(This grant)
W81XWH-20-1-0601 (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.

(New)
W81XWH2110011 (Godin, Frieboes) 03/01/2021 – 02/28/2024 0.24CM
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 0.0CM
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

(New)
U54CA210181 (Shen/Chang) 8/1/2020-7/31/2022 0.24CM
NIH/NCI
Harnessing Transport Properties of PMN-MDSC for Enhancement of Anti-Tumor Immunity
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.
Role: Co-I on Administrative Supplement

COMPLETED:

(Completed)
R01CA127483 (Chen) 04/01/2007-07/31/2021 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.

CHANG, J.C.

ACTIVE:

W81XWH-16-0418 (Wang, Partner PI - Chang) 09/30/16-9/29/21 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

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

(New)
3U54CA210181-05S1 (Shen, Chang) 08/17/20-07/31/22 0.12 CM
National Institute of Health (NCI)
Title: Targeting the Inflammasome As a Treatment Strategy for COVID-19 infected cancer patients
Role: MPI
Major goals: In this supplement application, we propose to perform correlatives to understand cytokines and immune profile changes in cancer vs. non-cancer patients with COVID-19.
Overlap: None

Breast Cancer Research Foundation (Chang) 10/01/15-09/30/21 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

(This grant)
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.

(New)

R01 CA251710 (Wong) 06/01/20-05/31/25 0.504 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.

(New)
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.

COMPLETED:

(Completed)
RP170466 (Chang) 12/1/16-11/30/20 1.2 CM
Cancer Prevention & Research Institute of Texas (CPRIT)
Title: Targeting the inflammatory cancer stem cell microenvironment of triple negative breast cancer with leukocyte- mimetic nanovesicles.
Role: PI
Major goals: The goal of this study is to develop leukocyte nanoparticle against breast cancer stem cell targets, including JAK2, STAT3, and WNT.
Overlap: None

(Ended)
W81XWH-17-1-0390 (Shen, Partner PI - Chang) 08/01/17-07/31/21 0.90 CM
DOD Breakthrough Award Levels 3 and 4
Title: A Nanodrug for the Cure of Metastatic Breast Cancer
Role: Partnering PI
Major goals: The goal of this study is to address the following FY16 BCRP Overarching Challenges: 1) revolutions treatment regimens by replacing interventions that have life-threating toxicities with one that are safe and effective; and 2) eliminate the mortality associated with metastatic breast cancer.
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