

AWARD NUMBER: W81XWH-19-10065, BC180931

TITLE: Quantitative Phase Microscopy for Real-Time Clinical Determination of Drug Therapy Response in Primary and Metastatic Breast Cancer

PRINCIPAL INVESTIGATOR: Thomas A Zangle

CONTRACTING ORGANIZATION: University of Utah

REPORT DATE: March 2022

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14. ABSTRACT There are no biomarkers that can accurately predict chemotherapy response in advanced cancer patients and less than 10% of patients with a detected targetable mutation are eligible for a clinical trial. There is a need for new diagnostic methods that can accurately stratify high-risk patients to effective, FDA-approved therapies. Our current patient-derived models for assessing tumor drug response involve expanding patient tumor cells as 3D patient derived organoids (PDO) in Matrigel or using in vivo drug sensitivity studies with patient-derived xenograft models (PDX). These experimental models typically exhibit the same phenotype and molecular alterations in vivo and ex vivo and have the same drug responses as in the patient. However, these methods require 1-8 months to obtain drug sensitivity profiles making this impractical for patient care. In this project, we will develop a functional assay with the new capability to predict cancer cell response to therapy for both cell population response and single-cell heterogeneity. In year 3, we completed the technical validation of the QPM platform using established cell lines and FDA-approved therapies. This work is under review for publication. In addition, we have begun using organoid breast cancer models to show analytic validity of drug response/resistance. Overall, our project will provide real-time feedback to oncologists on overall drug sensitivity/resistance and resistant subpopulations.					
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1. INTRODUCTION:

There are no biomarkers that can accurately predict chemotherapy response in advanced cancer patients and less than 10% of patients with a detected targetable mutation are eligible for a clinical trial. There is a need for new diagnostic methods that can accurately stratify high-risk patients to effective, FDA-approved therapies. Our current patient-derived models for assessing tumor drug response involve expanding patient tumor cells as 3D patient derived organoids (PDO) in Matrigel or using *in vivo* drug sensitivity studies with patient-derived xenograft models (PDX). These experimental models typically exhibit the same phenotype and molecular alterations *in vivo* and *ex vivo* and have the same drug responses as in the patient. However, these methods require 1-8 months to obtain drug sensitivity profiles making this impractical for patient care. In this project, we will develop a functional assay with the new capability to predict cancer cell response to therapy for both cell population response and single-cell heterogeneity. In year 3, we completed the technical validation of the QPM platform using established cell lines and FDA-approved therapies. This work is under review for publication. In addition, we have begun using organoid breast cancer models to show analytic validity of drug response/resistance.

2. KEYWORDS:

Quantitative phase microscopy (QPM), functional assay, precision medicine, breast cancer

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The SOW lists three major tasks to be accomplished during this project:

Major Task 1: Implement QPM imaging method (Zangle)

Target completion date: November 2019

Completion percentage: 100%

Major Task 2: Benchmark testing of drug panel on commercially available cell lines (Zangle/Bernard)

Target completion date: March 2021

Completion Percentage: 100%

Major Task 3: Conduct initial feasibility studies to assess the ability to predict chemotherapy response with previously collected, de-identified patient samples (Zangle/Bernard)

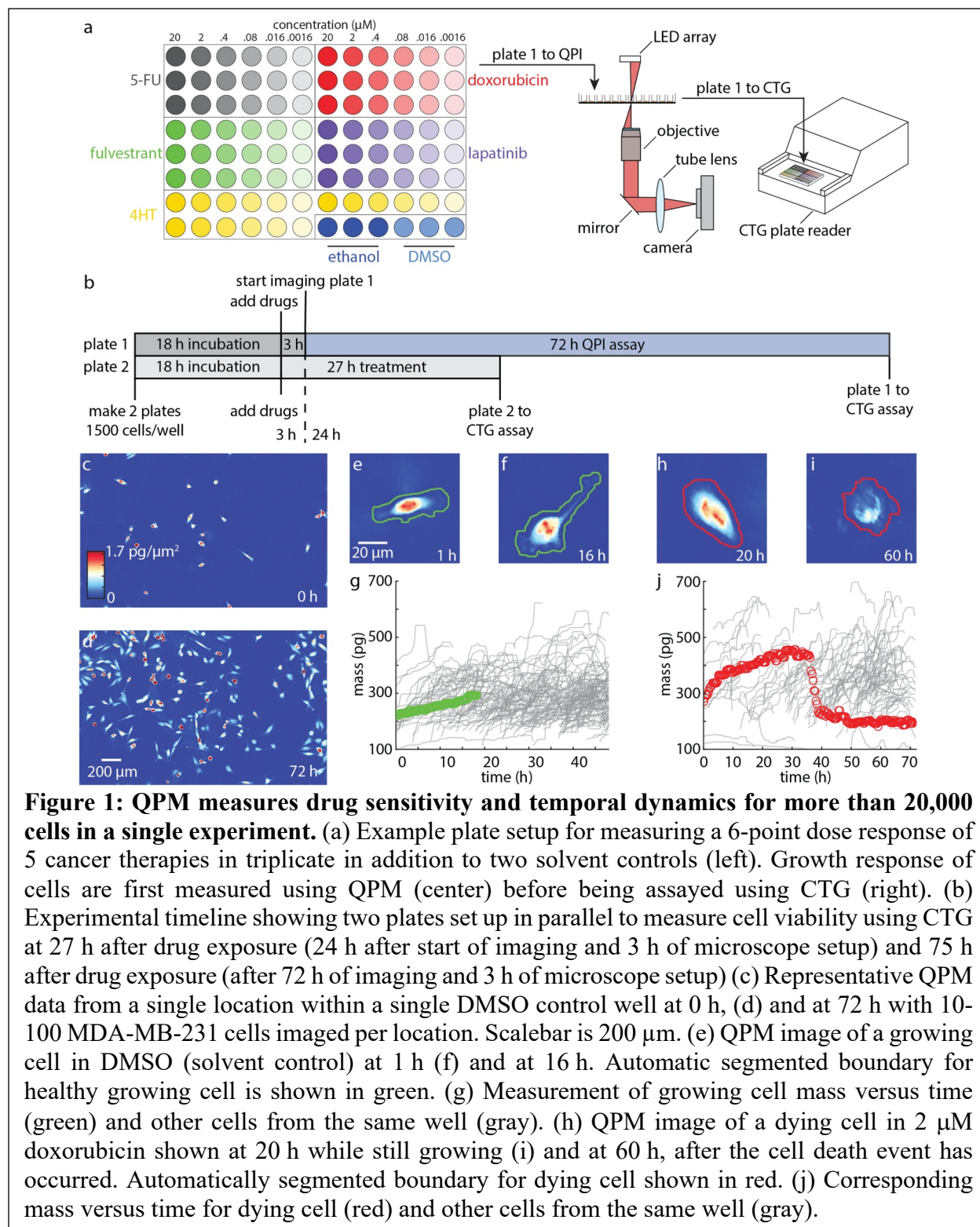
Target completion date: March 2023 *revised per No Cost Extension modification

Completion Percentage: 25%

What was accomplished under these goals?

During year 3 we completed analysis of data on an 8 drug panel (**Table 1**) across 3 immortalized breast cancer cell lines (MCF-7, BT-474, MDA-MB-231). This work is under review for publication (**Milestone 1**). The system has been optimized to conduct assays in a 96-well plate with 6-point dose response curves and up to five therapies in triplicate including solvent controls (**Figure 1**). Several key results and analyses developed specifically in Year 3 are described below.

Drug name	Target
5-Fluorouracil	DNA-RNA synthesis
Carboplatin	DNA synthesis
Docetaxel	Microtubule
Doxorubicin	DNA topoisomerase II
Fulvestrant	Estrogen receptor
Lapatinib	EGFR/HER2
Palbociclib	CDK4/6
Tamoxifen	Estrogen receptor
Vinblastine	Microtubule



One key result from year 3 of this work was the development of methods to characterize the time of response (**Figure 2**). These results indicate that the rapid, longitudinal measurements provided by QPM can dissect temporal responses to candidate therapies.

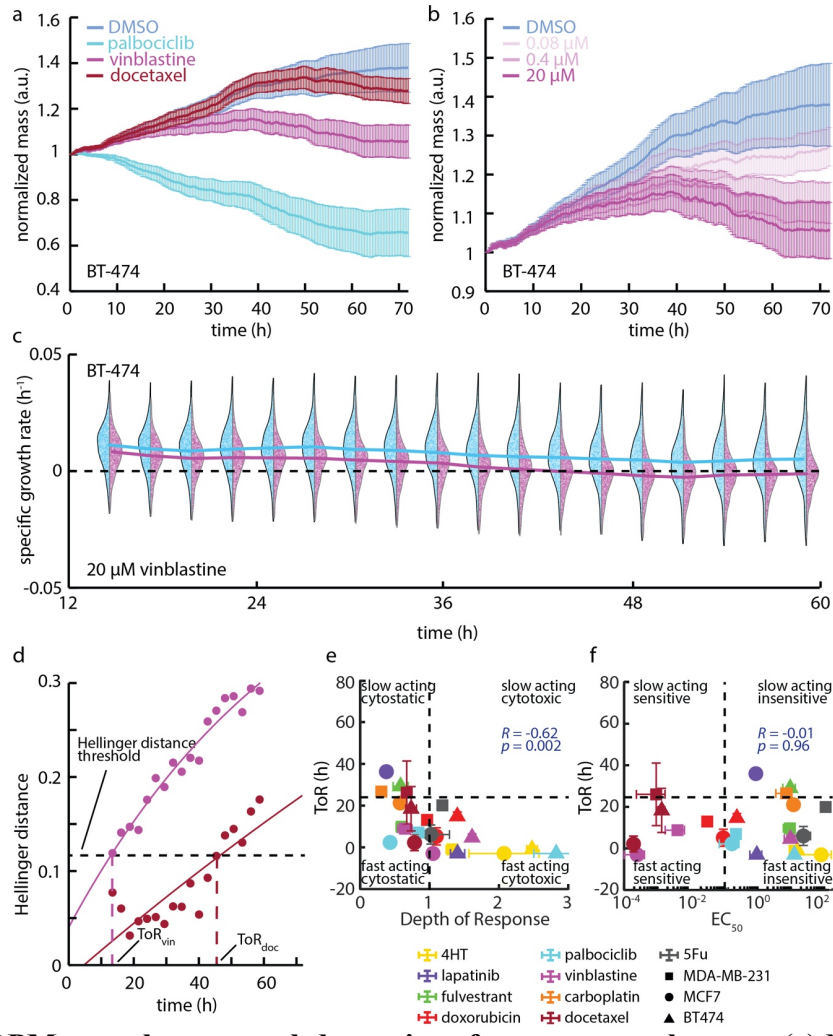
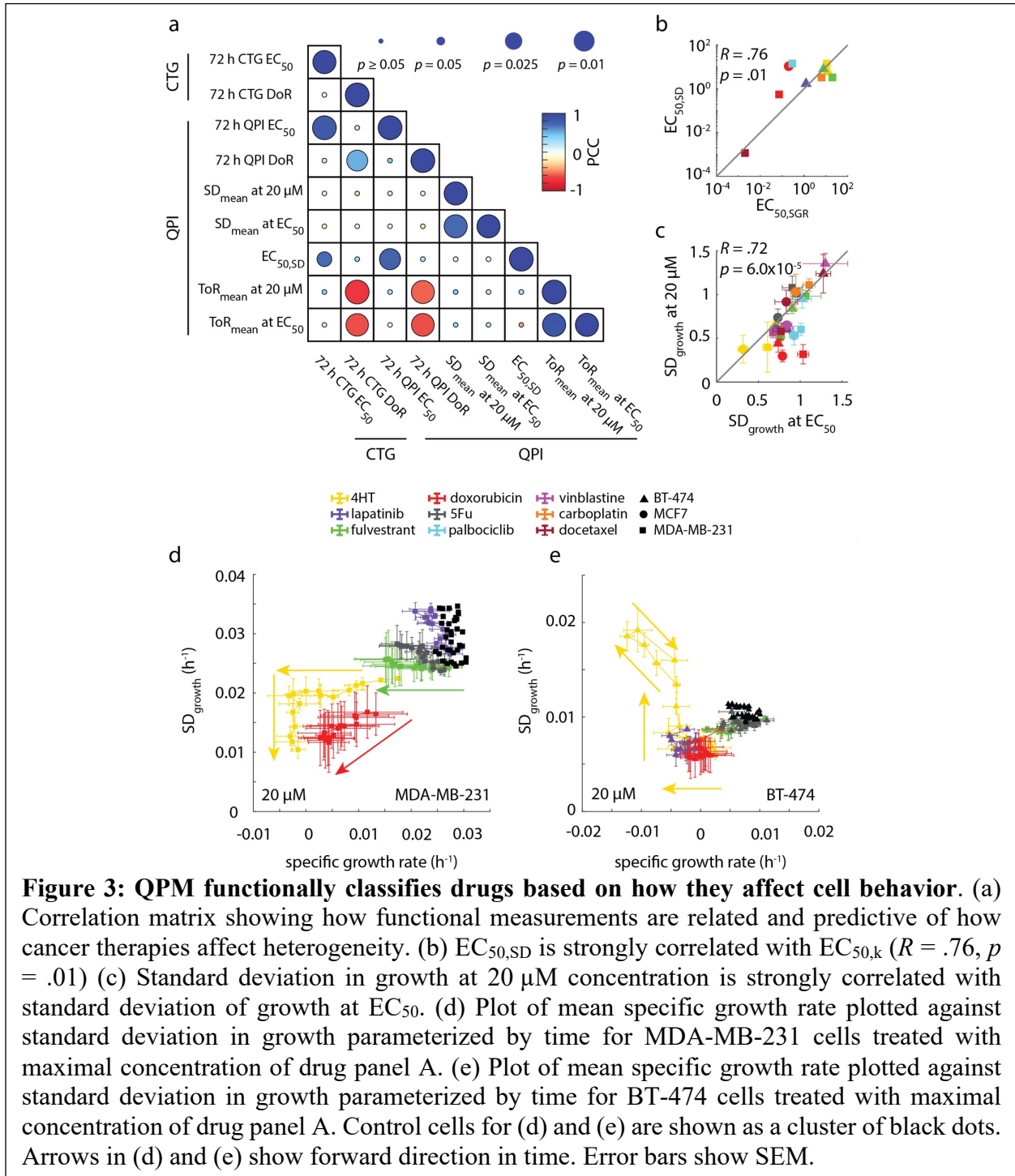
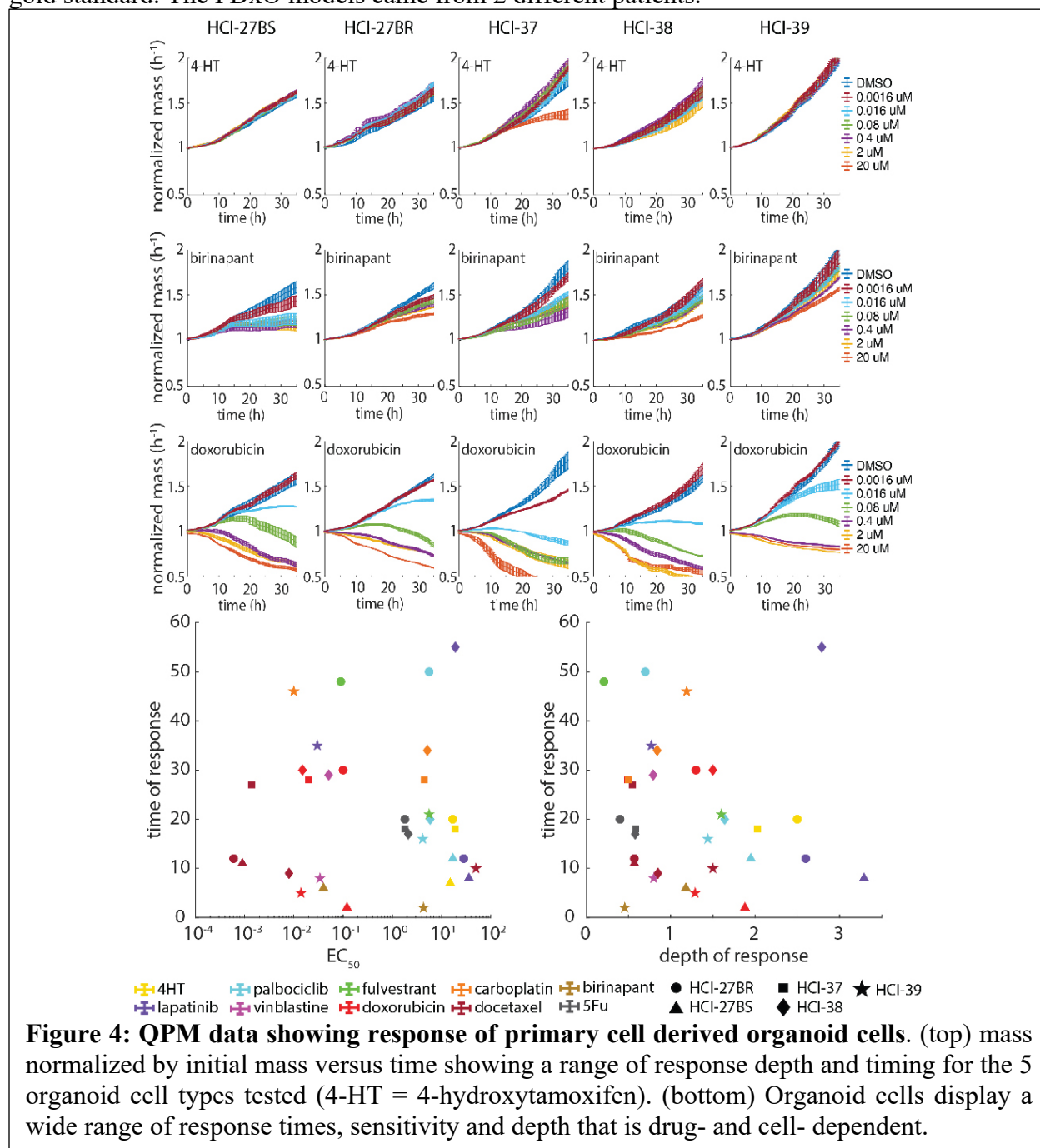


Figure 2. QPM reveals temporal dynamics of response to therapy. (a) Mass versus time normalized by the initial mass averaged over all BT-474 clusters at each time point for 20 μM palbociclib, 20 μM vinblastine, and 0.016 μM docetaxel (nearest concentration to the measured EC₅₀). Error bars show SEM. (b) Mass versus time normalized by the initial mass averaged over all cells at each time point for 0.08 μM, 0.4 μM, and 20 μM of vinblastine. Error bars show SEM. (c) BT-474 response to 20 μM vinblastine (magenta, *n* = 1944 cells) versus DMSO control (blue, *n* = 2414) in 24 h bins centered on different time points show an initially similar distribution that slowly begins to deviate over time. Solid lines represent the median of the distribution as a function of time. Individual data points show the specific growth rate of individual cells within population distributions. (d) Hellinger distance, a measure of the similarity between two probability distributions, versus time for 20 μM vinblastine and 0.016 μM docetaxel quantifies the difference between each drug treated group and the control to identify when the difference is significant enough to determine the ToR as shown by the threshold. Black dashed line represents the threshold determined by the maximum Hellinger distance between the DMSO and untreated control, the magenta dashed line shows the ToR for vinblastine, the maroon dashed line shows the ToR for docetaxel. (e) ToR near EC₅₀ versus depth of response (DoR) from QPM data classifies each drug based on its cytotoxicity and how quickly it affects cell growth. Vertical dashed line is at DoR=1 as the threshold between a cytostatic and cytotoxic response. Horizontal dashed line is at ToR=24 h, as the division between fast and slow-acting drugs. (f) ToR near EC₅₀ plotted against the EC₅₀ classifies responses as fast or slow relative to drug sensitivity. The shape of each data point shows the cell line and the color describes the drug condition. Error bars show SEM in panels (e) and (f).

Another key result of work in year 3 was analysis showing that multiparametric QPM parameters, while predictive of CTG results, are mostly orthogonal to one another (**Figure 3a-c**). These results therefore indicate that multiparametric QPM provides new information about drug responses that can be leveraged for clinical assays. We have also shown that QPM can be used to dynamically monitor changes in cell populations during drug responses (**Figure 3d-e**), providing a potentially new method for characterizing on-target versus off-target drug responses.

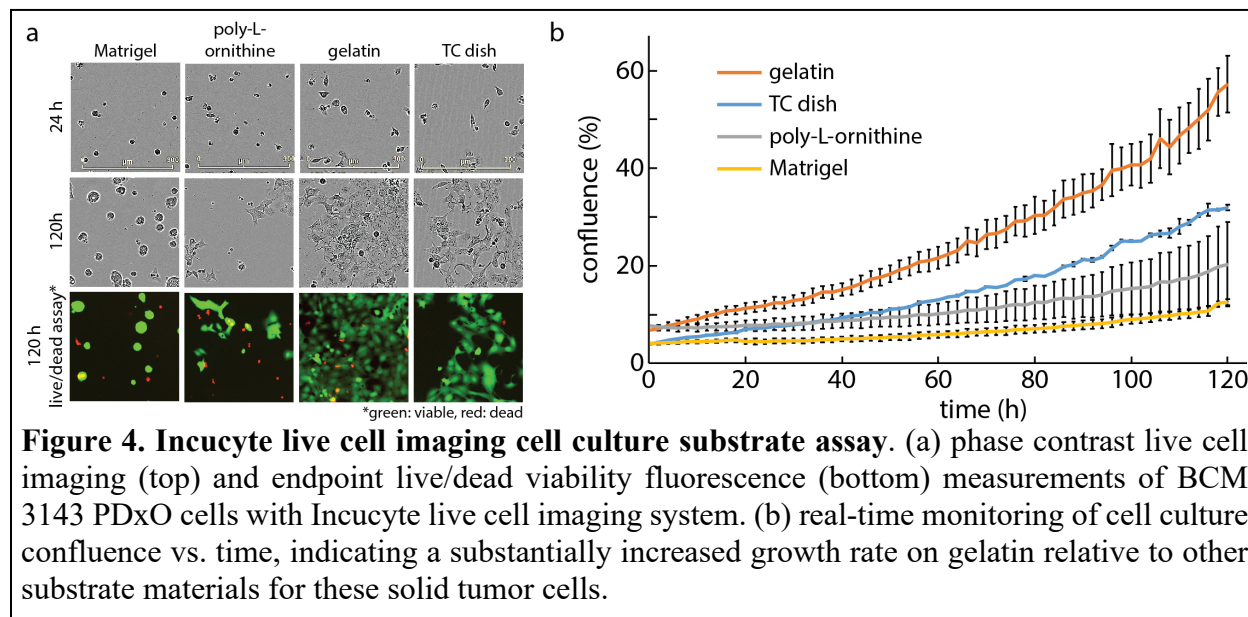


As an intermediate step before moving to direct-from-patient samples, we have optimized growth conditions for breast cancer organoids obtained from patient derived xenograft models (i.e. PDxO) (Task 3.4, Figure 4). Compared to direct-from-patient cells, these lines have a reduced technical challenge for QPM in that there is less heterogeneity from contaminating cells (i.e. stromal and immune cells) and they have been already established as *ex vivo* cultures. These lines have allowed us to optimize our QPM drug screening methods, which requires transitioning from 3D to 2D cell culture, for imaging. The PDxO models selected are triple negative breast cancers (ER-/PR-/HER2-) and have known drug sensitivity/resistance using the Cell Titer Glo (CTG) assay as a gold standard. The PDxO models came from 2 different patients.



One patient (HCI-27) grew 2 lines - one line was Birinapant resistant (HCI-27BR) and the other remained Birinapant sensitive (HCI-27BS). The other 3 models (HCI-37, HCI-38, HCI-39) are from another patient but established during progression of her disease from local recurrence (HCI-37) to femur bone metastasis (HCI-38) to lung metastasis (HCI-39). All the triple negative models were resistant to endocrine therapy (e.g. Lapatinib), as expected. HCI-27 received neoadjuvant therapy with carboplatin before recurring. Both HCI-27 lines that grew-out in the PDxOs remained relatively insensitive to carboplatin but sensitive to docetaxel. Interestingly, the HCI-37 local recurrence and corresponding pleural effusion (HCI-39) models had sensitivity to docetaxel and eribulin but the femur metastasis (HCI-38) was resistant. All these models showed Birinapant resistance. An in-depth analyses comparing the QPM to CTG drug screening results on the breast cancer organoids (PDxO) is underway towards a second manuscript on this work (**Milestone 2**).

We tested the impact of plating substrate on the growth of breast cancer derived PDxO cells using the Incucyte automated live cell imaging platform (**Figure 5**). These data show that a gelatin coating is the most favorable surface coating in terms of attachment and proliferation for this *ex vivo* line. BCM-3143, which is HER2+, ER-, PR-, exhibited nearly twice the growth rate on gelatin (doubling time 42 h) as on Matrigel (doubling time 82 h, **Figure 5b**). In addition, HCI-31, which is triple negative, also exhibited robust growth on gelatin (doubling time 66 h) and nearly zero growth on Matrigel.



We have previously obtained IRB and HRPO approval for use of human samples as outlined in our proposal (**Bernard, Task 3.1, 3.2, Milestone 2**). Patients have been consented for cancer research using our Huntsman Cancer Institute Total Cancer Care (IRB#89989) protocol, which allows for retrospective, de-identified clinical data linkage and analyses. Initial pleural effusions selected for study are detailed below (**Table 2**). Cells are counted, tested for viability, and stored as fresh frozen in glycerol at -80 C. Patients with consecutive visits for thoracentesis have been prioritized for testing in order to associate with emerging resistance. Clinical information is extracted from our Enterprise Data Warehouse (EDW) with tools developed by the Research Informatics Shared Resource (RISR) at Huntsman Cancer Institute (**Task 3.3**).

Table 2. Summary of Direct from Patient Samples to be tested								
Sample ID	Type	Vials	Count	Viability	Histologic Dx	IHC	Stage	Chemo?
20-0021985	Pleural Effusion Aspirate	20	37.1x10 ⁶	97%	Ductal Carcinoma NOS	ER+/PR+/HER2-	IV	Yes
20-0021986	Pleural Effusion Aspirate	5			Ductal Carcinoma NOS			
18-0005434	Pleural Effusion Aspirate	12	10.7x10 ⁶	81%	Ductal Carcinoma NOS	ER (weak 1%)/PR-/HER2-	IV	Yes
20-0024109	Pleural Effusion Aspirate	20	19.5x10 ⁶	95%	Ductal Carcinoma NOS	ER (moderate 75%)/PR (moderate 50%)/HER2-	IIIA	Yes
20-0024110	Pleural Effusion Aspirate	5			Ductal Carcinoma NOS			
21-0019109	Pleural Effusion Aspirate	1	1.11x10 ⁶	87%	Ductal Carcinoma NOS	ER-/PR-/HER2-	IIB	Yes
21-0019110	Pleural Effusion Aspirate	5			Ductal Carcinoma NOS			

Patients are de-identified and provided an alias that is used to associate samples with diagnosis, pathologic and clinical stage, treatments, and outcome. In many cases, there are matching PDX and PDXO models that have already been developed and drug screened by the Welms' lab (co-I) using their metabolic ATP assay. Testing the patient derived organoid models by QPM is being applied as an intermediate step to remove tumor contaminating cells, such fibroblasts and tumor-associated macrophages that could interfere with the QPM measurements. We have tested a variety of substrate-coated plates, including matrigel, laminins, fibronectin, poly-ornithine, and gelatin; in order to optimize short-term growth conditions for transitioning from 3D to 2D culture prior to drug screening (**Task 3.4**).

Moving towards the ongoing transition of the QPM from Zangle lab to Bernard lab (**Zangle/Bernard, Task 3.5**), we have continued monthly meetings among the Zangle, Bernard, and Welm labs. These meetings are held via Zoom meeting and serve to coordinate our combined efforts.

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

In year 3, this project has resulted in multiple training and professional development opportunities for students in the **Zangle** lab and the University of Utah. In terms of mentorship, two graduate students have been involved in this project. Specific mentorship activities include participation in lab workshops on manuscript writing, presentations with feedback at weekly group meetings, and participation in national scientific meetings. These graduate students have also gained experience presenting their research in an interdisciplinary group setting at monthly joint **Zangle/Bernard** group meetings and received training by postdocs in the **Bernard** and Welm labs.

In terms of undergraduate student mentorship, nine undergraduate students have worked in the **Zangle** lab during the reporting period. These students were supported through the University of Utah Undergraduate Research Opportunities Program (UROP). As part of this program, each student had to prepare a project proposal and statement of work. UROP students are also required to present their work at a public poster session in an annual Undergraduate Research Symposium. PI **Zangle** also sponsored a project group (involving one UROP student plus two additional chemical engineering undergraduates) for a capstone project in chemical engineering (described below).

How were the results disseminated to communities of interest?

This project was incorporated into an undergraduate capstone project class taught by PI **Zangle**. In this class, groups of chemical engineering seniors are asked to form teams of 2-4 students to solve problems they have identified. In the Spring of 2021, one team of seniors successfully designed and tested a microscope that combines QPM with darkfield microscopy for obtaining more quantitative data about the interaction of samples with light. This has potential future applications in screening compounds based on the morphological changes that occur during treatment in addition to the changes in mass and growth rate that we already screen for with QPM. Final results of this project were presented at a public (virtual) symposium and poster session held on April 1, 2021.

Additionally, this project was presented as an accepted poster at the American Association for Cancer Research (AACR) annual meeting in April 2021, as part an invited talk at a biomechanics retreat held at the University of Florida in October 2021, and as a public seminar hosted by the Department of Chemical Engineering at the University of Utah in October 2021.

Finally, the major results of **Major Tasks 1 and 2** of this project have been submitted for publication and are currently under review (**Milestone 1**). We have also made these results available as a preprint on biorXiv, <https://doi.org/10.1101/2021.11.26.467625> with associated software available at <https://github.com/Zangle-Lab/MultiparametricQPI>. An additional publication describing a data visualization platform for QPM data has also been presented at two conferences (IEEE VIS 2021 and Conference on Intelligent Systems for Molecular Biology) and published as a peer reviewed publication in *IEEE Transactions on Visualization and Computer Graphics*.

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

The manuscript describing the initial results with the QPM system is completed (**Tasks 1 and 2, Milestone 1**). We are presently working on a response to the initial review.

Our (**Zangle/Bernard**) primary work is now using our system to test cells derived from primary samples (**Task 3**). We are working on analyzing data on cells from a set of 5 organoids representing samples collected from two patients (**Tasks 3.6-3.7**). We will also perform patient sample screening with QPM in preparation for a manuscript detailing the comparison of QPM to CTG and clinical outcomes data (**Milestone 3**). This step is essential for future deployment as a clinical test and will inform our further steps towards translation to be determined by the completion of this project (**Task 3.8**).

4. IMPACT:

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

Cancer patients with advanced disease and no available treatment options will often have their tumors analyzed using genetic techniques. This is expensive and usually does not identify better therapies. For these patients, there is no quantitative way to predict how their cancer will respond to therapy fast enough to help doctors choose the best option. Our project uses a new approach based on weighing single cancer cells growing outside the body with light. By weighing cancer cells as they increase in size over time, we directly measure growth. We aim to use this method to observe a patient's cancer cells when treated with possible therapies. This will show us which therapies stop or slow cancer cell growth, suggesting they will likely be effective in the patient.

One key to translating this approach is identifying the expected impact of each therapy in the prospective drug panel. In the second and third years, we have developed methods to characterize the impact of each therapy and cell line combination in terms of four parameters: EC50, depth of response, response time, and heterogeneity of response. These data therefore provide key context for interpreting clinical sample test results in the next phase of this project. We have also validated the use of our instrument on patient-derived cells that are similar to samples that come directly from patients.

We are currently using this instrument to test many different therapies with the ultimate goal of providing options for the most appropriate treatment. Ongoing work includes testing our instrument with cancer cells collected directly from patients with advanced or metastatic breast cancer who have been treated at the Huntsman Cancer Institute. We will then compare our results to the known clinical outcome of each patient whose samples we tested. This will tell us how good our method is at predicting when a patient is likely to respond or not to a given therapy.

The overall potential impact of our project is to reduce patient suffering by reducing unnecessary side effects of ineffective treatments. We also hope to improve survival of breast cancer patients by telling doctors which therapy to use for each individual patient. We have chosen to start with patients who have advanced or metastatic breast cancer because we have the samples available at our institution and this patient population could benefit most from our testing. These patients have typically been through multiple rounds of treatments which allows us to compare our test predictions to how these patients responded in the past. However, the basic idea of our method could be applied to samples from any breast cancer. Ultimately, our approach will support the BCRP's mission of ending breast cancer by allowing doctors to give the right treatment to the right patient at the right time.

What was the impact on other disciplines?

The instrument and methods developed in this project have the potential to apply broadly outside of breast cancer research. This general approach developed in this project can be applied to other solid and blood tumor types. The QPM method and instrument developed in this project period can also be applied to study other basic biological processes that impact human health in immunity, infectious disease, and aging. Among these, PI Zangle has a currently funded sub-project through the NIH/NIAID studying B cell development via QPM that could benefit from the approach developed under this award and is currently pursuing applications in melanoma.

What was the impact on technology transfer?

One of the principal investigators (**Zangle** – initiating award PI) for this project is an engineer who helped develop the method we plan to use. The other principal investigator (**Bernard** – partnering award PI) is a board certified clinical pathologist that serves as a Medical Director for a large pathology reference laboratory that offers cancer testing using methods that he developed and validated. Bernard has also previously developed and commercialized a diagnostic test for breast cancer. As a team, we plan to move this promising technology, based on the results of years 1-3 of this project, into a method that can help patients following award completion.

What was the impact on society beyond science and technology?

The overall goal of this project remains changing the way decisions are made for patients with advanced metastatic disease. The results of this project, which build on the instrument development, validation, and human sample work done in years 1-3, could change the public perception of chemotherapy by making this a more focused approach with fewer side effects due to ineffective treatments.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

We experienced a delay in hiring and a lab shutdown due to the COVID-19 pandemic. This has been resolved and we anticipate finishing the proposed milestones with the remaining unobligated funds. Specifically, we will 1) perform additional QPM testing of cells from previously derived (derivation not supported by this grant) organoid cells; 2) QPM testing of direct from patient samples as described in the original grant; and 3) validation of QPM results relative to clinical histories and previously generated (mouse work not supported by this grant) *in vivo* mouse data.

Changes that had a significant impact on expenditures

There was a delay in hiring a postdoc- for the Bernard lab due to a lack of suitable candidates with the required expertise in growing cancer organoids and performing drug screens. This position was further compromised by the COVID-19 pandemic since our post-doc hire (Dr. Byeong-Il Kang) was from South Korea and was banned from traveling back to the United States. His position has since been filled by Dr. Ozlen Balcioglu who has extensive experience in breast cancer tumor modeling and cell culture. She is capable of performing the necessary work and has assisted with the project in Year 3.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS

Publications, conference papers, and presentations:

Journal publications.

Lange, D., Polanco, E.R., Judson-Torres, R.L., Zangle, T.A., and Lex, A., “Loon: Using Exemplars to Visualize Large Scale Microscopy Data,” *IEEE Transactions on Visualization and Computer Graphics*, 2021, 28. 248-258. doi: 10.1109/TVCG.2021.3114766

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

Nothing to Report.

Other publications, conference papers and presentations.

Polanco, E.R., Moustafa, T.E., Butterfield, A., Scherer, S.D., Cortes-Sanchez, E., Bodily, T., Spike, B.T., Welm, B.E., Bernard, P.S., and Zangle, T.A., “Multiparametric quantitative phase imaging for real-time, single cell, drug screening in breast cancer,” Preprint available at *bioRxiv*, 2021.11.26.467625; doi: 10.1101/2021.11.26.467625.

“Using cell mass to quantify cancer cell response to therapy in time and space,” Zangle, T.A. Invited talk, Biomechanics symposium, University of Florida, October 6, 2021.

Lange, D., Polanco, E.R., Judson-Torres, R.L., Zangle, T.A., and Lex, A., “Loon: Using Exemplars to Visualize Large Scale Microscopy Data,” IEEE VIS 2021, October 24-29, 2021. *Awarded Honorable Mention*

Lange, D., Polanco, E.R., Judson-Torres, R.L., Zangle, T.A., and Lex, A., “Loon: Using Exemplars to Visualize Large Scale Microscopy Data,” 29th Conference on Intelligent Systems for Molecular Biology (ISMB) and the 20th European Conference on Computational Biology (ECCB) 2021, July 25-30, 2021.

Moustafa, T.E., Polanco, E.R., Butterfield, A., Scherer, S., Welm, B.E., Bernard, P.A., and Zangle, T.A., “Real-time single-cell drug response assay in metastatic breast cancer cell lines using quantitative phase imaging,” American Association for Cancer Research Annual Meeting, April 10-15, 2021.

Website(s) or other Internet site(s)

MultiparametricQPI, a github repository containing code associated with this project. Available at: <https://github.com/Zangle-Lab/MultiparametricQPI>

Technologies or techniques

During the reporting period we (*Zangle*) validated a QPM system for dedicated screening of chemotherapies as described in the original project proposal.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

During this third year we developed:

- Methods to analyze the high content data generated by QPM to identify multi-modal measurements of breast cancer cell response to therapy
- Data demonstrating the use of QPM with cells from patient-derived organoids, as a significant step towards direct from patient samples.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Zangle (BC180931)

Name: Thomas Zangle, Ph.D.
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0001-5899-3517
Nearest person month worked: 1
Contribution to Project: Dr. Zangle co-directed the research project including experiment planning, data analysis, QPM development, presentations and personnel supervision.
Funding Support: NIH/NIAID

Name: Edward Polanco, B.S.
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0001-7388-962X
Nearest person month worked: 12
Contribution to Project: Eddie worked on QPM instrument development, cell culture, and preliminary drug screening.
Funding Support: N/A

Name: Tarek Moustafa, B.S.
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0001-5282-8246
Nearest person month worked: 12
Contribution to Project: Tarek worked on statistical modeling of QPM data and calibration of the instrument.
Funding Support: N/A

Name: Kenneth Boucher, Ph.D.
Project Role: Consultant
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0003-2833-0127
Nearest person month worked: 1

Contribution to Project: Dr. Boucher provided support for statistical analysis and power calculations for human subject testing.
Funding Support: NIH/NCI, NIH/NCATS, University of Utah, Pfizer Inc., American Cancer Society, Susan B. Komen Foundation

Bernard (BC180931P1)

Name: Philip Bernard, M.D.
Project Role: Principal Investigator (partner award)
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0002-1418-8521
Nearest person month worked: 1
Contribution to Project: Dr. Bernard led efforts to secure with approvals for specimen handling, oversaw personnel performing “gold standard” measurements, and performed data analysis and project planning.
Funding Support: NIH/NCI

Name: Bryan Welm, Ph.D.
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0002-1879-6612
Nearest person month worked: 1
Contribution to Project: Dr. Welm provided expertise in developing a clinical drug screen, working with patient derived cells, and selection of therapies for the QPM screening demonstration.
Funding Support: NIH/NCI

Name: Ozlen Balcioglu, M.D.
Project Role: Lab Manager
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0003-2782-3763
Nearest person month worked: 3
Contribution to Project: Dr. Balcioglu expanded cell lines for use with the QPM drug screen and performed initial validation of the cell assays. She picked up the duties for Dr. Kang when he was called home to South Korea due to the COVID-19 Pandemic.
Funding Support: NIH/NCI

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report.

What other organizations were involved as partners?
Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Tasks and personnel specific to the prime award, *Zangle* BC180931, and the sub-award, *Bernard* BC180931P1 have been indicated in the report above.

9. APPENDICES:

Nothing to Report.