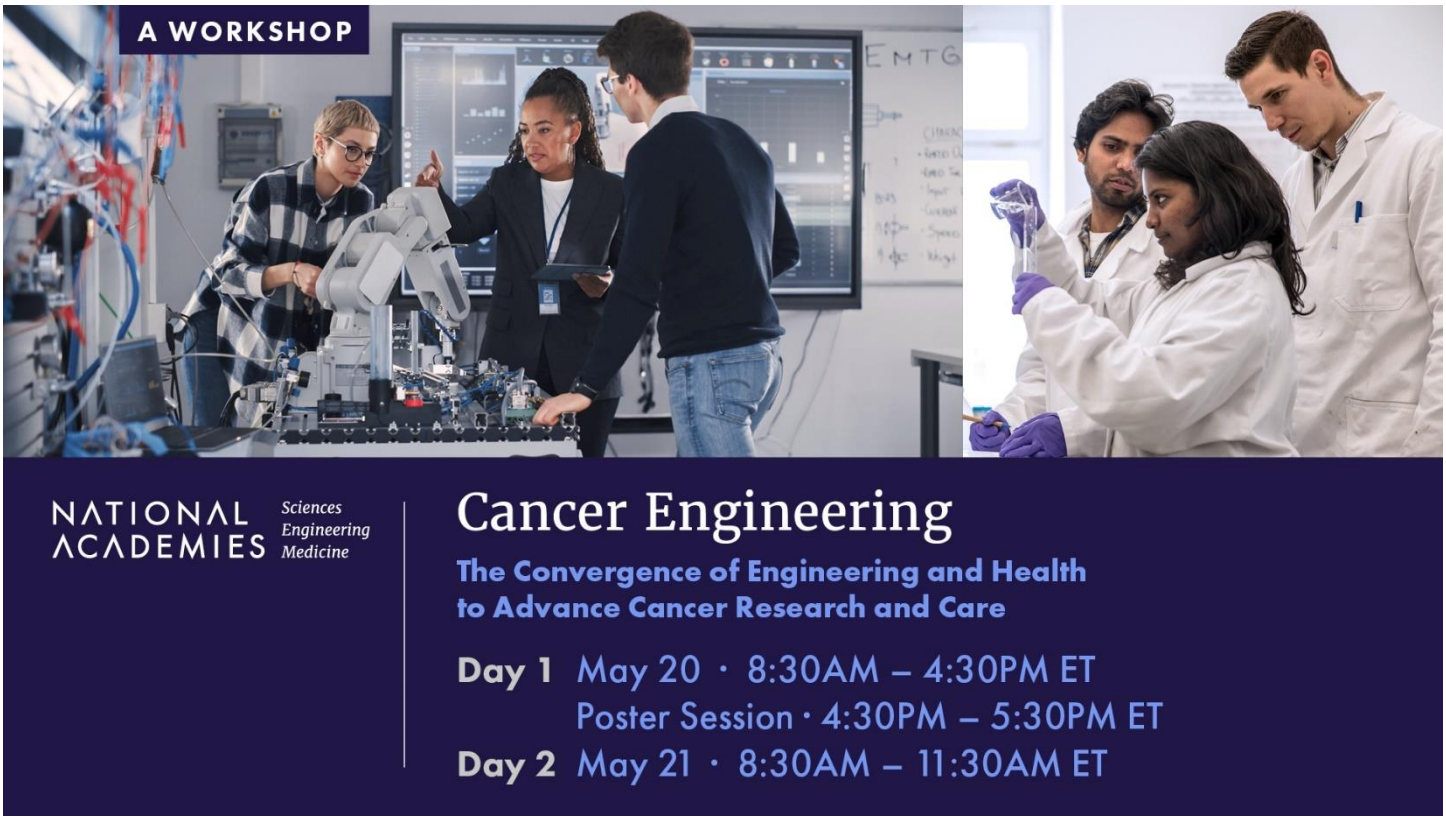
NATIONAL CANCER POLICY FORUM

PACKET FOR
POSTER PRESENTER ABSTRACTS AND BIOSKETCHES AND HONORABLE MENTION ABSTRACTS



The poster session will take place before the workshop reception:
Tuesday, May 20, 2025, from 4:30pm to 5:30pm ET

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NATIONAL ACADEMIES Sciences Engineering Medicine

Title: Biomimetic Peritoneal Cavity-on-a-Chip for Studying Cancer Progression and Metastasis

Authors: Rana J. Abbed[1] (presenting author), Edwin Quiñones-Cruz[1], and Susan E. Leggett[1,2]

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Abstract:
Peritoneal metastasis is a frequent and critical event in the progression of cancers such as ovarian, gastric, colorectal, and pancreatic, all of which commonly spread to the peritoneum. Once these cancers metastasize to the peritoneum, prognosis worsens, and survival rates decrease significantly after recurrence, with many patients surviving only a few months depending on cancer type and treatment. The peritoneal cavity, a fluid-filled space surrounding organs such as the liver and stomach, is lined by mesothelial cells and facilitates disease progression through interactions with circulating tumor cells. Despite the importance of these interactions, in vitro cancer models oversimplify the peritoneal microenvironment, failing to replicate the tissue complexity and fluid dynamics of the peritoneal cavity, while in vivo models provide limited resolution for studying these processes in detail.

To address these challenges, we have developed a biomimetic peritoneal cavity-on-a-chip to replicate the peritoneal microenvironment. Bioengineered peritoneal cavities were generated by seeding LP-9 mesothelial cells into a molded type I collagen cavity housed within a millifluidic chamber, mimicking a 3D peritoneal cavity microenvironment. We employed this system to study the dynamics of ovarian cancer spread in the peritoneal cavity. Circulating ovarian cancer (OVCAR3) cells were introduced into the biomimetic peritoneal cavity via gravity-driven flow to simulate tumor cell dissemination within the cavity. Additionally, we established a 3D-printed platform to streamline the fabrication of peritoneal cavity-on-a-chip devices in an arrayed format. This setup enables long-term culture and live-cell imaging, allowing real-time observation of critical processes such as tumor-mesothelial cell adhesion, invasion of the peritoneal lining, and formation of metastatic foci. By bridging the gap between traditional in vitro and in vivo models, this platform provides a high-throughput, low-cost solution for studying cancers that spread to the peritoneal cavity, offering valuable insights into cancer progression and therapeutic targets.

Title: Metabolic reprogramming in 3D ex-vivo lung adenocarcinoma cancer models

Authors: Suehelay Acevedo Acevedo[1,2] (presenting author), Hayley D. Ackerman[1,2], Vanessa Y. Rubio[1], John Lockhart[1,2], Nicole Hackel[1,2], Michelle Reiser[1,2], Christina Carr[1,2], Kaitlyn A. Miranda[1], Jaden Baldwin[1,2], John Koomen[1], Gina Nazario[4], Hilal Ozakinci[4], Duy T. Nguyen[3], Gina DeNicola[6], Theresa Boyle[4], Eric Haura[5], W. Gregory Sawyer[3], and Elsa R. Flores[1,2]

[1]Department of Molecular Oncology; [2]Cancer Biology and Evolution Program; [3]Department of Bioengineering, [4]Department of Pathology; [5]Department of Thoracic Oncology; [6]Department of Cancer Physiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa Florida.

Abstract:
TP53 (p53) mutations occur frequently in many types of cancer, including lung adenocarcinoma (LuAD), and are associated with poor prognosis. The Flores Laboratory has pursued alternative strategies, including targeting its family members, p63 and p73, to target the p53 pathway. Well-characterized in vivo mouse and in vitro organoid models have been used to study the role of the p53 family in LuAD progression. Here, 3D ex vivo models that recapitulate the in vivo lung tumor microenvironment were generated to study and validate mechanistic targets of LuAD progression under different p53 statuses. Tumors from Kras-driven mouse models with WT p53, p53 loss, p53 R172H, and TAp73 loss were minced to <1mm3 and cultured in inert hydrogel under constant medium perfusion using Darcy perfusion plates. Histology and extensive omics analyses were conducted on microtumors after 10 days of perfusion culture and compared to primary tumors and organoids. LuAD microtumors retained similar levels of epithelial cells and immune cell populations compared to the original tumors. Multi-omic analyses revealed molecular signatures like those of bulk tumors, while the organoids expressed contrasting signatures to those of initial tumors. Microtumors had increased fatty acid biosynthesis enzymes leading to increased acylcarnitines and polyunsaturated fatty acids. Previous research identified acylcarnitines increased in late-stage LuAD, suggesting tumor progression in the microtumors. Our data indicate LuAD microtumors recapitulate the original bulk tumor microenvironment while showing metabolic reprogramming towards a more aggressive phenotype. Microtumor cultures of patient LuAD samples received from lobectomies and the Rapid Tissue Donation (RTD) program at Moffitt were also established using this method. Patient samples retained the endogenous microenvironment and driver mutations. This model is a novel system to model LuAD ex vivo and unravel mechanistic information about p53 family member function in tumor progression in a way that mouse and organoid models cannot achieve.

Title: Weakly Supervised Cancer Grading Using Rank-Aware Contextual Reasoning on Whole Slide Images

Authors: Anirudh Choudhary[1] (presenting author), Angelina Hwang[2], Jacob Kechter[2], Krishnakant Saboo[1], Nneka Comfere[2], Steven Nelson[2], Emma Johnson[2], Leah Swanson[2], Olayemi Sokumbi[2], David DiCaudo[2], Ravishankar Iyer[1], Aaron R Mangold[2]

[1]University of Illinois Urbana-Champaign; [2]Mayo Clinic

Abstract:
Introduction: Squamous cell carcinoma (SCC) is a prevalent cancer subtype contributing to significant mortality. Tumor grading, a critical prognostic factor, relies on manual examination of histopathology whole slide images (WSIs), which is subjective and prone to intra- and inter-clinician variability. This leads to inconsistent diagnoses and understaging of high-risk cases. While artificial intelligence (AI)-assisted tumor grading has shown promise in other cancers, its application to SCC remains unexplored. We propose RACR-MIL, a novel weakly-supervised AI framework for SCC grading that requires minimal training labels and generalizes across anatomical sites.

Methods: RACR-MIL employs multiple instance learning incorporating rank-aware contextual reasoning and self-supervised pretraining. Three key innovations include: 1) rank-ordering to emulate clinician's ordinal grading protocol and prioritize severe tumors; 2) graph networks to capture local tissue semantics and global structural context; 3) dynamic graph learning with diversity constraints to model varied aspects of tumor morphology. The model was trained and evaluated on SCC datasets from skin (815 subjects), head and neck (672 subjects) and lung (289 subjects).

Results: RACR-MIL achieved 5-10% higher accuracy than existing weakly-supervised approaches by 5-10% with 0.810 F1 score and 0.841 Kappa score for skin cancer. It attained 5-10% higher accuracy on difficult-to-classify high-risk grade tumors with improved resilience to dataset imbalance. RACR-MIL improved worst-grade tumor localization by up to 50%, showing strong alignment with pathologist annotations and provided enhanced interpretability via tumor heatmaps. In a clinical study, RACR-MIL showed potential clinical utility by enhancing diagnostic efficiency in 70% of cases. Pathologists' qualitative comments supported our model's efficacy as a practical diagnostic assistant.

Title: Micro-milled high-throughput force sensor array for in situ mechanical testing of tumors-on-a-chip

Authors: Bashar Emon[1] (presenting author), Ahmadreza Kashefi[1], and M. Taher A Saif [1,2]

[1]Mechanical Science & Engineering; [2]Bioengineering; University of Illinois at Urbana-Champaign

Abstract:
Increasing evidence suggests that the biomechanical crosstalk within the tumor microenvironment (TME) is a critical determinant of cancer fate. Yet, lack of experimental platforms that allow biomechanical investigation of in vitro tumor models inhibits translational applications of mechanobiology in precision medicine. To address this challenge, we developed a novel device that quantifies cellular forces and matrix remodeling by measuring stiffness of three-dimensional (3D) extracellular matrices (ECM). [1]. We have manufactured a high-throughput array of such devices that host many patient-derived organoids and enables efficient drug optimization based on biomechanical readouts, advancing mechanobiological approaches toward personalized cancer treatment.

The underlying principle of each sensor involves the formation of a capillary bridge of cell-ECM mixture (comprising rat-tail collagen I and cells) between two grips connected to force-sensing springs. Each unit sensor, fabricated from polydimethylsiloxane (PDMS), comprises of beams that function as the force sensing springs. When the forces exerted by the cells cause the spring to stretch by a displacement df, the force is calculated using the relationship F = Kf * df, where Kf denotes the spring constant. Additionally, by stretching or compressing the tissue construct, the stiffness of the construct can be measured.

Using this novel high-throughput sensor system, we examined the effects of chemotherapeutic drugs on colorectal cancer-associated fibroblasts (CAFs), pancreatic stellate cells (PSCs), and patient-derived pancreatic ductal adenocarcinoma (PDAC) organoids. This study provides the first evidence of quantifying drug efficacy in 3D tumor models based on contractility and matrix remodeling. Results show that treatment with all-trans retinoic acid (ATRA) reversed matrix stiffening by the CAFs by softening the matrices. Similar effects were observed with PSCs and patient-derived organoids embedded in collagen-Matrigel (2 mg/ml + 1 mg/ml) matrices. We also found that the combination of Gemcitabine and ATRA is very efficient in inhibiting force and matrix stiffening. These results promise impactful clinical applications of our high-throughput biomechanical system in precision medicine.

Title: Effects of fluid shear stress on the metastatic potential of circulating tumor cells

Authors: Marie Floryan[1] (presenting author), Elena Cambria[1], Mark Coughlin[1], Roger Kamm[1]

[1]Massachusetts Institute of Technology

Abstract:
Motivation: Different cancers tend to metastasize to specific organs, and we hypothesize that this metastatic tropism is due to the differences in physical stressors among organs. Mainly, organs that see the highest metastatic incidence (ie. liver), have low blood flow rates, whereas organs with infrequent metastases (ie. skin), have high blood flow rates. Using microfluidics as a companion to animal studies, we study the effects of flow velocity and shear stress on the capability of CTCs to survive in the blood circulation and on their metastatic potential.

Methods: Engineered human blood vessels were formed in a microfluidic device and a microfluidic pump was connected to introduce fluid flow through the vessels. Breast cancer or melanoma cells were flown into the vessels and were subjected to either low flow (liver-like) or high flow (skin-like) for up to 25 days.

Results: The metastatic potential was first compared between a no flow condition (current standard in microfluidic-based vessel experiments), and with flow. The flow condition resulted in much fewer cancer cells in the surrounding tissue, however, migration of cancer cells into tissue occurred much faster under flow. As the flow speed increased, the number of metastatic events tended to decrease within the 48-hour window tested. A few devices were tracked for longer, and we were able to observe the growth of a metastatic tumor from a single cancer cell on day 8, to a tumor ~1 mm in diameter 25 days later.

Conclusion: This project extends in vivo studies by recapitulating the geometry and function of organ-specific vascular beds within microfluidic platforms while exerting systematic control over the physical environment. Taken together, our observations aim to establish a biophysical mechanistic basis of metastatic organ colonization and reveal novel therapeutic approaches to inhibit the metastatic process and, thereby, limit disease progression in cancer patients.

Title: Engineering High-Fidelity Early Cancer Models: Single-Cell Bioprinting in 2D and 3D to Mimic the Native Tumor Microenvironment

Authors: Haylie R. Helms[1,2,3] (presenting author), Anthony Tahayeri[1,3,7], Ellen M. Langer[1,3,4,5], Alexander E. Davies[1,3,4], and Luiz E. Bertassoni[1,2,3,4,6,7]

[1]Knight Cancer Precision Biofabrication Hub, Knight Cancer Institute, Oregon Health and Science University; [2]Department of Biomedical Engineering, School of Medicine, OHSU; [3] Cancer Early Detection Advanced Research Center (CEDAR), Knight Cancer Institute, OHSU; [4]Division of Oncological Sciences, School of Medicine, OHSU; [5]Molecular and Medical Genetics, School of Medicine, OHSU; [6]Center for Regenerative Medicine, OHSU; [7]Division of Biomaterials and Integrative Biosciences, School of Dentistry, OHSU

Abstract:
Our understanding of early cancer biology and associated biomarkers is limited, largely due to difficulties in obtaining clinical samples of early-stage cancers with sufficient throughput. Understanding the sequence of events that occur as a tissue evolves from dysplastic to malignant can aid biomarker discovery to enable detection and interception at its earliest point. Here we present two high-fidelity engineered cancer models in which we can controllably manipulate the cellular and extracellular environment to systematically identify which conditions promote or inhibit cancer initiation and progression. The first model leverages our single-cell bioprinting method to create 2D 'replicas' of regions of interest (ROIs) from a native histology section with subcellular resolution. Using a ductal carcinoma in situ (DCIS) patient biopsy as our model system, we matched the cellular microenvironment of the ROI using 5 cell phenotypes (MDA-MB-231, epithelial, fibroblast, macrophage, and mesenchymal stromal cells) with 1.6 ± 0.6 μm resolution. Live cell imaging of a TME containing an endothelial pocket in the stromal compartment revealed MDA-MB-231 cells migrated on average 929 μm over 24 hours compared to 352 μm in the control, demonstrating the effects of TME composition on cancer cell behavior. The second model creates 3D, heterogenous, cell-dense tissues closely recapitulating native cellular microenvironments. Again using a DCIS biopsy ROI, we recreated the observed cellular neighborhoods with 60 μm resolution and 6 cell phenotypes. Prints were cultured up to 7 days revealing cells maintain viability, proliferation, and migrational capacity. To assess function of the model, we perturbed TMEs with 10 ng/mL TGF-β1 and observed greater fibroblast density, matrix remodeling, and MCF10A elongation within 48 hours relative to control. We argue that these engineered models can provide controllable platforms to study the multiple variables regulating the transition of indolent to malignant disease for mechanistic discovery of cancer biomarkers.

Title: Novel mixed-cancer cell models designed to capture inter-patient tumor heterogeneity for accurate evaluation of drug combinations

Authors: Sampreeti Jena[1] (presenting author), Daniel Kim[1], Adam M. Lee[1], Weijie Zhang[2], Kevin Zhan[1], Yingming Li[3], Scott M. Dehm[3], and R. Stephanie Huang[1,2]

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Abstract:
Disease heterogeneity which gives rise to highly variable treatment responses among a cohort of patients, poses major challenges to cancer drug development. Currently, preclinical drug testing is performed in an arbitrary collection of cancer cell lines or xenografts derived from 1-2 patients, models which fail to depict tumor-intrinsic inter-patient diversity in large clinical cohorts. This in turn leads to a high failure rate when translating preclinical leads into clinical successes. Here, we created in-vitro models composed of rationally selected prostate cancer (PC) cell lines to depict inter-patient tumor heterogeneity in metastatic castration-resistant PC (mCRPC). mCRPC exhibits extensive heterogeneity with limited therapeutic options. Using a computational approach, we integrated the expression profiles of PC lines and CRPC patient tumors to identify cell lines that transcriptomically match distinct patient tumor subtypes in a cohort. Representative cell lines were co-cultured to create "mixture-cell" models that mimic the heterogeneous molecular landscape of mCRPC patient cohorts. The models were then employed to assess drug combinations whose clinical success has been widely linked to the presence of heterogeneity. When drug combinations of known clinical efficacy were tested as proof-of-concept, treatment responses measured in the models were found to concur with the clinical trial results. Additionally, computational pipelines utilizing cell-line monotherapy screens to predict combination potency in heterogeneous tumors, were implemented to nominate potentially efficacious drug combinations. When tested in vitro, these novel combinations exhibited efficacy in the heterogeneous mixture-cell model but not in individual cell lines, suggesting that they will likely benefit diverse clinical cohorts. Furthermore, we showed that the pharmacological norm of screening cell lines separately and aggregating their responses was incapable of detecting their efficacy. Application of proposed models in preclinical drug screening will enable accurate and high throughput evaluation of novel therapies and therefore, increase the success rate of subsequent clinical trials.

Title: Plasmonic gold nanorods for laser thermal therapy of gliomas in vitro and in tissue-mimicking phantoms

Authors: Rebecca J. Johnson[1] (presenting author), Sumiao Pang[1], Nikhil Pandey[2,3], Anshika Kapur[2,3], Pavlos Anastasiadis[2,3], Pranjali Kanvinde[2,3], Emylee McFarland[2,3], Jeffrey A. Winkles[2,3], Graeme F. Woodworth[1,2,3], Anthony J. Kim[1,2,3], Huang Chiao Huang[1,3]

[1]Fischell Department of Bioengineering, University of Maryland, College Park, Maryland, USA; [2]Department of Neurosurgery, University of Maryland School of Medicine, Baltimore, Maryland, USA; [3]University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, Maryland, USA

Abstract:
Glioblastoma (GBM) is an extremely aggressive, invasive, and deadly brain tumor, with a five-year survival rate of less than 5%. Treatment begins with a maximal safe resection, followed by multiple rounds of radiation and chemotherapy, typically temozolomide. However, GBM returns in over 90% of patients despite standard of care treatment, with limited repeat treatment options and a grim outlook. A new option for patients with a recurrent tumor is laser interstitial thermal therapy (LITT). LITT lacks GBM selectivity and the high laser powers needed to generate sufficient heat often causes side effects and damage to the healthy brain. Gold nanorods (GNR) can more efficiently convert laser energy to heat than biological chromophores, like water and hemoglobin, enabling a reduction in the required laser powers. Fibroblast growth factor-inducible14 (Fn14) is an overexpressed cell surface receptor for the TNF-like weak inducer of apoptosis (TWEAK) on GBM cells. We engineered polyethylene glycol decorated GNRs functionalized with anti-Fn14 antibodies to achieve GBM selectivity.

These decreased adhesivity, receptor-targeted GNRs (DART-GNRs) are excitable in the NIR range to leverage the optical window and improve photothermal efficacy in agarose phantom models. The phantom models were developed to capture mechanical and optical properties of the brain, in both large models and a mouse brain model. They allow for demonstration and measurement of improved photothermal efficacy and heat localization when introducing GNRs. Additionally, due to the great CT attenuation that GNRs provide, the phantom models are also leveraged to show the potential for pre- or intra-operative tracking. DART-GNRs show selective accumulation in Fn14-positive GBM cells and enhanced photothermal killing compared to non-targeted GNRs. DART-GNRs are an engineered clinically viable agent that show potential to improve recurrent GBM patient outlook.

Title: Engineering a Dual-antigen Targeting Cell-based Therapy Directed Against CD70 and Active Integrin β2 for Acute Myeloid Leukemia

Authors: Amrik S. Kang[1,2] (presenting author), Haley Johnson[1], Nabeel Razi[3], Nicole Lei[3], Jeremiah Wong[3], Aaron C Logan[3], Benjamin J Huang[4], Arun P Wiita[1]

[1]Department of Laboratory Medicine, University of California, San Francisco, San Francisco, CA; [2]Medical Scientist Training Program, University of California, San Francisco, San Francisco, CA; [3]Department of Medicine, Division of Hematology and Oncology, University of California, San Francisco, San Francisco, CA; [4]Department of Pediatrics, University of California San Francisco, San Francisco, CA

Abstract:
Introduction: Acute myeloid leukemia (AML) is a devastating disease with a need for new therapies. Our group recently developed CAR-T therapies against two targets specific to AML cells and absent from normal hematopoietic stem and progenitor cells (HSPCs), aITGB2 (Mandal et al, Nat Cancer 2023) and CD70 (Kasap et al, ASH 2023). Both antigens are heterogeneously expressed on AML, however, preventing complete tumor clearance. Here, we engineer a combined dual-CAR therapy that targets both antigens, capable of more effectively eliminating AML cells while maintaining low toxicity.

Results: We first profiled primary AML samples for co-expression of CD70 and aITGB2 using flow cytometry. We showed that a dual-targeting approach could eliminate 86±11% of blasts, compared to 69±27% for aITGB2 or 46±29% for CD70 alone ($p=0.006$, 1-way ANOVA).

We next tested eight dual-targeting CAR-T constructs in vitro, identifying a design with superior tumor cytotoxicity ($p<0.0001$, 2-way ANOVA) against three AML cell lines. We then generated CD70 and ITGB2 knockouts for each cell line and observed that our dual-targeting CARs maintained tumor killing while single antigen-targeting CARs could no longer target their respective knockout lines.

We then tested our best-performing CAR constructs in vivo in a model of AML antigen heterogeneity, utilizing a mixed population of ITGB2 and CD70 KO tumor cells. We observed tumor control and extension of survival ($p<0.0001$, Log-rank test) for our dual-targeting constructs, while single-antigen targeting CARs failed to control tumor.

Finally, we performed overnight co-culture and HSPC colony-forming assays to evaluate off-tumor toxicities of our dual-targeting CAR construct, observing no cytotoxicity compared to a negative control.

Conclusion: Overall, we demonstrate that a CAR-T therapy directed against both aITGB2 and CD70 is a promising approach for targeting AML, with significant potential for translation to the clinic, without the notable toxicities seen in other AML CAR-T therapies under development.

Title: Targeting VEGF-A induced lymphatic remodeling as a new approach to boost immunity in PDAC

Authors: Anna Kolarzyk[1] (presenting author), E. Carter[2], S. Leddon[2], I. Cano[1], R. Lou[3], D. Fowell[2], E. Lee[1,3]

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Abstract:
Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest tumors in humans. PDAC has an immunosuppressive tumor microenvironment (TME), constituting poor immunotherapeutic outcomes. Lymphatic vessels (LVs) traffic leukocytes and antigens from tumor peripheries to draining lymph nodes for effective activation of anti-cancer immune responses. Impairment of the lymphatic function may result in delayed or ineffective immune activation. A better understanding of immune cell trafficking dynamics through lymphatic vessels may be an avenue for scientists to develop more successful immunotherapies in PDAC. In this study we aim to investigate PDAC-induced LV remodeling and its consequences for immune cell egress from primary tumors through LVs. We use our innovative engineered three-dimensional (3D) LV-on-chip technology to track phenotypic and functional changes in lymphatic endothelial cells (LECs) in co-culture with PDAC. Our studies discovered that PDAC progression tightens adherens junctions on LECs resembling “zipper-like” junctions, making them less permeable, compared to physiological LECs with jagged “button-like” junctions. This led us to hypothesize that altered LEC morphologies affect leukocyte transmigration through the LVs in PDAC. We demonstrated that VEGF-A secreted by PDAC cells activates tightening of endothelial junctions in a VEGFR2 (vascular endothelial growth factor receptor 2) -dependent manner in vitro. Finally, we use the Kaede spatio-temporal mouse model to track the migration of leukocytes to the primary PDAC tumor site and the draining lymph nodes (dLNs). Our optogenetic system has the power to decipher simultaneously what leukocytes accumulate in the tumor parenchyma, and infiltrate or leave the TME. We found that VEGFR2/VEGF-A clinical inhibitors dramatically change leukocyte intratissue migration capacity. Historically, anti-VEGF-A therapies have been used to target tumor angiogenesis, unfortunately with only moderate success. We are excited to reveal a novel mechanism behind VEGF-A- induced lymphatic vessel remodeling that impacts immunity in cancer which can be leveraged to boost immunotherapies in PDAC.

Title: Tumor-wide RNA splicing aberrations generate immunogenic public neoantigens across various cancers

Authors: Darwin W. Kwok[1] (presenting author), Nicholas O. Stevers[1], Inaki Etxeberria[2,3], Takahide Nejo[1], Maggie Colton Cove[1], Lee H. Chen[1], Jangham Jung[1], Kaori Okada[1], Senthilnath Lakshmanachetty[1], Marco Gallus[1], Abhilash Barpanda[4], Chibo Hong[1], Gary K.L. Chan[1], Jerry Liu[1], Samuel H. Wu[1], Emilio Ramos[4], Akane Yamamichi[1], Payal Watchmaker[1], Hirokazu Ogino[1], Atsuro Saijo[1], Aidan Du[1], Nadia Grishanina[1], James Woo[1], Aaron Diaz[1], Susan M. Chang[1], Joanna J. Phillips[1,5], Arun P. Wiita[4,5,6], Christopher A. Klebanoff[2,3,8,] Joseph F. Costello[1], Hideho Okada[1,9]

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Abstract:
Background: Immunotherapy in gliomas is limited by tumor heterogeneity and low mutational burden. Aberrant RNA-splicing (neojunctions) offers a new source for targets, and our neoantigen discovery platform (SNIPP) characterizes a novel class of clonally-expressed splicing-derived neoantigens that elicit a CD8+ T-cell-mediated tumor killing response.

Methods: SNIPP identified public neojunctions expressed in TCGA RNA-seq (positive sample rate (PSR) > 10%) and not in GTEx normal tissue RNA-seq data (PSR < 1%) across 12 cancer types. To characterize intratumorally-conserved neojunctions, we performed maximally-distanced multi-site biopsies (n=535) within glioma patients (n=56) and obtained RNA-seq data from each intratumoral site. Two independent algorithms then predicted peptide processing likelihood and HLA-binding affinity of ASN candidates. Neoantigen-specific TCR sequences characterized from subsequent PBMC in vitro sensitization and 10x V(D)J scRNA-seq were transduced into CD8+ T-cells for immunogenicity and cytotoxicity assays against glioma cell lines.

Results: Our pipeline identified 789 public neojunctions, with 32 neojunctions concurrently identified in transcriptomic and proteomic glioma data and predicted to be presented by HLA-A*02:01 with high confidence. IVS and subsequent 10x VDJ scRNA-seq identified TCR clonotypes reactive against neojunctions in RPL22 (n=7) and GNAS (n=1), the latter being highly intratumorally-conserved (detected in > 90% of spatially-mapped biopsies across 17/56 patients (26.78%)). TCR-transduced T-cells demonstrated recognition and immunogenic activation against endogenously processed and presented neoantigens in multiple GBM PDX cell lines. Furthermore, IDH1-mutant oligodendroglioma samples demonstrated significantly elevated expression of neojunctions over IDH1-mutant astrocytoma and IDH1wt subtypes. Differential gene expression (DESeq2) identified decreased expression of splicing factors due to oligodendroglioma-specific co-deletion of Chromosomes 1p/19q. siRNA knockdown of these splicing factors (e.g. SF3A3, SNRPD2) in IDH1wt glioma cells resulted in significantly increased expression of corresponding neojunctions.

Conclusion: Our unique SNIPP neoantigen discovery platform identified novel public tumor-wide splice-derived neoantigens and reactive TCRs, and its pan-cancer application characterized candidates targetable across multiple diseases.

Title: One-Step Engineering of Allogeneic CAR-NK Cells with Enhanced Anti-Tumor Activity and Resistant to Rejection

Authors: Fuguo Liu[1,2] (presenting author), Mubin Tarannum[2], Yingjie Zhao[1], Yiming J. Zhang[1], James Dongjoo Ham[1], Kewen Lei[1], Yuhao Qiang[1], Xingyu Deng[2], Maily Nguyen[2], Khanhlinh Dinh[2], Shaobo Yang[2], Alaa Kassim Ali[2], Toni K. Choueiri[3], Jerome Ritz[2], Rizwan Romee[2], and Jianzhu Chen[1]

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Abstract:
Allogeneic cellular immunotherapy is promising, although donor cell rejection remains a major barrier. Here, we describe the development of a single novel lentiviral construct incorporating a novel shRNA that selectively targets prevalent HLA-A, -B, -C (referred to as HLA-ABC) alleles while maintaining endogenous HLA-E and simultaneously expressing a CAR and a single chain HLA-E (SCE) or PD-L1. Our screening of shRNAs helped identify a shRNA (shRNA #1) targeting a unique sequence common to 121 prevalent HLA-ABC alleles but has two mismatches with HLA-E alleles, and shRNA #1 universally decreased surface HLA-ABC without affecting HLA-E expression. The HLA-ABC-reduced NK cells are resistant to allogeneic $CD8^+$ T cell killing. To further suppress allogeneic T cell responses, we overexpressed PD-L1 in NK cells, which moderately inhibits these responses. To inhibit allogeneic NK cell killing of HLA-ABC reduced cells, we tested three SCE variants: SCE WT, SCE Y84A, and SCE Y84C. SCE Y84C demonstrated the most effective inhibition of allogeneic NK cell killing. Finally, the combination of HLA-ABC knockdown, CAR, and PD-L1 or SCE overexpression was achieved by one-step lentiviral transduction of NK cells with a novel CAR construct incorporating shRNA#1, CAR, and PDL-1 or SCE. We assayed the killing of Raji cells and OVCAR8 cells by HLA-ABC reduced and PD-L1 or SCE overexpressed CD19-CAR NK cells and MSLN-CAR NK cells, respectively, both *in vitro* and in xenografts-bearing NSG mice, in the presence of HLA mismatched PBMCs. The CAR NK cells efficiently controlled tumor growth, and unexpectedly, PD-L1 and SCE overexpression significantly enhanced CAR NK cell cytotoxicity, likely related to the upregulation of cytotoxicity-related genes and better proliferation fitness. Our simple one-step approach to engineer allogeneic CAR NK cells that efficiently evade rejection while mediating enhanced anti-tumor responses represents a significant advancement in enabling “off-the-shelf” allogeneic cellular immunotherapies.

Title: Enhancing Interdisciplinary Training through Biodesign: Development of a Tumor Margin Tracking System

Authors: Alexandra McLennan[1,2,3] (presenting author), Amanda Hudson[2], Jade Lee[2], Ishika Mukherjee[2], John Tran[1], Savannah Morreale[1], Justin Bird[1,4]

[1]Surgery Innovation Program, Division of Surgery, University of Texas MD Anderson Cancer Center, Houston, TX; [2]Department of Bioengineering, Rice University, Houston, TX; [3]School of Medicine, Baylor College of Medicine, Houston, TX; [4]Department of Orthopedic Oncology, Division of Surgery, University of Texas MD Anderson Cancer Center, Houston, TX

Abstract:
Soft tissue sarcomas are rare, aggressive, and complex tumors that demand precise margin orientation and labeling to optimize histopathological evaluation and margin assessment. Such precision is essential to reducing the alarmingly high recurrence rates and improving patient outcomes. Current methods, including ligation clips, sutures, and tissue dyes, suffer from a lack of standardization, specificity, and the inability to mark defects, which creates significant challenges in postoperative surveillance and communication between surgeons and pathologists. Overcoming these limitations necessitates innovative solutions that integrate engineering principles into surgical oncology practices.

To address this challenge, we collaborated with The University of Texas MD Anderson Cancer Center to develop the Dual-Sided Tag Applier (DSTA). Utilizing the biodesign process—a systems design engineering framework pioneered at Stanford University—the project included stakeholder interviews, CAD modeling, and low- to medium-fidelity prototyping among its developmental stages and tools. The DSTA is a versatile device designed to attach to surgical tools used for resection or function as a standalone device, enabling simultaneous labeling of tumor specimens and defects. By providing real-time, accurate orientation tracking at the point of resection, the DSTA enhances accuracy and integrates seamlessly into surgical workflows. Its tags are constructed from radiopaque, biocompatible materials compatible with MRI and CT imaging, facilitating the postoperative monitoring of previous tumor beds. Regulatory considerations, such as FDA De Novo classification and ISO compliance, were integral to the development process, offering students hands-on experience in navigating these essential pathways.

This project not only produced a promising device for standardizing tumor margin tracking but also served as a valuable platform for interdisciplinary education. Engineering students gained critical skills in clinical problem-solving, regulatory navigation, and iterative prototyping, bridging gaps in cancer care knowledge. Future efforts will focus on refining prototypes, testing, and business plan development, positioning trainees to drive innovation in cancer care.

Title: Characterizing the immunosuppressive role of myeloid-derived suppressor cells in glioblastoma under radiotherapy

Authors: John Metzcar[1] (presenting author), Xuanming Zhang[1], Kamran Kaveh[1], Jasmine Foo[1], Kevin Leder[1]

[1]Therapy Modeling and Development Center, University of Minnesota-Twin Cities, Minneapolis, MN

Abstract:
In this work, we address the treatment of glioblastoma (GBM), a difficult-to-treat brain cancer. Upon discovery of GBM, patients are treated with both surgery and chemoradiotherapy but suffer from eventual recurrence due to unresectable microscopic disease evading adjuvant therapy. The disease is characterized by an immunosuppressive tumor microenvironment. Immunotherapies, including immune checkpoint inhibitors, have been trialed in GBM but have failed to improve outcomes for GBM patients. One possible way GBM tumors sustain this immune suppression is through recruitment and sustaining a population of myeloid-derived suppressor cells (MDSCs). These potently immunosuppressive cells decrease T-cell activity through a range of mechanisms including direct cell-cell interactions, secretion of T-cell inhibitors, and alteration of the metabolic environment. Radiotherapy (RT), which can lead to both immunosuppression and immune stimulation, represents an option to tip the environment in favor of immune stimulation. To understand the interplay between MDSCs, effector cells, and RT, we developed a dynamic, computational model of the tumor immune microenvironment of GBM. Using ordinary differential equations, we model a population of GBM, which both stimulates immune response through antigen-presenting dendritic cells recruitment of activated T-cells and suppresses immune effector cells through recruitment of MDSCs. We model fractionated RT through the linear-quadratic formula as well as surgery through gross reduction of tumor cell count. We calibrate model parameters to clinical data including white-blood cell counts and immune panel flow cytometry. With the model, we recapitulate the suppressive effects of MDSCs on activated T-cell populations. We also use the model to explore the effects of hypofractionated RT on immune cell populations and present possible optimal RT dosing regimes. Finally, we use the calibrated model to produce an in silico virtual clinical trial, characterizing variability in patient response across different treatment scenarios including different fractionation regimens and the addition of the anti-inflammatory agent ibudilast.

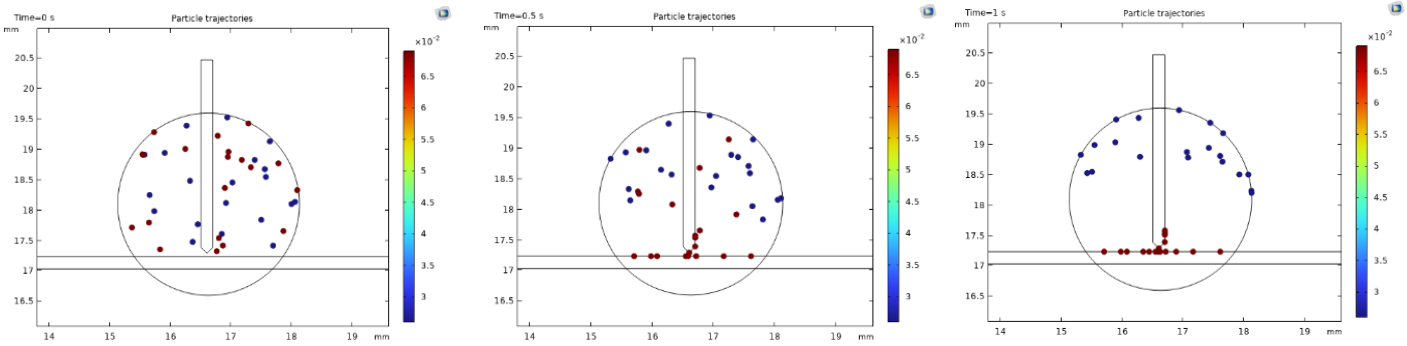
Title: Dielectrophoretic Analysis of Peripheral Blood Mononuclear Cells in Stage III and IV Breast Cancer Models

Authors: Raphael Oladokun[1] (presenting author), Christopher Smith[1], Timothy Eubank[2], and Soumya Srivastava[1]

[1]Department of Chemical & Biomedical Engineering, West Virginia University, Morgantaown, WV; [2]Microbiology, Immunology & Cell Biology, West Virginia University, Morgantaown, WV

Abstract:
Peripheral blood mononuclear cells (PBMCs), produced from hematopoietic stem cells (HSC), are critical in surveilling for signs of infection, foreign invaders, and cells associated with diseases, including cancer cells. These cellular communication and interactions induce alterations in PBMCs' electrophysiological properties, which are detectable using dielectrophoresis. In this study, we explore the dielectric properties of PBMCs from FVB/N MMTV-PyMT+ (stage III and IV breast carcinoma, PyMT-PBMC) and FVB/N (wild-type, WT-PBMC) age-matched mice at 10-12 and 14+ weeks. Our approach uses a DEP-based microfluidic platform, to probe changes in subcellular components like the cytoskeleton, lipid bilayer membrane, cytoplasm, focal adhesion proteins, and extracellular matrix (ECM). We hypothesize that these changes, which occur at the onset of breast carcinoma, regulate the dielectric properties (conductivity, σ, and permittivity, ε) of PBMCs, affecting their bioelectric signals and making breast cancer detectable from whole blood.

In our preliminary results published [1], ANOVA analysis indicated significant differences in the crossover frequencies of stage IV PyMT-PBMCs at conductivity levels of 0.01 S/m and 0.05 S/m. Post hoc pairwise analysis of WT-PBMCs confirmed distinct crossover frequencies from 0.01 to 0.05 S/m across the conductivity range. PyMT PBMCs showed increased crossover frequency, polarizability, higher membrane capacitance, and folding factor. We also used 3DEP to compare stages III and IV, and the results showed clear changes in the DEP properties of the analyzed PBMCs. Our proposed system is designed to require minimal user expertise to detect breast cancer by measuring the dielectric properties of PBMCs in patients. The dielectric properties obtained are essential for designing a DEP-based sorting microdevice. Distinct cell responses under the same electric field gradient and medium conductivity suggest favorable sorting conditions for 14+ week age-matched PyMT+ and WT PBMCs at 0.02 S/m, 250 kHz, and 8 Vpp, as demonstrated by our COMSOL Multiphysics modeling result. The ultimate goal is to apply this non-invasive technique to enhance early detection of breast cancer, thereby minimizing the limitations of traditional screening methods like mammography.



DEP response of PyMT and WT-PBMCs at 0.02 S/m, 250 kHz, and 8 Vpp. (●) represents PyMT-PBMCs, experiencing pDEP, and (●) represents WT-PBMCs, experiencing nDEP. The distinct responses of the cells under the same electric field suggest a favorable separation frequency region for the two cell types.

Reference:

[1] Oladokun, R., et al., Dielectric Signatures of Late Carcinoma Immune Cells Using MMTV-PyMT Mammary Carcinoma Models. ACS Omega, 2024.

Title: Embedded Bioprinting of Immunocompetent Tumor Models via Microporogen-Structured Collagen Matrices

Authors: Daniel S. Reynolds[1](presenting author), Irene de Lazaro[1,2], Manon Blache[1], Yutong Liu[1], Nicholas C. Jeffreys[1], Ramsey Doolittle[1], Estee Grandidier[1], Jason Olszewski[1], Mason T. Dacus[1], Yoav Binenbaum[1,3], Nicoletta Cieri[3], David J. Mooney[1], and Jennifer A. Lewis[1]

[1]John A. Paulson School of Engineering and Applied Sciences and the Wyss Institute for Biologically Inspired Engineering, Harvard University, Cambridge, MA USA; [2]Tandon School of Engineering, New York University, New York, NY USA; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA USA

Abstract:
Bioprinting offers tremendous potential for enabling the rapid design and fabrication of complex tumor models that better recapitulate the in vivo tumor microenvironment (TME). However, few biological matrices enable good print fidelity, while simultaneously facilitating cell viability, proliferation, and migration. Here, we have developed a new approach using microporogen-structured (μPOROS) matrices for embedded bioprinting, in which matrix rheology, printing behavior, and porosity are tailored by adding sacrificial gelatin microparticles to a prepolymer collagen solution. As an initial proof-of-concept, we fabricated an immunocompetent murine melanoma model via the embedded printing of a murine melanoma cell ink within a μPOROS collagen matrix laden with antigen-specific cytotoxic T cells at 4oC. Upon warming to 21oC, the collagen matrix is subsequently crosslinked around the microparticles followed by their melting and removal at 37oC. The printed tumor compartment possesses a physiologically-relevant cell density (~250 million cells mL-1) embedded within a μPOROS collagen matrix, which exhibits a fibrillar network akin to that observed in vivo. Moreover, printed cells remained viable and proliferated, while antigen-specific cytotoxic T cells migrated through the μPOROS collagen matrix to the printed tumor compartment and induced tumor cell death. Recently, we have moved towards bioprinted human melanoma tumor models with antigen-specific human T cells. In summary, our approach opens new avenues for creating complex tissue microenvironments that may find widespread use in drug discovery and disease modeling for cancer and beyond.

Title: Science Simplified - A Digital Strategy to Promote Cancer Research and Raise Awareness and Inspire

Authors: Craig Richard[1] (presenting author), Marcia Pool[1,2], Stephanie Dietrich[1], Jessica Clegg[1]

[1]Cancer Center at Illinois; [2]Department of Bioengineering, University of Illinois Urbana-Champaign

Abstract:
Social and digital media has become an integral part of our society, especially among the younger generations. The rapid rise in use of social media by today's youth offers a unique opportunity to influence attitudes and awareness towards cancer related research fields. Strategies to reach these demographics must shift to continue to engage with them in an effective manner. With the decline in youth interest and engagement in STEM fields, the U.S. may continue to fall short on maintaining an adequate pipeline of STEM-educated professionals. The Cancer Center at Illinois is developing a unique cancer-focused educational social media and digital messaging strategy to connect with these groups and raise awareness of the efforts by the organization to advance cancer research. We implement a strategy of highlighting the work that cancer researchers do, provide unique insight on what research is like and link that research to current events. Combined with the Cancer Center at Illinois' community based formal and informal outreach, this forms an integral component to our efforts to engage with and expand our education and engagement efforts and build a holistic program to engage future generations of cancer researchers.

Title: An Automated, Standardized and Open-source End-to-end Pipeline using Multiplexed Immunofluorescence Imaging Reveals Clinically Prognostic Spatial Metrics in Triple-negative Breast Cancer Post-neoadjuvant Chemotherapy

Authors: Abishek Sankaranarayanan[1] (presenting author), Lisa Carr[1], Madeline Gabriela Hernandez[1], Abigail D. Mapili[1], Anum Kazerouni[2], Shaveta Vinayak[3,4], Laura C. Kennedy[5], Savannah C. Partridge[2], Shachi Mittal[1,6]

[1]Department of Chemical Engineering, University of Washington; [2]Department of Radiology, University of Washington School of Medicine; [3]Division of Hematology and Oncology, University of Washington School of Medicine; [4]Clinical Research Division, Fred Hutchinson Cancer Center; [5]Department of Medicine, Vanderbilt University Medical Center; [6]Department of Laboratory Medicine and Pathology, University of Washington

Abstract:
Multiplexed immunofluorescence (mIF) is used in clinical studies to profile the tumor microenvironment and investigate spatial single-cell metrics that can inform treatment outcomes. Currently available image analysis pipelines are expensive, not customizable, and/or involve slow and user-dependent manual steps hindering the discovery of new prognostic spatial insights. We have developed an open-source digital pipeline for fully automated single-cell spatial immunoprofiling of mIF images. This pipeline was batch-applied to surgical resections (mIF-stained to identify T cell populations and neutrophil cells) of a triple-negative breast cancer (TNBC) patient cohort (n=43) that had residual disease after neoadjuvant chemotherapy to investigate spatial signatures in the residual immune response indicative of recurrence. First, nuclear segmentation was performed on spectrally unmixed DAPI signal by fine-tuning a Cellpose model with an object-level F1-score accuracy of 0.85 on randomly sampled regions. Cell phenotype classification for each marker was then performed with custom-trained CNN-based models using spectrally unmixed channel data for each marker, with high accuracy (e.g., 89% for CD8 phenotype (+ vs. -) classifier). Novel insights prognostic of recurrence-free survival were uncovered by extracting spatial metrics like nearest neighbor distance between cell phenotypes, followed by Kaplan-Meier analysis and log-rank test. Patients had a better response ($p<0.05$) when the median distance from CD8+ cytotoxic T cells was within two cells' distance to the next nearest CD8+ cytotoxic T cell. A similar trend is seen for the median distance from CD4+ helper T cells to the nearest CD45RO+ memory T cell ($p<0.05$). We also discovered that patients who had lower densities for CD8+ cytotoxic T cells and CD45RO+CD8+ memory cytotoxic T cells had worse prognosis ($p<0.05$). This work provides a robust and reproducible mIF analysis pipeline and identifies novel immune-immune localizations in TNBC patients. The predicted recurrence risk post-neoadjuvant chemotherapy can be used for personalized and tailored patient management.

Title: FGF1 regulates breast cancer growth and metabolic reprogramming through ETV4

Authors: Barbara Mensah Sankofi[1] (presenting author), Stevi Johnson-Murguia+, William Berry[2], Elizabeth A. Wellberg[1]

[1]Department of Pathology, University of Oklahoma Health Sciences Center; [2]Department of Surgery, University of Oklahoma Health Sciences Center

Abstract:
Breast cancer is the most frequently diagnosed cancer in women worldwide. Obesity increases resistance to breast cancer therapies and patient mortality, particularly for estrogen receptor-positive (ER+) tumors that represent 70% of all cases. Adult weight gain in women with obesity, characterized by adipose tissue expansion, is an independent prognostic factor for breast cancer. In a preclinical model, we found that weight gain promoted ER+ tumor growth after endocrine therapy through adipose-derived fibroblast growth factor 1 (FGF1). To determine the underlying mechanisms, we used cultured ER+ breast cancer cells (MCF7, tamoxifen-resistant MCF7 cells, and UCD12 cells) treated with FGF1, combined with gene expression profiling and metabolic analysis. ETS variant 4 (ETV4), which regulates ER activity and cancer cell glycolysis, was the top gene induced by FGF1 in multiple ER+ lines. ETV4 was shown by others to regulate breast cancer metabolism and stemness, contributing to disease progression. We hypothesized that ETV4 mediates the FGF1-dependent effects on breast cancer glycolytic reprogramming in obesity-associated breast tumors. ETV4 was upregulated in human PDX tumors grown in obese versus lean mice. In invasive human breast cancer specimens, high versus low ETV4 expression predicted a shorter recurrence-free survival for patients with ER+ tumors. ETV4 knockdown in cultured endocrine-resistant breast cancer cells prevented the proliferation and induction of glycolytic genes with FGF1 treatment. Conversely, overexpression of ETV4 was sufficient to increase glycolytic gene expression and enzyme activity, as well as cell proliferation. Taken together, our data suggest a mechanism by which FGF1 supports breast cancer endocrine therapy resistance in the context of obesity through ETV4 induction and glycolytic metabolic reprogramming. Understanding this process may aid in designing effective treatments, especially for patients resistant to current ER-targeted therapies. Furthermore, ETV4 may be a biomarker to identify breast tumors with excess FGF signaling and patients at high risk for progression.

Title: Phosphatase-Excluding Polymer Micropatches for Enhancing Cytotoxic T-Lymphocytes-Based Cancer Therapy

Authors: Suyog Shaha[1,2] (presenting author), Vineeth Chandran Sujaa,b, Anujan Ramesh[1,2], Kolade Adebowale[1,2], Yu Xing Teo[1,2], Michael Griffith Bibbey[1,2], Tatsuya Fukuta[1,2,3], Leah Lourenco[1], Bolu Ilelaboye[1], Danika Rodrigues[1,2], Kyung Soo Park[1,2], Samir Mitragotri[1,2]

[1]Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Allston, MA 02134, USA; [2]Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA 20115, USA; [3]Present address: Department of Physical Pharmaceutics, School of Pharmaceutical Sciences, Wakayama Medical University, Wakayama 640-8156, Japan

Abstract:
Despite decades of progress in cytotoxic T Lymphocyte (CTL) therapies, their potential in solid tumors falls short of the remarkable success achieved in blood cancers. Solid tumors present unique challenges, primarily due to their hindered accessibility, which renders adoptively transferred CTLs hypofunctional before they can reach their targets. Strikingly, recent studies reveal a rapid decline in CTL effector function within hours of adoptive transfer, even in CTLs primed with robust activation and proliferation capacity. Thus, strategies to sustain CTL functionality post-transfer are of great interest to improve solid tumor therapies. Here, we present a purely biomaterial approach using Polymeric-Micropatches for CD45-Phosphatase Exclusion (PMPEs) that comigrate with CTLs and locally reinforce CTL functionality post-transfer. Fabricated from polylactic-co-glycolide (PLGA), PMPEs are stable for over two weeks at 37°C. These PMPEs bind robustly to CTLs, withstand physiologically relevant disturbances and freeze-thaw processing, and induce micron-scale exclusion of CD45-phosphatase at the CTL contact site. This exclusion, validated through mathematical modeling and experimental evidence, is an effective means of CTL stimulation simply through binding. Furthermore, the PMPE modification drives transcriptomic changes that boost CTL effector potential. Adoptively transferred PMPE-modified CTLs show superior persistence, potent type 1 immunostimulatory responses, and excellent tolerability. They significantly improve tumor control in aggressive solid tumor models, with 50% of B16F10 melanoma-bearing mice surviving beyond 25 days, compared to none in the CTL alone group. When combined with IL15sa, a systemic therapy that amplifies CTL proliferation, 46% of mice with aggressive B16F10 melanoma survive beyond 35 days, with 15.4% achieving complete remission compared to none with the IL15sa and CTL combination alone. Altogether, with their simplicity, effectiveness, and clinical translation potential, PMPEs offer new opportunities for seamless integration into clinical CTL manufacturing, advancing solid tumor management.

Title: Ultrasensitive Protein Detection using Proximity Initiated Nucleic Acid Target Amplification with Photonic Digital Detection

Authors: Skye Shepherd[1,2] (presenting author), Weinan Liu[1,3], Brian T. Cunningham[1,2,3,4,5]

[1]Holonyak Micro and Nanotechnology Laboratory, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [2]Department of Bioengineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [3]Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [4]Carl R. Woese Institute of Genomic Biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [5]Cancer Center at Illinois, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

Abstract:
Protein expression can provide a real-time window into cancer progression and disease states. Point-of-care simple diagnostics for rapid, ultrasensitive testing is important to measure longitudinal changes of protein biomarkers for treatment monitoring, prognosis, or early detection. Proximity assays are a type of solution-based assay using antibody pairs that can achieve high sensitivity, specificity, and be applied for high-throughput applications. However, standard proximity assays require complicated design, enzymatic amplification such as polymerase chain reaction (PCR), and thermocycling with expensive laboratory equipment and specialized laboratories. This limits the use for longitudinal monitoring or liquid biopsies for cancer detection. We demonstrate here a Proximity Initiated Nucleic Acid Target Amplification (PINATA) assay, which is a novel proximity immunoassay for protein detection that can be performed completely at room temperature in a single step using a small point-of-care benchtop detection instrument. The PINATA assay combines linear amplification using toehold-mediated strand displacement reactions of antibody-oligonucleotide conjugates with digital detection of gold nanoparticle tags for ultrasensitive, rapid protein quantification in the femtomolar range, allowing <2-hour detection for sub pg/mL concentrations of human IL-6, a biomarker of inflammation. These results showcase the promise of entropy-driven strand displacement proximity assays for fast and ultrasensitive point-of-care applications of cancer monitoring or liquid biopsy.

Title: Targeted lipid nanoparticle-encapsulated PROTAC delivery inhibits senescent pancreatic ductal adenocarcinoma

Authors: Ashley Sullivan[1] (presenting author), Magdalini Panagiotakopoulou[1], Riccardo Mezzadra[2], Emma Grabarnik[1], Scott W. Lowe[2], Daniel A. Heller[1,3]

[1]Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Cancer Biology and Genetics, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Weill Cornell Graduate School of Medical Sciences, Weill Cornell Medicine, New York, NY

Abstract:
Introduction: Pancreatic ductal adenocarcinoma (PDAC) arises from malignant modification of the epithelial cells in the duct system. Desmoplasia of PDAC tumors hinders vascularization and, subsequently, inhibits drug delivery. Despite recent therapeutic advances, long-term treatments remain ineffective, and patients face a 5-year survival rate of 12%. Previous work has shown that inducing cell cycle arrest via senescence exposes therapeutic vulnerabilities in PDAC through the senescence-associated secretory phenotype (SASP). In SASP, senescent cells secrete pro-angiogenic factors which increase vascularization around the tumor site. In this work, we designed a lipid nanoparticle-based delivery system for a senolytic proteolysis-targeting chimera (PROTAC) molecule which selectively targets senescent cells.

Hypothesis: A combination approach of inducing senescence followed by delivering a senolytic degrader to the tumor site will inhibit PDAC.

Methods: C57BL/6 mice received orthotopic transplants of murine PDAC cells. Two weeks later, senescence was induced by MEK and CDK4/6 inhibitors. Lipid nanoparticles (LNPs) encapsulating a PROTAC BRD4 degrader were synthesized via microfluidics and tagged to target proteins present on PDAC tumor endothelium, including galectin-3. Mice received PROTAC LNPs, free PROTAC, or no treatment. PDAC progression was monitored by ultrasound measurements.

Results: PROTAC-encapsulating LNPs form with sizes between 25 and 50 nm and ~80% drug encapsulation efficiency. In assessing in vivo efficacy, PDAC mice receiving gal-3 targeted PROTAC LNPs showed no significant difference in survival compared to mice receiving free PROTAC, untargeted LNPs, and no treatment. However, in the senescent PDAC model, mice receiving gal-3 targeted LNPs survived significantly longer than all other groups. Poor survival outcomes coupled with elevated weight loss in free drug-treated mice also suggests off-target toxicity of the unencapsulated PROTAC. Moreover, mice receiving gal-3 LNPs showed significant tumor growth inhibition compared to those receiving untargeted LNPs or no treatment. BRD4 degradation measured by immunohistochemistry also showed significant decrease in BRD4 for mice receiving gal-3 targeted LNPs compared to vehicle.

Conclusion: Targeted delivery of a senolytic drugs to tumors may facilitate anti-tumor efficacy in PDAC with a significant degree of senescent cells.

Title: Engineering Dormancy: Insights from a 3D Model of Microscopic Colorectal Cancer Liver Metastasis

Authors: Sabrina N. VandenHeuvel[1] (presenting author), Sanjana Roy[1], Brinlee Goggans[1], Scott Kopetz[2], Shreya A. Raghavan[1]

[1]Department of Biomedical Engineering, Texas A&M University, College Station, TX; [2]Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX

Abstract:
Liver metastasis is responsible for two-thirds of colorectal cancer deaths1. Despite surgical resection and chemotherapy, most patients relapse within 18 months, from delayed outgrowth of microscopic residual disease2. Clinically undetectable, dormant microscopic colorectal cancer liver metastases (μCRLM) provide little data to inform in vitro modeling, making them inherently difficult to study. New models are imperative to understanding mechanisms by which the liver harbors μCRLM and subsequently permits delayed invasive outgrowth. Here, we present a μCRLM dormancy model adapted from our previously established metastasis model3. In this model, decellularization of porcine liver tissue sections produced scaffolds of intact extracellular matrix, which were repopulated with HCT116 colorectal cancer spheroids to establish in vitro μCRLM. Spheroids and μCRLM scaffolds were cultured in low-serum medium with sub-IC50 oxaliplatin chemotherapy to induce dormancy.

Serum starvation and chemotherapy combined to induce spheroid dormancy, evidenced by an 84% reduction in spheroid size (****$p<0.0001$), reduced Ki67 expression (41%; **$p<0.01$) and gene signatures consistent with altered metabolism (SLC2A1, G6PD) and early (G0/G1) cell cycle arrest (TP53, CDKN1A, CDKN2B increased 1.7-, 2.2-, 3.3-fold; ****$p<0.0001$).

μCRLM scaffold culture amplified dormancy, as dormant nests grew 93% slower than full-serum controls (****$p<0.0001$). Extracellular matrix presence was further found to actively drive dormancy in μCRLM nests, interestingly disrupting G2/M phase regulators like CDC20 and AURKA rather than the serum/chemotherapy-induced G0/G1 arrest. To assess the reversibility of this phenotype, dormant μCRLM scaffolds were allowed 5 days of recovery in complete medium. During this time, the speed of nest growth doubled (****$p<0.0001$), and the G0/G1 arrest gene profile was reversed while late-stage factors persisted. These results demonstrate the model's competency in mimicking not only dormancy but also subsequent outgrowth of μCRLM.

Future studies will assess functional consequences and recovery from matrix- and chemotherapy-driven dormancy to understand mechanistic adaptations and identify therapeutic targets in recurrent μCRLM.

References:
[1] Clark ME. J Gastrointest Oncol. 2014; 5:374-87.
[2] Benoist S. J Clin Oncol. 2006;24:3939-45.
[3] VandenHeuvel SN. Soft Matter. 2022;18(31):5791-806.

Title: Extracellular matrix hydrogel provides on-demand tuning of viscoelastic properties to mimic development of myelofibrosis

Authors: Kexin Zhang[1] (presenting author), Hardik Makkar[2], Nghi Tran[3], Kyle H. Vining[1,2,3,4]

[1]Department of Materials Science and Engineering, School of Engineering and Applied Sciences, University of Pennsylvania; [2]Center for Innovation & Precision Dentistry (CiPD), School of Dental Medicine, University of Pennsylvania; [3]Department of Bioengineering, School of Engineering and Applied Sciences, University of Pennsylvania; [4]Department of Preventive and Restorative Dentistry, School of Dental Medicine, University of Pennsylvania

Abstract:
Myelofibrosis (MF) is characterized by extracellular matrix (ECM) deposition that commonly result from somatic mutations, hematological malignancies, or prolonged chemotherapy and radiotherapy. This abnormal ECM deposition disrupts normal hematopoiesis and leads to anemia, thrombocytopenia, and in advanced stages, is associated with dysregulated inflammatory cytokine production due to impaired myeloid-stromal interactions. Biomaterials designed to replicate the mechanical properties of fibrotic bone marrow offer an innovative tool for studying MF pathophysiology and for developing therapeutic strategies. These biomaterials provide an environment to investigate how altered stiffness in the ECM affects cell behavior and tissue function. Here, we present a biopolymer-based hydrogel platform that mimics the progressive stiffening of the bone marrow niche. An interpenetrating network (IPN) was formed using ionically crosslinked tetrazine-functionalized alginate (Tz-VLVG) and self-assembled collagen type I, which replicates the fibrillar architecture of the bone marrow ECM. Norbornene-functionalized multi-arm polyethylene glycol (2- and 4-arm-PEG-Nb) crosslinkers provide controllable stiffening of the hydrogel through bio-orthogonal click chemistry between the norbornene and tetrazine groups. This process resulted in a tenfold increase in the storage modulus (G') and significantly slower stress relaxation, indicating a shift to a stiffer, more elastic matrix. We integrated this hydrogel into a organ-on-chip system that models features of the bone marrow vascular niche. Bone marrow mesenchymal stromal cells, monocytes, and endothelial cells were co-cultured on the chip, enabling the study of their responses to increased matrix stiffness. This work presents a novel platform for studying the dynamic interactions between cells and their ECM, providing insights into MF pathophysiology and offering a model for testing new therapies.

Title: 3D multi-modal photoacoustic and super-resolution ultrasound localization imaging to probe the tumor microenvironment

Authors: Shensheng Zhao[1,2] (presenting author), Sayantani Basu[3], Roy H. Campbell[3], Yang Zhao[1,2,5], Yun-Sheng Chen[1,2,4,5]

[1]Department of Electrical and Computer Engineering; [2]Beckman Institute for Advanced Science and Technology; [3]Department of Computer Science; [4]Carle Illinois College of Medicine; [5]Cancer Center at Illinois, University of Illinois at Urbana-Champaign

Abstract:
The tumor microenvironment, including tumor vasculature and hypoxic regions, is critical for tumor progression, metastasis, and therapy resistance. Imaging these features is essential for understanding tumor biology and assessing treatment response. However, existing imaging methods face limitations: optical microscopy lacks deep tissue penetration, while MRI/CT cannot simultaneously capture both vasculature and oxygenation with sufficient resolution.

To address these challenges, we developed a low-cost multimodal imaging system integrating photoacoustic (PA) and ultrasound localization (UL) imaging. PA provides detailed tissue oxygenation and physiological maps, while UL imaging offers super-resolution images of blood microvasculature and hemodynamics by tracking injected microbubbles. Together, these techniques enable deep-tissue visualization of tumor vasculature and hypoxia.

We designed a custom imaging sequence to integrate both modalities using a pre-clinical ultrasound system. A key challenge is that UL imaging requires several minutes to capture enough microbubble events for vasculature reconstruction, far longer than PA acquisition time (0.1 seconds). This disparity limits simultaneous data acquisition. To overcome this, we developed a deep learning-based U-Net model to accelerate UL frame rates using sparse microbubble events and power Doppler images. This approach enables faster UL acquisition, allowing the simultaneous capture of PA and UL images.

Our system demonstrated up to 16-fold improvement in acquisition speed, capturing microvasculature as small as 22 μm in in vivo mouse skin tumor models. The hybrid imaging system visualizes blood microvasculature and oxygenation with less than 2 seconds per frame. This rapid dual-imaging scheme enables longitudinal monitoring of 3D tumor with mechanical scanning of the ultrasound transducer.

In A431 tumor models, we observed significant decreases in tumor vasculature density and oxygen saturation from Day 7 to Day 17 of tumor growth, showing a positive correlation between oxygen saturation and vessel density. These findings highlight the potential of this technique for high-resolution, multi-parametric imaging in oncological research.

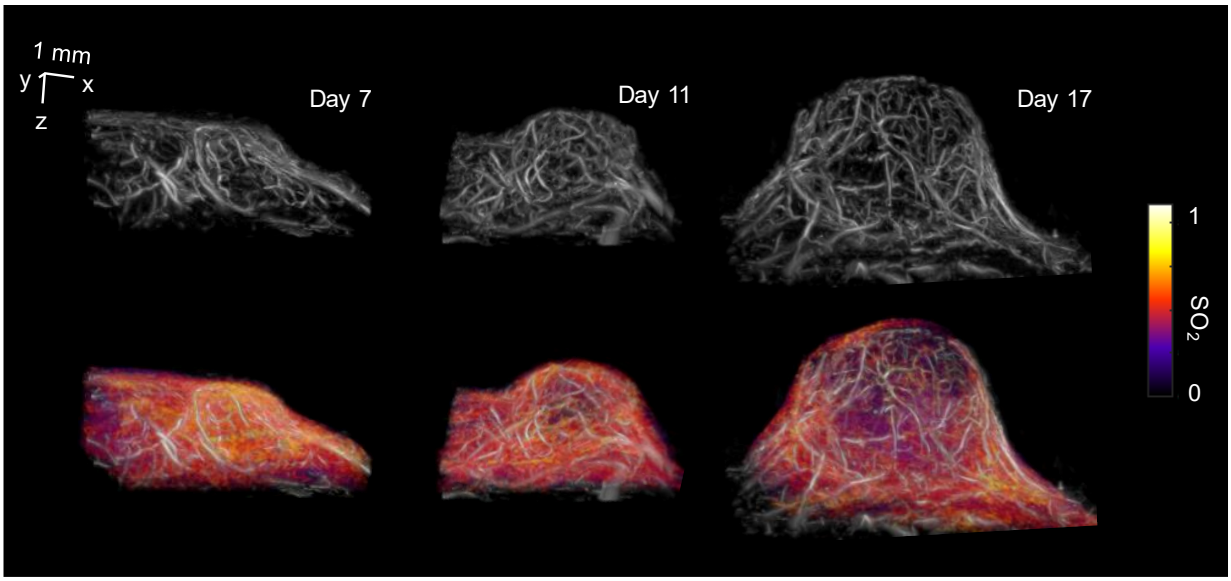


Figure 1. A longitudinal study of tumor growth using dual-modal PA/UL imaging reveals the tumor vasculature and oxygen saturation (SO2) of the tumor in 7,11,17 days after implanting A431 cancer cells.

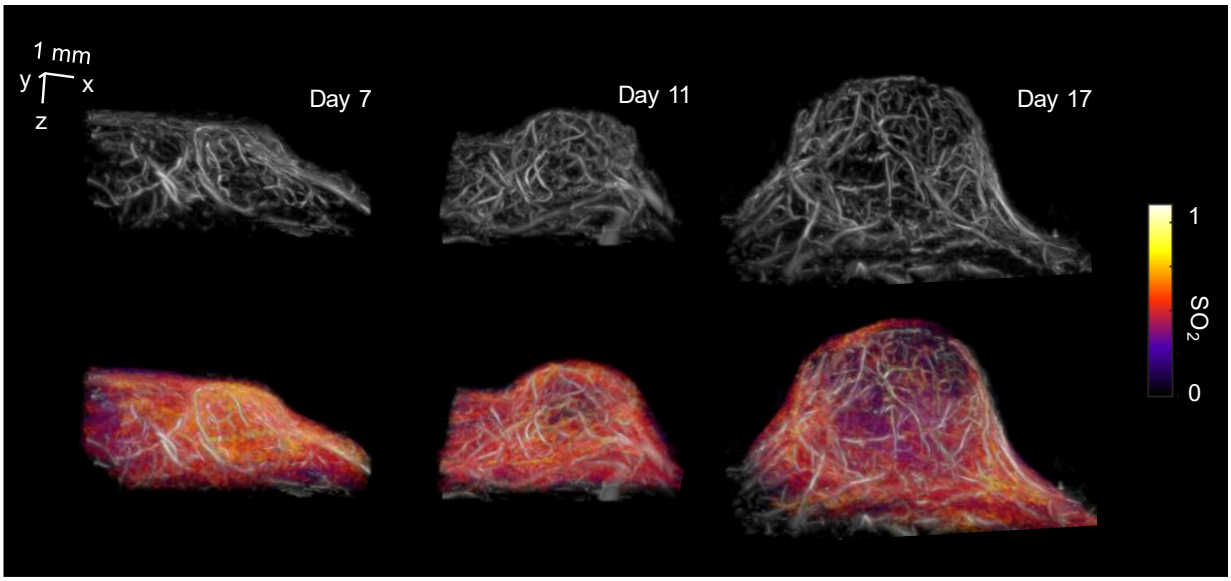


Figure 1. A longitudinal study of tumor growth using dual-modal PA/UL imaging reveals the tumor vasculature and oxygen saturation (SO2) of the tumor in 7,11,17 days after implanting A431 cancer cells.

Rana J. Abbed, BS
University of Illinois Urbana-Champaign

Rana Abbed is a second-year PhD student in Bioengineering at the University of Illinois Urbana-Champaign. She earned her bachelor's degree from the University of Illinois Chicago in 2023, where she conducted research in Dr. David T. Eddington's lab, focusing on microfluidics for cell culture applications. Currently, Rana is a member of Dr. Susan E. Leggett's lab, where her research centers on microfluidics and organ-on-a-chip applications for ovarian cancer. Her work aims to advance personalized medicine and disease modeling through bioengineering and live imaging techniques.

Suehelay Acevedo Acevedo, PhD
H. Lee Moffitt Cancer Center and Research Institute

Dr. Suehelay Acevedo Acevedo is a postdoctoral fellow in the laboratory of Dr. Elsa R. Flores in the Molecular Oncology Department at the H. Lee Moffitt Cancer Center. Her current research efforts are focused on developing novel 3D models of non-small cell and small-cell lung cancers from both mouse and patient samples while investigating the molecular interactions between mutant p53 and other p53 family members. She obtained her Ph.D. in Biomedical Engineering from the University of Wisconsin-Madison, where she characterized the metabolic interactions between breast cancer cells and lymphatic endothelial cells using 1H NMR metabolomics. Her research interests include 3D ex-vivo cancer models, drug delivery using nanomaterials, development of targeted therapies for p53-deficient and mutant cancers.

Anirudh Choudhary, MS, BS
University of Illinois Urbana-Champaign

Anirudh Choudhary is a Ph.D. candidate in Electrical and Computer Engineering at the University of Illinois at Urbana-Champaign, where he is part of the DEPEND group at the Coordinated Sciences Lab. His research focuses on developing machine learning techniques to support clinicians in cancer diagnosis and prognosis, particularly in limited data settings. He collaborates closely with the dermatology group at Mayo Clinic to create multimodal AI-driven diagnostic tools for squamous cell cancer and colon cancer. Prior to his Ph.D., he earned a Master's in Computational Science and Engineering from Georgia Tech, where he conducted research on reinforcement learning for clinical decision-making using electronic health records. His earlier academic background includes an MBA from Indian Institute of Management Calcutta and a Bachelor's degree from Indian Institute of Technology Kharagpur, where he researched texture-based oral cancer prediction. Beyond academia, he has five years of industry experience developing machine learning models for e-commerce and retail consumer data analysis.

Bashar Emon, PhD
University of Illinois Urbana-Champaign

Bashar Emon is a postdoctoral researcher in the Department of Mechanical Science and Engineering at the University of Illinois at Urbana-Champaign, working with Prof. Taher Saif. He earned his Ph.D. in Theoretical & Applied Mechanics in 2023, where he investigated how cellular forces regulate cell-cell and cell-matrix interactions, driving cancer progression and metastasis. A key contribution of his research is the development of a novel microfabricated sensor that enables real-time measurement of mechanical and chemical changes within three-dimensional in vitro tumor models, bridging fundamental biomechanics with clinical applications. Bashar has been recognized with multiple fellowships, including the Beckman Institute Graduate Fellowship, CCIL Tissue Microenvironment (TiME) fellowship (NIH T32), and the MAVIS Future Faculty Fellowship. His future research will focus on understanding the role of mechanics in health and disease and drive translational breakthroughs in cancer research, precision medicine, and mechanobiology-driven therapies.

Marie Floryan, MS
Massachusetts Institute of Technology

Marie Floryan is a PhD candidate in mechanical engineering whose research is focused on designing microfluidic platforms to model human organ function. As a MathWorks Fellow, Marie will study the effect of fluid shear stress on tumor cell survival through the various stages of metastasis. She has designed a microphysiological system (MPS) that recapitulates the physical environment of tumor cells in vivo. In her previous work, Marie made significant contributions to the development of a novel microfluidic pump that provides recirculating flow through engineered tissues, which she used to study the role of luminal flow in the long-term culture of self-assembled microvascular networks. She is now using her vascularized system to study the cellular dynamics of metastasis; her experiments are coupled with an in vivo collaborator, creating the opportunity to compare the two and advance MPS as a companion to, and potential replacement for, preclinical animal models. MathWorks products are an essential resource for these projects. Marie's work could ultimately help to explain why cancers tend to metastasize to specific organs, identify novel therapeutic targets, and advance microfluidics research.

Haylie Helms, MS
Oregon Health and Science University

Haylie Helms is a PhD candidate in Biomedical Engineering at Oregon Health and Science University within the Cancer Early Detection Advanced Research Center, Knight Cancer Institute and the Knight Cancer Precision Biofabrication Hub. Under the mentorship of Dr. Luiz Bertassoni, her PhD work has focused on the development of new tools to model the early tumor microenvironment with single-cell spatial resolution. Combining single-cell bioprinting, live-cell imaging, spatial transcriptomics, and computational techniques, she aims to systematically manipulate engineered tumors to complement clinical sample analysis and identify interception targets.

Sampreeti Jena, PhD
University of Minnesota

Sampreeti Jena is a researcher in Dr. Stephanie Huang's lab in the dept. of Experimental & Clinical Pharmacology at the University of Minnesota. Her research is focused on the development of preclinical models that realistically capture the complex biology and heterogeneous molecular landscape of patient tumors for the accurate validation of novel drugs/drug combinations prior to their clinical translation. During her previous postdoctoral appointment in the dept. of Biochemistry, Molecular Biology and Biophysics (BMBB), she was involved in the development of peptide probes for measurement of live kinase activity in cells with potential utility in the screening of small molecule inhibitors.

Rebecca J. Johnson, BS
University of Maryland, College Park

Rebecca Johnson is a PhD student in Bioengineering at the University of Maryland, where she has been honored as a Clark Doctoral Fellow. Her research focuses on engineering nanotechnology and optical therapeutics for the treatment of recurrent glioblastoma. Under the mentorship of Dr. Huang Chiao Huang, Rebecca's work aims to improve clinical outcomes for patients with this aggressive form of cancer.

Amrik S. Kang, BS
University of California, San Francisco

Amrik is a 5th year MD/PhD student in the University of California, San Francisco's Medical Scientist Training Program. He is co-mentored by Drs. Arun Wiita and Justin Eyquem, studying novel approaches to develop cellular immunotherapies for blood cancers. His thesis research focuses on using AI-assisted methods to identify improved binding domains for natural ligand CAR-T therapies to treat acute myeloid leukemia. Amrik previously graduated with a B.S. in Biology from the University of California, Riverside, and grew up in Southern California.

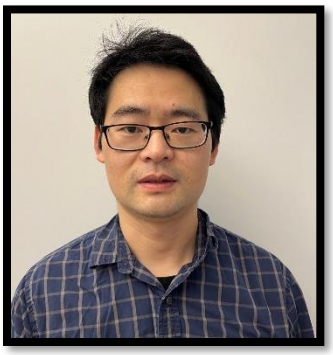
Anna Maria Kolarzyk, MS
Cornell University

Anna received her master's from the University of Warsaw, Poland. She began her scientific journey abroad at the University of Chicago, investigating ion channel structure. Kolarzyk's current research interests include lymphatic vessel-mediated immunity in cancer, using organ-on-chip systems and optogenetic mouse models. This summer, she will join the lab of Deb Fowell as a postdoctoral scientist to continue my research on immune cell trafficking in the context of cancer.

Darwin Kwok, PhD, MS
University of California, San Francisco

Dr. Darwin Kwok completed a PhD in Biomedical Sciences at UCSF in 2024 under the dual mentorships of Dr. Hideho Okada and Dr. Joseph Costello. His thesis work is primarily focused on the discovery of tumor-wide public neoantigens derived from cancer-specific splicing events (neojunctions), and how aberrant splicing factor expression levels can potentially influence the recognition of neojunctions. Utilizing multi-site sampling from the same brain tumors, the research team captured neojunctions found tumor-wide across all biopsied sites. CD8+ T-cells engineered to express neojunction-derived neoantigen-specific T-cell receptors demonstrated robust recognition and killing of various cancer cell lines. His first author work has recently been published this February in Nature.

Kwok is now a medical student at UCSF School of Medicine, and leads a few exciting derivative projects from his thesis work. Firstly, Kwok works on investigating how standard-of-care treatments, such as chemotherapy and radiation, reshapes the landscape of neojunction expression post-treatment. Secondly, he is engineering ways of augmenting specific cancer-splicing events to increase neoantigen expression levels and subsequently cytotoxicity. Kwok's thesis proved that dysregulated expression of normal splicing factors can reliably increase spliceosome recognition of specific neojunctions. Finally, he is exploring novel approaches of developing personalized cell-based immunotherapies through peripheral blood applications.



Fuguo Liu, PhD
Massachusetts Institute of Technology; Dana-Farber Cancer Institute, Harvard Medical School

Fuguo Liu, Ph.D., is a postdoctoral scholar in the Romee Lab at Dana-Farber Cancer Institute, Harvard Medical School, where he specializes in bioengineering chimeric antigen receptor natural killer (CAR-NK) cells for cancer immunotherapies. Fuguo received his Ph.D. from Ocean University of China, where he built foundational skills in molecular biology and immunology. Through his postdoc training, Fuguo has gained extensive skills in immunogenetics, particularly for investigating polymorphisms in human leukocyte antigen (HLA) class I and leukocyte immunoglobulin-like receptors (LILR), cell biology, and immunotherapies. Recently, he has developed a simple one-step approach to generate CAR-NK cells resistant to host immune cell killing and with enhanced anti-tumor activity. His current work has centered on bioengineering CAR-NK cells to enhance their infiltration into the tumor microenvironment and increase persistence in treating patients with solid tumors.

Alexandra L. McLennan, MBE
University of Texas MD Anderson; Rice University; Baylor College of Medicine

Alexandra "Alex" McLennan is a biomedical engineer, aspiring dermatologic surgeon, and medical device innovator passionate about improving patient outcomes through scalable healthcare solutions. After completing her third year of medical school at Baylor College of Medicine, she pursued a Master's in Bioengineering through the Global Medical Innovation Program at Rice University to bridge the gap between clinical medicine and engineering. Her goal is to develop medical technologies that enhance diagnostic accuracy, surgical precision, and global accessibility.

At MD Anderson Cancer Center's IDEAS Lab, Alex is actively involved in designing and prototyping novel medical devices to address unmet clinical needs, particularly in surgical oncology. Her background in biomedical engineering, combined with her medical training, allows her to take a multidisciplinary approach to problem-solving, integrating clinical insight with technical innovation.

Beyond research and device development, Alex is dedicated to mentorship and education. She advises undergraduate senior design teams, guiding students in translating engineering principles into practical healthcare applications.

Additionally, she mentors pre-medical and medical students, helping them navigate the intersection of medicine, technology, and research.

Originally from Austin, Texas, Alex grew up immersed in live music, outdoor adventures, and sports. As a former collegiate athlete, she developed resilience and teamwork—qualities that continue to shape her approach to problem-solving in medicine. She also has a creative side, translating her love for painting into an interest in medical tattooing, which she is currently exploring as a potential tool for dermatologic care.

Alex is excited to contribute to the convergence of engineering and healthcare, leveraging technology to advance cancer research and improve patient care on a broader, more scalable front.

John Metzcar, PhD
University of Minnesota-Twin Cities

John Metzcar is a postdoctoral researcher at the Therapy Modeling and Design Center located at the University of Minnesota-Twin Cities. At this cross-disciplinary center focused on applying mathematical modeling to accelerate translational and clinical research, he combines mathematical modeling and preclinical and clinical data to produce actionable knowledge to support experimental and clinical trial design. He currently has projects in glioblastoma and neuroendocrine tumors. He previously worked on agent-based modeling of cell-extracellular matrix interactions and multiscale modeling focused on the impacts of intracellular dynamics on multicellular systems.

Raphael Oladokun, BSc
West Virginia University

Raphael Oladokun is a fourth-year doctoral student in the Chemical and Biomedical Engineering Department at West Virginia University (WVU). He demonstrates academic excellence, engages in innovative research, and exhibits a relentless commitment to community engagement through STEM-related projects and initiatives. His academic journey began at Obafemi Awolowo University (OAU) in Nigeria, where he earned his undergraduate degree in Chemical Engineering. During his time at OAU, Raphael's exceptional performance was recognized with the 2016/2017 West African Portland Cement Company Prize for the graduating student with the best score in process design. His innovative approach to problem-solving was evident early on when he won the prestigious First Prize Award in the 2018 Nigerian Society of Chemical Engineers (NSChE) Annual Students' Project Design Competition among all recent chemical engineering graduates from all Nigerian universities.

At WVU, Raphael's academic excellence continued. Raphael recently won the NSF Bridges in Digital Health Fellowship in January, he was awarded the prestigious WVU Statler College Doctoral Research Fellowship in August 2022, a premier award with three renewal cycles. Raphael's research in Dr. Srivastava's MESA Lab focuses on designing biomedical microdevices for health applications. His work has gained significant recognition, resulting in 24 oral and poster presentations at international, national, regional, and state conferences and annual meeting, as well as graduate research symposiums across various universities in his region. He’s very productive in research, and this is evidenced by two first-author research articles published in 2023 and another two in 2024.

Raphael's excellence in research and academics has been recognized with other numerous awards. Some of these include the 2024 AES Electrophoresis Society Blue Fingers Student Award for the second most outstanding student paper, a poster award at the 2024 Federation of Analytical Chemistry and Spectroscopy Societies (FACSS) conference, 2024 NOBCChE Graduate Rising Star Award – Northeast, the 2023-24 WVU Statler College of Engineering Excellence in Research Award at PhD Level, First Place Poster Award at the 98th Annual West Virginia Academy of Science meeting,

NSBE Golden Torch Award for the Graduate Student of the Year 2023-2024, and 2022 First Place in Cell Bio Poster at the 13th Annual Pharmaceutical Sciences Research Symposium, just to mention a few.

Raphael's commitment to community impact is as impressive as his academic achievements. He has taken on significant leadership roles, serving as the President of the International Fellowship of Believers (IFB), RCCG Morgantown Youth President, WVU Statler College of Engineering Ambassador and 2023-24 West Virginia Science Public Outreach Team (WV SPOT) ambassador. His community engagement efforts have been substantial and far-reaching, with Raphael accumulating 179 volunteering hours since October 2022, making significant impacts at the university level, state, and even at the national level. His involvement along with the WVU science behind the spot team in the 2023 National Scout Jamboree provided an unforgettable experience for 15,000 youths from different parts of the country. His dedication was recognized in the West Virginia Daily News.

Raphael's commitment to mentoring the next generation of STEM leaders is evident in his selection as a finalist nominee for the 2024 WVU Award for Distinction in Mentoring of Undergraduates in Research. He was also nominated for the 2024 WVU Graduate Student Employee of the Year award. His enthusiasm in community engagement was recognized with the prestigious 2024 WVU Graduate Student Award for Excellence in Community Engagement.

Raphael's journey is a testament to his exceptional ability to balance rigorous academic pursuits with impactful community engagement.

Daniel S. Reynolds, PhD
Harvard University

Dr. Reynolds is a postdoctoral research associate in Prof. Jennifer Lewis' lab at Harvard University. His research focuses on developing novel biomaterials and bioprinting methods for drug discovery, disease modeling, and therapeutic applications. More specifically, he has made important contributions to bioprinted tumor models for investigating novel immunotherapies. Prior to Harvard University, Dr. Reynolds received his Ph.D. in Biomedical Engineering from Boston University in the laboratory of Prof. Muhammad Zaman, where he studied how physical properties of the tumor microenvironment contribute to cancer progression, and received his B.S. in Biomedical Engineering from the University of Rochester.

Craig Richard, PhD, BS
University of Illinois Urbana-Champaign

Dr. Craig Richard, PhD., is a postdoctoral scholar for education and engagement in the Cancer Center at Illinois. He earned his PhD in Bioengineering in 2023 at the University of Illinois Urbana-Champaign. His research background focused on the use of nanotechnology and nanoparticle conjugates to qualify and quantify cancer biomarkers in the tissue microenvironment. Dr. Richard draws upon his research background in bioengineering and interests that span the fields of material science, molecular biology, and nanotechnology as well as expertise as a science communicator to create engaging science centered content. As part of the Cancer Center at Illinois' broader impacts, he develops educational modules for various programs ranging from the graduate to k-12 level and designs activities for the Cancer Center's public engagement and outreach efforts. He also designs social media content for communicating science to the local and broader Illinois community highlighting the importance of cancer research and the cutting-edge science done at the Cancer Center at Illinois.

Abishek Sankaranarayanan, MS, BS
University of Washington

Abishek Sankaranarayanan is a Ph.D. student in the Department of Chemical Engineering at the University of Washington. He earned his B.S. in Chemical and Biomolecular Engineering from the Georgia Institute of Technology in 2022. His Ph.D. research focuses on single-cell spatial analyses of the tumor microenvironment using multiplexed immunofluorescence proteomic imaging and discovering prognostic spatial insights for personalized breast cancer medicine and patient management. His undergraduate research focused on developing microneedle- and capsule-based delivery systems for transdermal and oral drug delivery. He received the Thomas L. Gossage International Enrichment Endowment in 2020 and the Anton Paar PNW Graduate Research Impact Award in 2023.

Barbara Mensah Sankofi, MS
University of Oklahoma Health Sciences Center

Barbara Mensah Sankofi is a Ph.D. candidate in Experimental Pathology at the University of Oklahoma Health Sciences Center. Her research focuses on understanding the role of obesity and metabolic reprogramming in breast cancer progression, particularly in the context of endocrine therapy resistance. She investigates how FGF1 signaling regulates the transcription factor ETV4 to alter estrogen receptor (ER) activity and metabolism in obesity-associated breast cancer. Her goal is to identify novel therapeutic targets that could improve treatment outcomes for patients, especially those from vulnerable populations disproportionately affected by obesity and aggressive breast cancer subtypes.

Suyog Shaha, MS, BS
Harvard University

Suyog Shaha is a fifth-year Ph.D. candidate in Prof. Samir Mitragotri's lab at the School of Engineering and Applied Sciences/Wyss Institute at Harvard University. He earned his B.S. in Chemical Engineering from the Institute of Chemical Technology (formerly UDCT), India. He is interested in integrating his expertise in immunoengineering with genetic engineering to develop innovative technologies that enhance T cell therapies for solid tumors. Notably, Suyog has developed Polymeric Micropatches for Phosphatase Exclusion (PMPE), a novel biomaterial-based approach that co-migrates with T cells, enhancing their persistence and boosting therapeutic efficacy. He has extensive experience in immunology, biomaterials, biological transport, and adoptive cell transfer, working with a diverse cell type, including T cells, neutrophils, macrophages, and stem cells. His contributions have led to multiple preclinical studies with strong translational potential. Beyond research, Suyog has served as a teaching fellow in three courses and has actively mentored undergraduate and graduate students in their thesis work. Suyog is also deeply involved in STEM outreach, presenting at multiple research open house events and recently co-directing the MEDISTAR high school outreach program at Harvard. Suyog is excited to engage with leading scientists and clinicians at the National Academies Workshop on Cancer Engineering to explore new opportunities in cancer therapy and immunoengineering.

Skye Shepherd, BS
University of Illinois Urbana-Champaign

Skye Shepherd is a bioengineering graduate student working in the Nanosensors Group with Prof. Cunningham. She has been developing non-enzymatic methods using toehold-mediated strand displacement for ultrasensitive nucleic acid and protein detection. Her research focuses on optical biosensors using digital detection.

Ashley N. Sullivan, BS, BA
Memorial Sloan Kettering Cancer Center

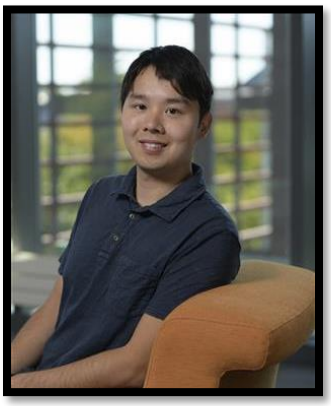
Ashley is a first year graduate student in the Cancer Engineering PhD program at Memorial Sloan Kettering's graduate school. In Dr. Vinod Balachandran's lab, she will focus on developing vaccines for pancreatic cancer.

Sabrina VandenHeuvel, BS
Texas A&M University

Sabrina VandenHeuvel is a 5th year PhD Candidate in Biomedical Engineering at Texas A&M University under the mentorship of Dr. Shreya Raghavan. She earned her Bachelor of Science in Materials Science and Engineering from the University of Wisconsin-Madison, specializing in biomaterials and translational clinical cancer immunotherapy research. Building upon this foundation, Sabrina's doctoral work is dedicated to pioneering biomimetic models of cancer metastasis, leveraging decellularized extracellular matrix scaffolds to elucidate organ-specific metastatic mechanisms and complex cancer-immune dynamics. Driven to advance the frontiers of cancer engineering, Sabrina is honored to share her latest findings on colorectal cancer dormancy at the National Academies Cancer Engineering Workshop.

Kexin Zhang, BEng
University of Pennsylvania

Kexin Zhang is a Ph.D. student in the Department of Materials Science and Engineering at the University of Pennsylvania. Her research focuses on the development of biopolymer-based 3D hydrogel networks and the dynamic interactions between cells and their extracellular environment, with an emphasis on the on-demand tuning of mechanical and microstructural cues in polymeric matrices.



Shensheng Zhao, BEng
University of Illinois Urbana-Champaign

Shensheng Zhao is a Ph.D. candidate in the Department of Electrical and Computer Engineering and a Beckman Graduate Fellow at the University of Illinois at Urbana-Champaign. His research focuses on advancing photoacoustic imaging, super-resolution ultrasound imaging, functional imaging, and image-guided cancer therapy.

Title: A Perfusion-Based 3D Chemotactic Platform for High-Resolution Studies of Cellular Migration and Tumor Microenvironment Modeling

Authors: Said Cifuentes[1], Diego Pedro[1], Alfonso Pepe[1], Duy Nguyen[1], Gregory Sawyer[1]

[1]Department of Bioengineering, Moffitt Cancer Center, Tampa Florida.

Abstract:
Chemotaxis is a fundamental process underlying critical biological events, including immune surveillance, wound healing, and cancer metastasis. Existing methods for chemotactic studies often lack the ability to combine precise gradient control, high-throughput analyses, dynamic flow, and physiologically relevant –3D culture environments and –samples. To address these limitations, we developed a perfusion-based chemotactic platform that integrates novel liquid-like solid (LLS) microgel medium and well-defined fluid flow for microtissue culture. The platform allows for high-throughput analyses, continuous chemotactic gradients and supports real-time microscopy, enabling high-resolution tracking of cellular migration under sustained chemical gradients.

Preliminary evaluations demonstrated the capability of the device to investigate glioblastoma cell migration mediated by growth factors. Using a collagen-coated LLS scaffold as the extracellular 3D support, glioblastoma cells exhibited directed migration along the gradient and against fluid flow direction, highlighting the platform's ability to recapitulate physiological conditions. In addition, T-cell migration in response to an IL-2 gradient was successfully assessed. Real-time tracking with confocal microscopy revealed precise and directional T-cell migration for 48 hours, underscoring the platform's utility for ex-vivo immunotherapeutic assays. Sustained chemotactic gradient formation and stability were validated by adding fluorescent dextran (FITC-dextran 40) to one end of the chemotactic device. Real-time tracking for the green-fluorescent signal revealed a fast gradient formation – in less than 30 min – which persisted for up to 24 hours.

This platform's capability to support diverse chemotactic studies in 3D is enabled by its independent control over factors such as cell adhesion, scaffold bioconjugation, mechanical properties, and interstitial space. By mimicking physiologically relevant scaffolds with controlled gradients, it enables studies of complex cellular behaviors, including cancer cell invasion, immune cell trafficking, and drug screening under more realistic in vitro conditions. This innovative tool for chemotaxis could facilitate the development of targeted therapies and deepen our understanding of fundamental biological processes.

Title: Developing a Paper-Based Assay Detecting TOP2A Protein for Point-of-Care Cervical Cancer Screening

Authors: Sayeh Dowlatshahi[1], Scott Charles Bolton[1], Samrin Habbani[2], Lucy Tecle[1], Francesca Hamacher[3], Jacqueline C. Linnes[1]

[1]Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN, USA; [2]Department of Comparative Pathobiology, Purdue University, West Lafayette, IN, USA; [3]Department of Agricultural and Biological Engineering, Purdue University, West Lafayette, IN, USA

Abstract:
Cervical cancer (CC) is the second most common cancer in women and the second leading cause of cancer-related deaths among them globally. Current gold-standard CC screening techniques are expensive and time-consuming, possess low sensitivity or specificity, and require trained personnel and sophisticated instrumentation, limiting their implementation in low-resource settings. Therefore, a low-cost, rapid, sensitive, and specific point-of-care early-stage CC diagnostic assay is urgently needed. Topoisomerase II alpha (TOP2A), an enzyme innately involved in DNA replication, tends to be overexpressed in CC patients, making it a promising CC protein biomarker. This study focuses on developing a TOP2A lateral flow immunoassay (LFIA) for CC screening. The test's colorimetric labels are 40-nm gold nanoparticles (AuNPs) conjugated to mouse anti-TOP2A detector antibody (dAb) molecules. Conjugation efficiency was assessed through commercial quality control dipstick assays and dynamic light scattering. Of the tested dAb-to-AuNP molar ratios, 100:1 produced the highest grayscale intensity (Figures 1A and 1B). It was also the most stable throughout a 7-day study and was accordingly chosen as the optimal conjugate for the LFIA. This conjugate was then used with in-house dipsticks to optimize the test and control lines. 1.5 mg/mL anti-mouse immunoglobulin G was selected as the LFIA control line's antibody concentration. So far, the test line has detected as low as 50 ng/mL of TOP2A (Figures 1C and 1D), showing promise that the platform will work in the 20-100 ng/mL clinical range. This range was obtained through extensive studies measuring TOP2A in clinical cervical swab lysates using commercial enzyme-linked immunosorbent assay kits. The optimized parameters will be incorporated into the TOP2A LFIA design and its performance will be evaluated with lysates of clinical specimens. This low-cost rapid test will enable sensitive and specific CC screening in LMICs, leading to more timely diagnosis and earlier effective treatment.

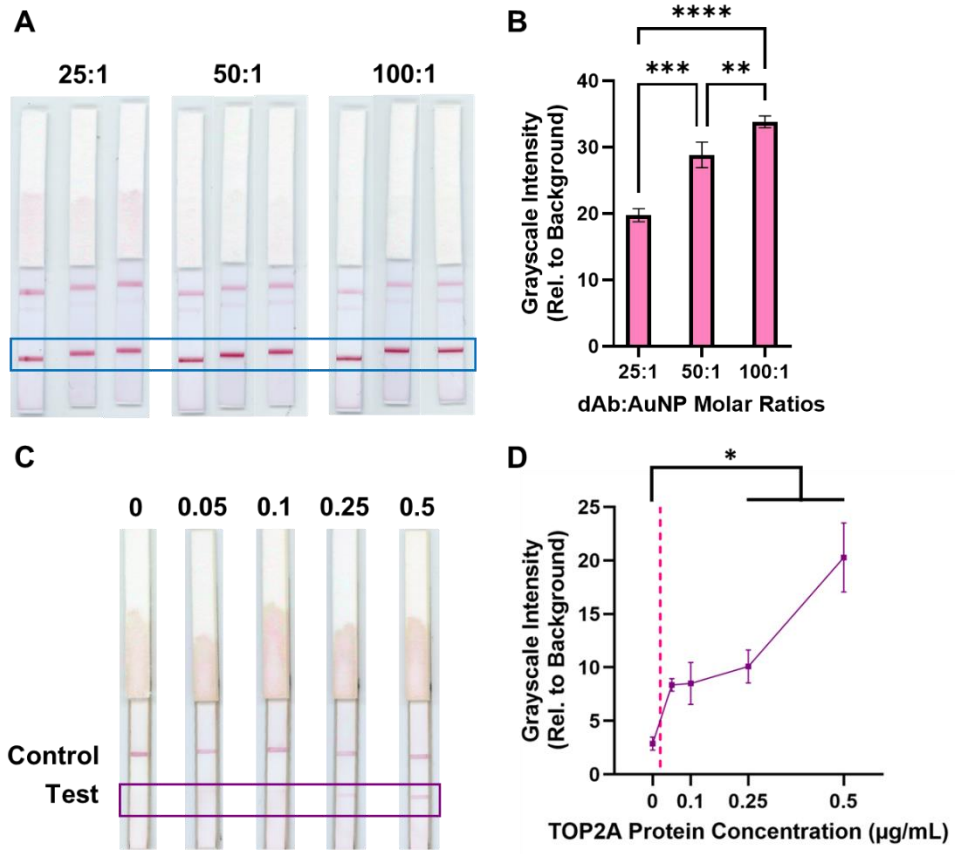


Figure 1. (A) Scans and **(B)** quantified grayscale signal intensities of the 3 anti-topoisomerase II alpha (TOP2A) detector antibody (dAb)-to-gold nanoparticle (AuNP) molar ratios. The blue rectangle highlights the anti-mouse immunoglobulin G lines of the commercial quality control dipsticks. (Tukey's multiple comparisons test, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$, n = 3, error bars: standard deviations.) **(C)** Scans and **(D)** quantified grayscale signal intensities of the in-house dipsticks' test lines for different purified TOP2A protein concentrations (0, 0.05, 0.1, 0.25, and 0.5 µg/mL). The pink dashed line is the 20-ng/mL cut-off that distinguishes between the negative for intraepithelial lesion or malignancy and epithelial cell abnormalities classes. (Dunnett's multiple comparisons test, *: $p < 0.05$, n = 3, error bars: standard deviations.)

Title: Engineering DNA nanostructures for targeted cancer therapy

Authors: Abhisek Dwivedy[1,2,], Dhyanesh Baskaran[3], Gaurav Sharma[4], Wei Hong[1,2,5,6], Dhanush Gandavadi[1], Abhichart Krissanaprasit[4], Joonsu Han[3], Yusheng Liu[3], Zack Zimmers[4], Tshepo Mafokwane[5], Ichrak Hayah[5], Neha Chauhan[1,2,5], Mengxi Zheng[1,2,5,6], Sherwood Yao[4], Keith Fraser[7], John S. Decker[4], Xiaohe Jin[4], Hua Wang[1,3,5,8,9,10,11], Adam D. Friedman[4], Xing Wang[1,2,5,6,8]

[1]Department of Bioengineering, Grainger College of Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [2]Holonyak Micro & Nanotechnology Lab, Grainger College of Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [3]Department of Materials Science and Engineering, Grainger College of Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [4]Atom Bioworks Inc., Cary, NC 27513, USA; [5]Carl R. Woese Institute for Genomic Biology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [6]Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [7]Department of Biological Sciences, Rensselaer Polytechnic Institute, Troy, NY 12180, USA; [8]Cancer Center at Illinois, Urbana, IL 61801, USA; [9]Carle College of Medicine, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [10]Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; [11]Materials Research Laboratory, Grainger College of Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

Abstract:
We present a versatile "plug and play" platform utilizing DNA nanostructures and aptamers to precisely target cancer cell surface biomarkers, effectively addressing the challenge of off-target effects commonly encountered in traditional anticancer drug delivery approaches. We demonstrate the effectiveness of our cell targeting strategy in treating acute myeloid leukemia (AML), a disease known for its resistance to chemotherapy. We developed biologically functional aptamers targeting CD117- a common surface marker for AML cells. These aptamers devoid of any chemotherapeutic payload, demonstrated a notable ~40% decrease in AML cell viability within a 72-hour period. Through total RNA sequencing, we present evidence indicating that the binding of our aptamers to CD117 alters major MAP kinase pathways and triggers apoptotic signals. Computational structural analyses further support these findings, suggesting an allosteric modulation of CD117 by our aptamers. Through the utilization of CD117 and CD123-targeting aptamers arranged on programmable DNA nanoarchitectures, we observe a significant decrease in cell viability and activation of apoptotic signals specifically in CD117+CD123+ AML cells. Of note, this approach results in minimal toxicity to non-target cells while efficiently delivering the anticancer drug daunorubicin to CD117+CD123+ AML cells. Our nanostructures also reduced the effective therapeutic concentration of daunorubicin by nearly 500 folds in culture. This was demonstrated by an effective clearance of AML cells at much lower concentration of the drug highlighting the platform's target drug delivery efficacy. Of note, these nanostructures also effectively hindered and reversed AML progression in mouse while utilizing only one tenth of the previously reported in vivo daunorubicin therapeutic concentration, further showcasing its targetability. Our platform's adaptability is highlighted by its ability to target specific combinations of cancer cell surface proteins, suggesting potential applications across various cancer types.

Title: Engineering Sonogenetic EchoBack-CAR T cells

Authors: Longwei Liu[1,2], Peixiang He[1,2], Yuxuan Wang[1], Fengyi Ma[1], Dulei Li[3], Zhiliang Bai[4], Yunjia Qu[1,2], Linshan Zhu[1], Chi Woo Yoon[1], Xi Yu[1], Yixuan Huang[1], Zhengyu Liang[2], Tianze Guo[1], H. Kay Chung[5,6], Rong Fan[4], Yingxiao Wang[1,2]

[1]Alfred E. Mann Department of Biomedical Engineering, University of Southern California, Los Angeles, CA90089, USA; [2]Department of Bioengineering, Institute of Engineering in Medicine, University of California San Diego, La Jolla, CA92093, USA; [3]Acoustic Cell Therapy, Inc., San Diego, CA92130, USA; [4]Department of Biomedical Engineering, Yale University, New Haven, CT 06520, USA; [5]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [6]Department of Cell Biology & Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract:
Chimeric antigen receptor (CAR) T cell therapy marks a significant advancement in oncology, offering the promise of durable remissions in hematological malignancies. However, solid tumors present formidable challenges, including on-target off-tumor toxicity, exhaustion, and limited persistence of therapeutic T cells. Here, we engineered sonogenetic EchoBack-CAR T cells using a highly heat-sensitive promoter, evolved through a sort-seq platform, and integrated it with a positive feedback loop from CAR signaling pathways that enables the conversion of tumor engagement into CAR production, resulting in long-lasting CAR expression upon remote stimulation by focused ultrasound (FUS). EchoBack-CAR T cells with a high-affinity single-chain variable fragment (scFv) targeting disialoganglioside GD2 (EchoBack-hGD2CAR) exhibited potent cytotoxicity and persistence in an in vitro glioblastoma spheroid model. In both subcutaneous and orthotopic glioblastoma models in mice, EchoBack-hGD2CAR T cells achieved robust and safe tumor suppression without off-tumor toxicity. Through single-cell RNA sequencing, we uncovered a distinctive transcriptomic landscape that underscores the enhanced cytotoxicity and reduced exhaustion of EchoBack-CAR T cells after chronic antigen stimulation compared to standard CAR T cells that constitutively express CAR. The EchoBack-CAR can also be generalized and extended to treat prostate cancer by targeting prostate-specific membrane antigen (EchoBack-PSMACAR), demonstrating a remarkable tumor suppression but minimal off-tumor toxicity to healthy tissues. Collectively, these findings not only highlight the potential of EchoBack-CAR T cells to promote solid tumor immunotherapy via ultrasound remote control but also present a modular approach adaptable to various cancer targets, poised to mitigate the limitations of current CAR T cell therapies.

Title: Photo-activated Combinatorial microRNA Delivery Induces Apoptosis in Head and Neck Cancer

Authors: Angelica Helton [1], Tyus Yeingst [1], Neerav Goyal [2], Daniel J. Hayes [1,3,4]

[1]Department of Biomedical Engineering, The Pennsylvania State University, University Park, Pennsylvania 16802, United States; [2]Department of Otolaryngology—Head and Neck Surgery, College of Medicine, The Pennsylvania State University, Hershey, PA, 17033 USA; [3]Huck Institutes of the Life Sciences, The Pennsylvania State University, University Park, PA, USA; [4]Materials Research Institute, Millennium Science Complex, The Pennsylvania State University, University Park, Pennsylvania 16802, United States

Abstract:
By 2030 the incidence rate of head and neck cancer (HNC) is predicted to increase by 30%, specifically in younger populations. Despite the success of chemotherapy and radiation therapy, up to 62% of patients have potentially severe treatment-related toxicities including permanent disabilities in speech, respiration, swallowing, and cosmesis due to tissue loss. Current research explores the delivery of nucleic acid therapeutics, specifically microRNA (miRNA) for the modulation of cancer cell function. MiRNAs, small non-coding RNA consisting of 18-22 nucleotides, block mRNA translation into proteins to regulate gene expression. To advance cancer treatment and decrease off-target effects, we have developed a nanoparticle (NP) for light-controlled miRNA mimic delivery. The NP is composed of an Au/Ag/Au core-shell-shell (CSS) NP, a Diels-Alder (DA) linkage chemistry, and nucleic acid mimics. The CSS composition of the NP induces plasmonic resonance in the near infrared (nIR) region, which generates intense plasmonic fields when illuminated by nIR light. These plasmons catalyze the retro-DA reaction at the surface of the particle, resulting in mimic release. Our *in vitro* results show that multiple miRNA can be effectively attached to the NP, the combination of multiple miRNA improves apoptosis in HNC cell lines nonresponsive to a single microRNA, and knockdown of target genes – such as BCL2L11, ROCK1, NRAS, and CASP2 - occurs in as little as 3 hours after miRNA release from CSS nanoparticles. Notably in FaDu cells, the combination of 90% miR-34a-5p and 10% miR-148b-3p provides the most significant knockdown while 100% of either miRNA has minimal effect. RNA sequencing and in vivo studies are underway with completion expected by April 2025.

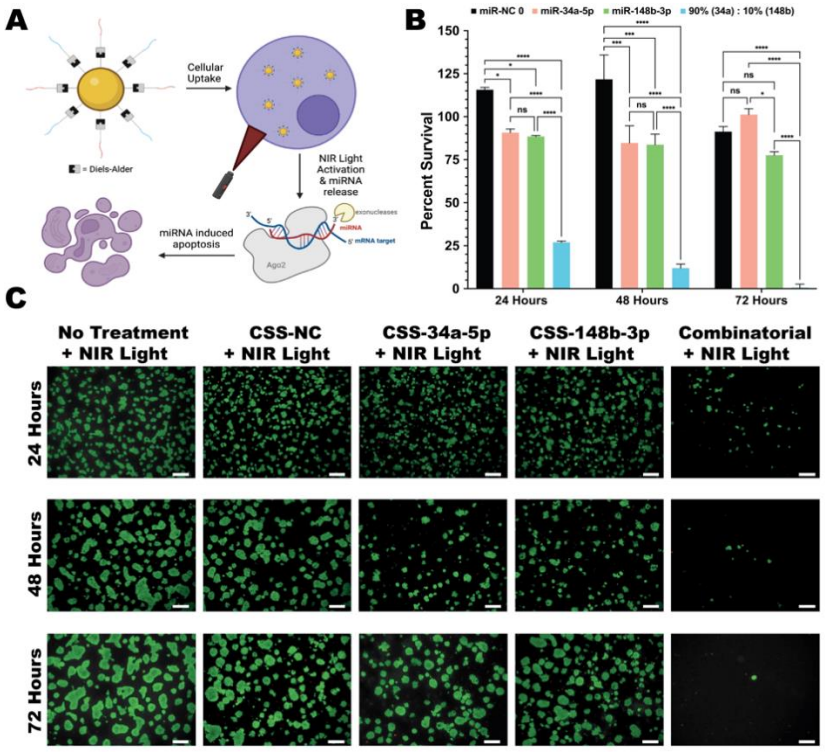


Figure 1 (A) Graphical Abstract of CSS NP uptake and microRNA release. **(B)** PicoGreen quantitative and **(C)** LIVE/DEAD qualitative analysis of FaDu cell survival after treatment with 50 nM CSS NP and niR illumination.

Title: Minimalizing Tissue Damage during Tumor Resection with Digit Integrated Tumor Curette: A Proof of Concept

Authors: Caroline Miller[1], Brandon Look Fong[1], Zachary Mendoza[1], Sarah Hakam[1], Rhome Hughes[1]

[1]Texas A&M School of Engineering Medicine

Abstract:
Introduction: Bone tumors often require removal with a curette, which scrapes away tumor tissue and margins of healthy bone to strive for complete removal. For large or deeply embedded tumors, surgeons create a "window" to access the tumor to enable curettage. Traditional curettes are rigid and fixed-angle, leading to two issues: (1) windows must be large enough to allow maximal range of motion of the curette, compromising bone integrity, and (2) incomplete tumor removal due to inaccessible angles. These limitations contribute to high recurrence rates, especially for giant cell tumors of bone (GCT). This study aimed to design a device that retains the curettage method while reducing the need for enlarged windows and maximizing tumor removal.

Materials and Methods: The proposed device combines the functionality of a curette with the dexterity of one's hand. Critical characteristics for assessment include ease of use and ergonomic design. Design A is an externally fixed apparatus on one finger, mimicking a curette's shape when the finger flexes. Dynamic flexion allows flexible movement of the curette while inserted in the bone window for curettage. Design B employed similar features but is one solitary piece. Both designs were tested by scraping a model bone tumor from a fixed cavity, using an accessible material chosen to mimic the physical characteristics of a bone tumor. Effectiveness was analyzed based on their ability to remove the material efficiently.

Results and Discussion: Both designs enhanced tumor removal by leveraging finger movement and preserving the curettage method. Design A was difficult to apply and remove, while Design B's tip required frequent cleaning, limiting efficiency. Future iterations will focus on effectiveness, ease of use, and user preference. Limitations include the lack of quantitative confirmation of improved tumor removal. Future designs will incorporate flexible materials to enhance manipulation while maintaining edge strength.

Title: 3D High Density Collagen I Improves Modeling of Metastatic Pancreatic Cancer

Authors: Kim Nguyen-Ta[1], Sural Ranamukhaarachchi[2], Jeffrey Turner[2], Utsav Joshi[1], Himangshu Sonowal[1], Jorge de la Torre Medina[1], Hana Russo[3], Herve Tiriac[1], Stephanie Fraley[2], Rebekah White[1]

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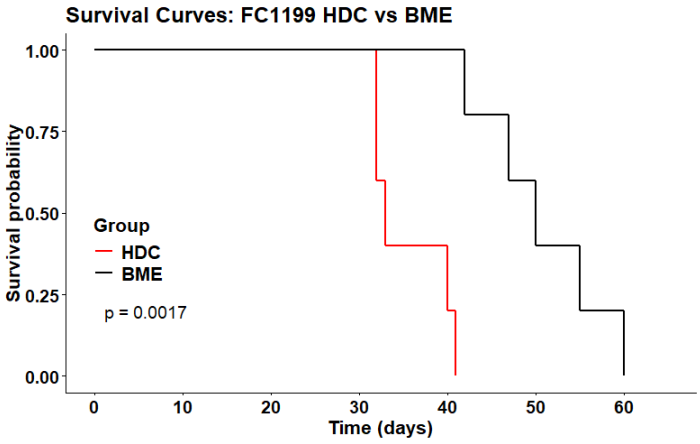
Abstract:
Background: Fibrillar collagen type I constitutes most of the extracellular matrix in pancreatic ductal adenocarcinoma (PDAC) and is directly associated with worse prognosis, yet most in vivo murine models involve the use of basement membrane extracts (BME), which instead contain collagen type IV, as matrices to embed cells. Our hypothesis is that PDAC cells grown in high density collagen (HDC) gels behave more aggressively compared to the same cells grown using conventional BME (Matrigel®).

Methods: The FC1199 cell line was previously generated from a pancreatic tumor that developed in a genetically-engineered male mouse. Cells were cultured in vitro in HDC or BME for one week. Orthotopic tumors were established by embedding cells in HDC (N=10) or BME (N=10) in the pancreas of syngeneic C57BL/6J mice via laparotomy. Collagen was imaged by second harmonic generation (SHG) microscopy.

Results: In vitro imaging of cells grown in HDC revealed clonal network-like structures compared to spheroids for cells grown in BME. SHG confirmed consistent collagen formation but minimal in HDC and BME tumors, respectively. Gross and histological examinatio showed 80% and 20% with liver metastasis in HDC and BME mice, respectively. The entire HDC group died before any of the BME group (Figure, $P < 0.01$). Western blot results show increased vimentin (a marker of epithelial-to-mesenchymal transition) expression in HDC tumors.

Conclusions: Cells embedded in HDC showed an aggressive phenotype in vitro with resultant tumors demonstrating more robust collagen organization compared to cells grown in BME, translating to worse survival with liver metastasis formation prior to death from primary tumor burden. This is atypical for most PDAC mouse models but is typical for human PDAC patients. We are exploring the molecular mechanisms underlying these phenomena. Our findings support our novel approach of using HDC as an alternative substrate for modeling the aggressiveness of PDAC.



Title: Nanotechnology-assisted photoimmunotherapy to overcome drug delivery barriers for peritoneal metastasis

Authors: Sumiao Pang[1], Carla Arnau Del Valle[2], Robert Perttilä[3], Nada Fadul[1], Payal Srivastava[1], Benjamin Powers[4], Dana Roque[5,6], Tayyaba Hasan[7], Petteri Uusimaa[3], Huang Chiao Huang[1,5]

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Abstract:
Peritoneal metastasis results from direct shedding of tumor cells from ovarian, colorectal, and other cancers, leading to studding and growth on tumors the peritoneal surfaces and abdominal organs. Standard chemotherapy and cytoreductive surgery can transiently improve symptoms, but long-term disease control and survival extension has not significantly improved in the past 30 years. Photoimmunotherapy (PIT) is an emerging modality that involves administration of antibody-photosensitizer drug conjugate (or photo-immunoconjugates, PICs), followed by harmless red-light activation to generate singlet oxygen that kills cancer cells. Clinical translation of PIT has been limited due, in part, to poor uptake of PIC by cancer cells and heterogeneous treatment response. Here, we leverage nano-engineering and fluorescence-guided approaches to integrate PIT, imaging, and monitoring of treatment responses to overcome the current limitations of PIT.

We have previously demonstrated that our novel targeted photoactivatable multi-agent liposomal (TPMAL) nanoplatform combined with fluorescence-guided drug delivery and light dosimetry can improve PIC delivery and improve treatment consistency in mouse models of peritoneal metastasis (Liang et al. 2020, Liang et al. 2023). This new study aims to further investigate the combination of TPMAL PIT and standard chemotherapy for survival enhancement. Our TPMAL nanoplatform demonstrated high batch-to-batch consistency and long-term stability for up to 1 year. The TPMAL formulation also enhanced in vivo PIC drug delivery and penetration depth into peritoneal tumors by 160% and up to nearly 3,000 □m penetration depth, respectively, compared to using PIC alone. The combination of TPMAL-assisted PIT and chemotherapy is not only safe but also enhanced animal survival by 2.4-fold compared to chemotherapy alone. In summary, TPMAL-assisted, fluorescence-guided PIT combined chemotherapy is a promising regimen for patients with peritoneal metastasis

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Liang, B. J., Pang, S., Perttila, R., Ma, C.H., Gaitan, B., Sorrin, A.J., Fadul, N., Rahman, I., Ylo¨niemi, Z., Roque, D.M., Hasan, T., Uusimaa, P., Huang, H.C. (2023) Fluorescence-guided photoimmunotherapy using targeted nanotechnology and ML7710 to manage peritoneal carcinomatosis. Science Advances, 9, 36.

Title: The mechanical Influence of TPD52L2 on cellular Rigidity via the Actin-Cytoskeleton in Breast Cancer Cells

Authors: Amirabbas Parizadeh[1], Alexander Plesche[2], Muhammad Zahoor[3], Veronika Reiterer[2], Hesso Farhan[2]

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Abstract:
TPD52L2 regulates cellular Rigidity via the Actin-Cytoskeleton in Breast Cancer Cells Tumor protein D52 like 2 (TPD52L2) is part of the TPD52 protein family and is known to be overexpressed in a variety of malignant diseases. This including breast cancer, where its overexpression correlates with a reduced overall survival. Recently, TPD52L2 was reported to be associated with intracellular nanovesicles, thereby being involved in a variety of membrane trafficking pathways.

Our study unravels the role of TPD52L2 as a regulator of the actin cytoskeleton in breast cancer cells. Depletion of TPD52L2 results in a strong reduction of stress fibers, altered dynamics of actin protrusion and finally an enlarged cortical actin layer. Mechanistically, we demonstrate that TPD52L2 interacts with Cullin-5, a central component of the cullin-RING ubiquitin ligase (CRL) complex. The interplay at this CRL complex with members of the Rab40 protein family might be responsible for the observed effects on the actin cytoskeleton. Depletion of both TPD52L2 and Rab40c results in a partial rescue of the actin phenotype, which can be explained by downstream regulatory functions of the Rab40 proteins on focal adhesions and components of the actin cytoskeleton.

Atomic force microscopy measurements conform an increase in the rigidity of affected cells. Due to these mechanical alterations, TPD52L2 silenced cells have a mechano-adaptability defect. Furthermore, a significant reduction in migratory speed was observed in a 3D random migration assay. Remarkably, both the mechanoadaptability and the migration defect were rescued by low-dose treatment with Y-27632, a ROCK-signaling inhibitor. Y-27632 reduces cellular stiffness, thereby reversing the effects of the aberrant cytoskeleton on the cellular rigidity. This demonstrates that the mechanoadaptability and the migration defect are caused by the altered stiffness profile of the cell, implying TPD52L2 as a coordinator of these factors via its regulatory capacities on the actin cytoskeleton.

Title: A rapid 3D in vitro drug screening platform of glioblastoma utilizing hydrogel microparticle encapsulation

Authors: Brittany A. Payan[1], Annika Carrillo Diaz de Leon[1], Gunnar B. Thompson[1], Brendan A.C. Harley[1]

[1]University of Illinois Urbana Champaign, IL, USA

Abstract:
Background. We report a method to encapsulate glioblastoma (GBM) cells in maleimide-functionalized gelatin (GelMAL) microparticles for in vitro drug screening. GBM is the most common primary malignant brain tumor. Standard of care is surgical resection followed by treatment with the alkylating agent temozolomide (TMZ). GBM cells that evade surgery eventually become resistant to TMZ and lead to recurrence of tumors in patients. Hydrogels have been implemented as matrices for 3D culture that can recapitulate tumor biology and tumor microenvironment. However, bulk hydrogels require large numbers of cells per construct and possess scalability limitations. With only four drugs currently FDA-approved for GBM treatment, there is a need for a platform capable of accelerating the identification of new therapies in a highly controlled and physiologically relevant environment. Hydrogel microparticles allow encapsulation of GBM cells in a tailorable 3D matrix amenable for high-throughput screens (HTS).

Methods. U87MG cells are encapsulated in GelMAL microparticles using a flow-focusing microfluidic device. Viability and proliferation of GBM cells is assessed via LIVE/DEAD cell imaging kit and double stranded DNA (dsDNA) quantification, respectively. We record a response from encapsulated cells after TMZ exposure (0-1000 μM) via cellular activity using alamarBlue.

Results. Cellular viability within microfluidic emulsion is limited by shear forces exhibited in the microfluidic device. Here, we report a method to encapsulate GBM cells in microgels and retain cellular viability. Increasing levels of dsDNA suggest maintenance of cellular health in microgels and indicate a proliferative population of encapsulated cells. Metabolic profile of encapsulated cells shows a decrease in cellular activity in response to increasing concentrations of TMZ, concurrent with 2D and bulk hydrogel culture. Ongoing experiments will assess cellular behavior post-movement by liquid handler of encapsulated cells to establish a drug screening platform amenable for HTS.

Title: Application of Polarization Sensitive Optical Coherence Tomography to Evaluate Surgical Margins in Head and Neck Cancer

Authors: Sindhura Sridhar[1], Daniel Phan[2], Yunqin Zhao[2], Audrey K. Bowden[2], Michael C. Topf[1]

[1]Vanderbilt University Medical Center, Department of Otolaryngology—Head and Neck Surgery; [2]Vanderbilt University, Vanderbilt Biophotonics Center, Department of Biomedical Engineering

Abstract:
Introduction: Achieving clear surgical margins in head and neck cancer surgery is essential to reduce the risk of disease recurrence and mortality. Intraoperative assessment of margins is conducted using frozen section analysis, a process that can take 20-45 minutes and delay progression of surgery. Polarization-sensitive optical coherence tomography (PSOCT) could be used to rapidly visualize changes in collagen structure, allowing for differentiation of normal mucosa and tumor.

Methods: Tumor margin samples were obtained from patients undergoing surgical resection for head and neck cancer. A Telesto series PSOCT imaging system was used to obtain a volumetric dataset (C-scan) of 8mm x 1mm x 3.56mm for each sample. H&E-stained images of the biopsy samples were obtained as the gold standard to measure the distance from specimen margin to invasive cancer.

Results: PSOCT was performed on five patients who underwent head and neck cancer resection. Nine samples were imaged, and 5-7 scans obtained for each sample, resulting in a total of 48 scans with an average duration of 30 seconds per scan. Each C-scan was processed using MATLAB to generate attenuation coefficient (AC), retardation, and optic axis images. The AC, retardation and optic axis images were more homogeneous in cancerous tissues compared to normal mucosa. Entropy and birefringence maps were generated for two samples. In these samples, the entropy and birefringence maps provided clear color differences between tumor and normal mucosa indicative of quantitative differences in polarized light response, with green and dark blue representative of cancer, respectively, compared to normal tissue which appeared orange and light blue, respectively.

Conclusion: PSOCT is a rapid method of imaging tumor specimen margins that may be able to differentiate between normal mucosa and head and neck cancer. Data collection is ongoing to more objectively compare PSOCT results to standard of care frozen section analysis.

Title: MetaboCore: A rapid companion diagnostic drug sensitivity assay for functional precision oncology

Authors: Yin Tang[1], Hui-yu Chuang[1], Heidi L. Kenerson[2], Raymond S. Yeung[2], Wei Wei[1]

[1]Institute for Systems Biology; [2]University of Washington School of Medicine

Abstract:
Over the past several decades, cancer treatment has advanced significantly with numerous novel drugs and therapies. However, a persistent challenge in oncology remains: prescribing the most appropriate drugs for individual patients. While current treatment guidelines reflect average drug responses in a particular patient subset, the inherent heterogeneity within tumor tissues and among patients complicates the selection of optimal treatment regimens.

Previous attempts to develop clinically viable drug sensitivity assays using organoids and patient-derived xenograft (PDX) models for common cancers have faced limitations due to lengthy propagation time and substantial tissue requirements. To address these challenges, we present the MetaboCore assay, a rapid metabolic-activity-based drug sensitivity test that requires only 20-30mg of needle biopsy tissue from human cholangiocarcinoma and colorectal cancer specimens.

Our assay interrogates an organic tissue culture system with single-cell metabolic cytometry to evaluate drug responses by monitoring key metabolic pathways, including glycolysis, oxidative phosphorylation, and oxidative stress in individual tumor cells. The streamlined tissue culture system enables drug sensitivity reporting within one week, making it clinically feasible. We anticipate that the MetaboCore assay will facilitate the implementation of personalized cancer treatments in clinical settings.

Title: In silico reconstruction of primary and metastatic estrogen receptor positive breast tumor architecture using geographic information science-augmented spatial transcriptomics

Authors: Jin Young Yoo[1], Sabrina Akter[1], Qianying Zuo[1], Mahima Goel[2], Audrey Lam[3], Debapriya Dutta[3], Betsy Barnick[3], Maria Grosse-Perdekamp[3], Aiman Soliman[4], Zeynep Madak-Erdogan[1,2,4,5]

[1]Department of Food Science and Human Nutrition, University of Illinois Urbana-Champaign; [2]Carle Illinois College of Medicine, University of Illinois Urbana-Champaign; [3]Carle Foundation Hospital, Urbana, IL; [4]National Center for Supercomputing Applications, University of Illinois Urbana-Champaign; [5]Cancer Center at Illinois, Urbana, IL

Abstract:
Tumor microenvironment(TME) consists of different cell populations, whose interactions contribute to tumor heterogeneity and plasticity and pose challenges to therapy efficacy and prognosis prediction. Estrogen receptor positive(ER+) breast cancer(BC), one of the highly heterogeneous diseases and the most common subtype, shows worse prognosis once metastasized. Spatial transcriptomics(ST) emerges as a powerful tool offering valuable insights into spatial complexity of TME and cellular interactions. In this study, we developed a geographic information science(GIS)-augmented ST analysis pipeline to delineate tumor heterogeneity of ER+ metastatic BC.

Visium datasets were prepared from eighteen primary and metastatic tumors from xenograft mouse model and BC patients. We integrated geospatial tools, such as multivariate spatial association analysis, with spatial omics data structures to check degree of auto-correlations and visualize localizations of gene sets. We further compensated for multi-cellular resolution of our spatial data via cell type mapping and deconvolution.

We identified hotspot regions displaying extensive co-localization between estrogen response and lipid metabolism gene sets in the fulvestrant-treated metastatic liver tumors. These hotspots were not concentrated in the same area within the tumor and differed by gene sets, suggesting intra-tumor metabolic heterogeneity of the endocrine responsive cells. Primary samples from patients showed similar pattern of co-occurrence with metabolic and cell-cycle gene sets, whereas mutual exclusivity was observed with immune-related and metastasis-related gene sets. Metastatic bone tumors showed inter-tumor heterogeneity as such consistency in spatial pattern was obscured. Deconvoluting cell type proportions mapped a higher proportion of mature luminal cells in endocrine responsive hotspots and cancer-associated fibroblasts and pericytes in metastasis-related pathway hotspots.

Our study fully utilized the potential of ST data by delineating the TME in relation to intra-tumoral heterogeneity and cell type distribution. Our findings support the development of strategies to target different endocrine resistant cell populations with a combination of metabolic and metastasis-related signaling inhibitors.