

AWARD NUMBER: W81XWH-19-1-0066

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

PRINCIPAL INVESTIGATOR: Philip S Bernard

CONTRACTING ORGANIZATION: University of Utah

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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 population response and single-cell heterogeneity. In year 2 we have validated the technical platform for this work with a panel of cell lines and FDA-approved therapies. Overall, our project will provide real-time feedback to oncologists on overall drug sensitivity/resistance and resistant subpopulations.

2. KEYWORDS:

Quantitative phase microscopy, 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 full 26 drug panel on 8 commercially available cell lines (Zangle/Bernard)

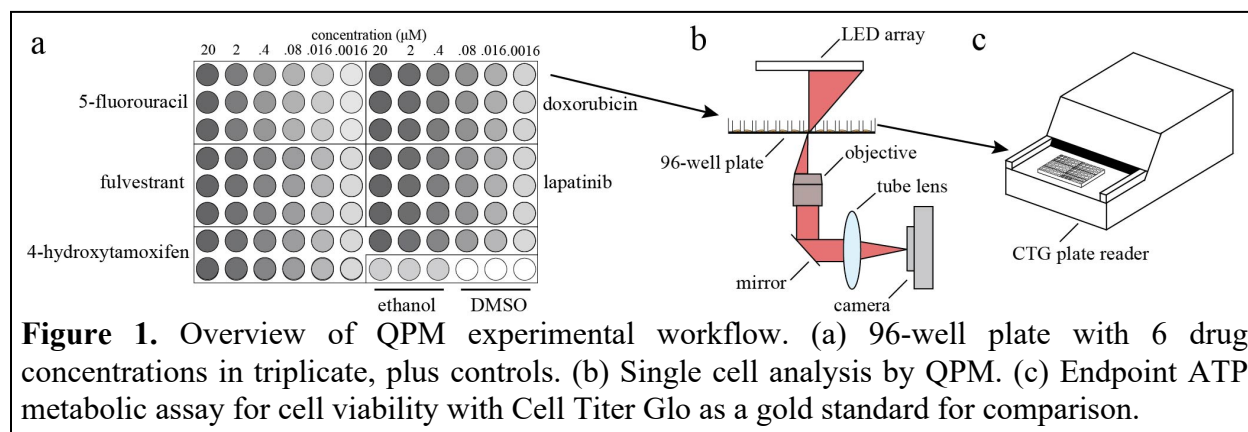
Target completion date: March 2021

Completion percentage: 70%

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 2022

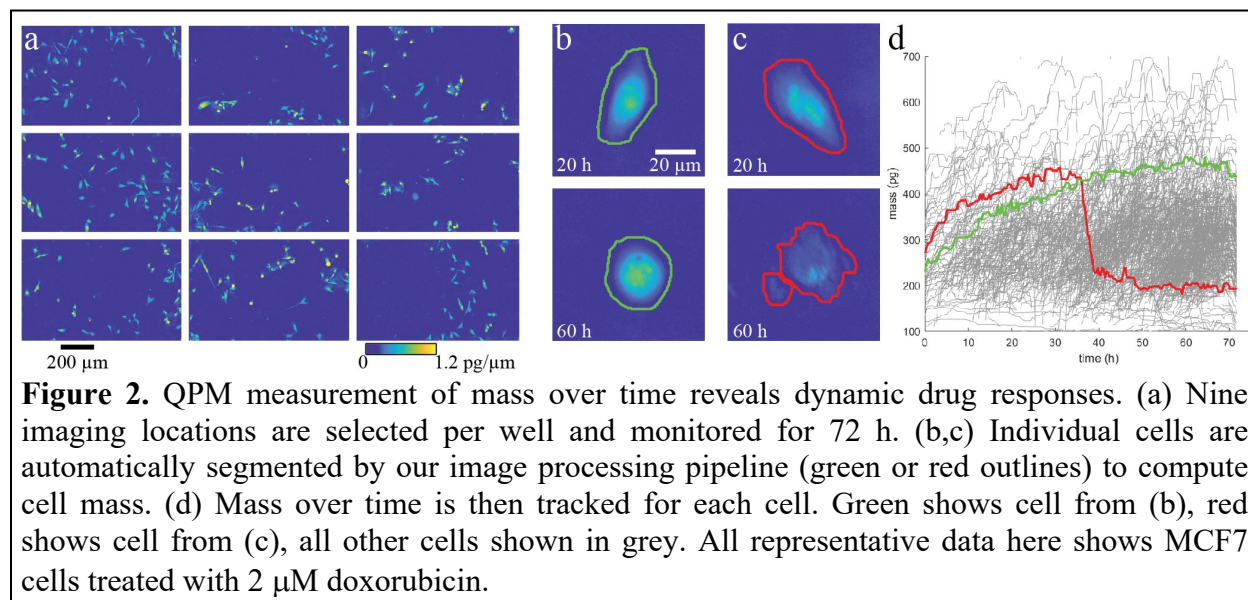
Completion percentage: 15%



What was accomplished under these goals?

In year 2, we (*Zangle*) conducted benchmark testing of the quantitative phase microscopy (QPM) system constructed in year 1. We validated our system by performing a series of screens in a 96-well format. Breast cancer cell lines were plated sub-confluence and treated with drug concentrations from 1.6 nM to 20 μ M with conditions repeated in triplicate, plus triplicate carrier controls (**Figure 1a**). The plate was imaged via our custom-built QPM system once per 20 minutes using the focusing and movement approach (developed in year 1, **Task 1**) at a time of less than 1 second per acquired QPM image (**Figure 1b**). QPM data was acquired for 72 hours to capture the full dynamic response to each therapy (*Zangle*, **Task 2.2**) and for direct comparison to gold-standard Cell Titer Glo (CTG) metabolic endpoint assay results. In parallel with QPM data collection, we performed two CTG measurements per QPM experiment (**Figure 1c**) at 24 and 72 h after the start of imaging (*Bernard*, **Task 2.1**).

During imaging, QPM data was collected at 9 imaging locations per well (**Figure 2a**), for a total of 384 imaging locations per experiment (*Zangle*). This results in mass over time data from approximately 10,000 cells per experiment. From these data, a wide range of dynamic responses can be identified. These include cells that persist, increasing mass even during exposure to high concentrations of chemotherapies (**Figure 2b**) and cells that die during this exposure (**Figure 2c**). These behaviors are evident as a slowing of growth as indicated by a reduced rate of increase of mass over time (green trace, **Figure 2d**), or a dramatic decrease in mass over time accompanying cell death (red trace, **Figure 2d**). We have identified four significant parameters that categorize responses from QPM mass over time data: sensitivity, depth of response, time of response, and heterogeneity of response. Identification and validation of these four parameters is the primary focus of a manuscript in progress resulting from this work (**Milestone 1**).



Sensitivity and depth of response are determined by measuring the average growth rate of individual cells from QPM mass over time data. For each cell, we perform a least squares linear fit to mass over time data. The slope of this line is the cell growth rate. We divide this growth rate by the mass of the cell or cell cluster to yield the specific growth rate. This normalization accounts for variations in growth rate due to cell or cell cluster size, with more mass typically

resulting in a proportional increase in growth rate. The resulting distribution of specific growth rates as a function of drug concentration reveals the dose-dependent response (**Figure 3a**). To compare specific growth rates across populations with variable baseline growth rates, we further normalize specific growth rate relative to control as: $GR = 2^{(SGR/SGR_{control})} - 1$, where GR is the growth rate coefficient and SGR is the specific growth rate (Hafner *et al. Nature Methods* 13(6) 2016 521-527). As part of **Task 2.2**, we then perform four parameter Hill equation (sigmoid curve) fitting to the corresponding dose response curve. The resulting four parameter Hill equation fit is tested against a flat line (no response). If the sum of squared errors from the Hill equation fit is larger than that computed for a flat line, we identify this condition as ‘no response’. For conditions with a better fit to the Hill equation, this fit is then used to extract data on sensitivity as effective concentration 50% (EC50) and depth of response (**Figure 3b**).

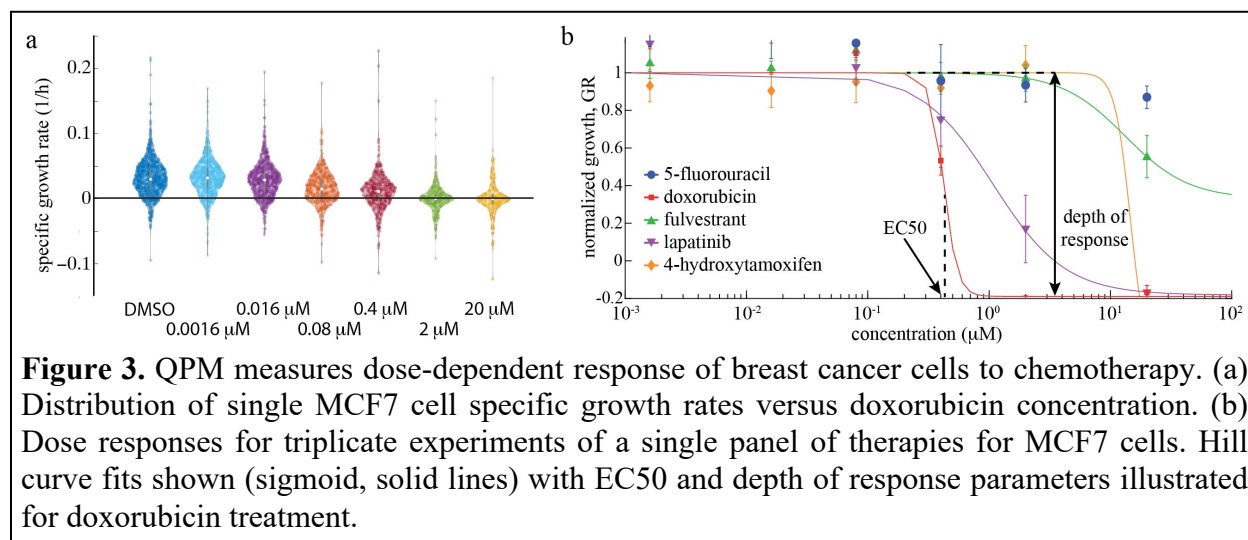


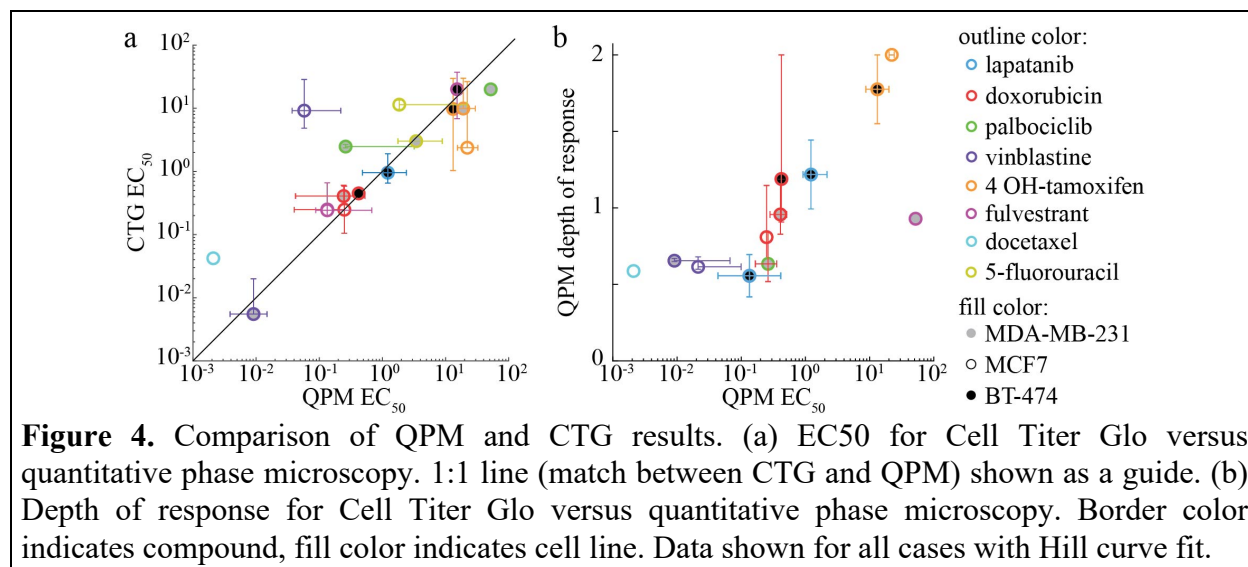
Figure 3. QPM measures dose-dependent response of breast cancer cells to chemotherapy. (a) Distribution of single MCF7 cell specific growth rates versus doxorubicin concentration. (b) Dose responses for triplicate experiments of a single panel of therapies for MCF7 cells. Hill curve fits shown (sigmoid, solid lines) with EC50 and depth of response parameters illustrated for doxorubicin treatment.

We performed dose response measurements for cell lines spanning a range of receptor statuses (**Table 1**) and compounds with a range of different mechanisms (**Table 2**).

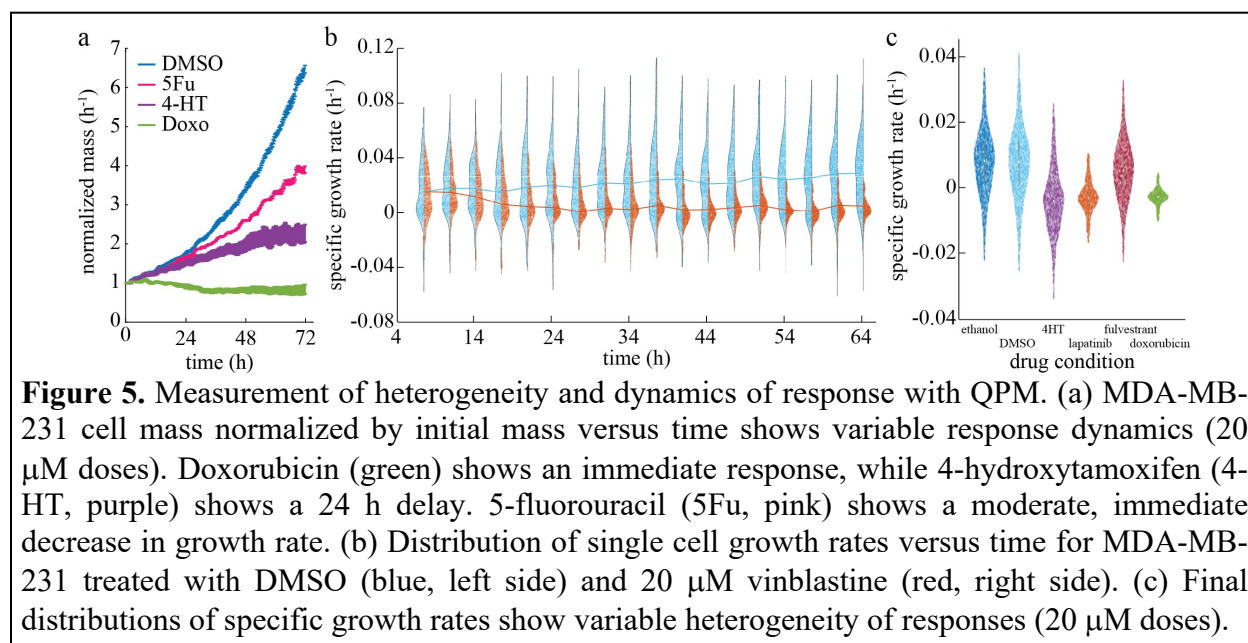
| Cell line | Receptor status |
|------------|-----------------|
| MCF-7 | ER+/PR+/HER2- |
| MDA-MB-231 | ER-/PR-/HER2- |
| BT-474 | ER-/PR+/HER2+ |

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

QPM sensitivity results agree well with the expected EC50 from 72 h CTG results across five orders of magnitude in concentration (**Bernard and Zangle, Task 2, Figure 4a**). These data also show that EC50 correlates with depth of response (**Figure 4b**). The depth of response is a QPM measurement that we associate with cytotoxicity. Therefore, these data suggest that cytotoxic drugs, such as doxorubicin, will have a larger depth of response by QPM and lower EC50.



We have also used our QPM data to model cell drug response in terms of heterogeneity and dynamics of response (**Task 2.3**). One finding from our work in year 2 is that these two factors are directly linked to each other. Population average response changes in concert with cell to cell heterogeneity. Representative time-dependent variation in response dynamics is shown in **Figure 5a**. Some compounds show an immediate response to therapy (ex. doxorubicin), while others show a substantial delay (ex. 4-hydroxytamoxifen). Therefore, key to measuring response has been moving to a 72 h imaging duration for these initial validation experiments. With this data, we have then studied the time-dependent population dynamics (**Figure 3b**). Finally, heterogeneity varies significantly from drug to drug (**Figure 3c**), another parameter we have quantified from QPM data. Characterization and modeling of these parameters is essential for interpreting future clinical response data. Crucially, we have also demonstrated the ability to detect non-responders (ex. upper population at 64 h in **Figure 5b**) which may indicate emergence of drug resistance.



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. We have now procured approximately 35 metastatic breast pleural effusions. 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**). 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 started testing a variety of substrate-coated plates, including matrigel, laminins, fibronectin, gelatin, and poly-ornithine; in order to optimize growth conditions for each sample prior to drug screening (**Task 3.4**). Supplements include varying FBS amount and adding growth ligands, such as estradiol for ER+ tumors.

Moving towards the eventual 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 2, 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, six 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 + 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. As part of the project selection process, in December 2020, PI *Zangle* presented the concept of precision medicine screening to the senior class in chemical engineering (65 students). One team of three seniors selected this project direction. During the spring semester this team 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. These students then presented their project results to the class in a series of formal presentations. Additionally, final results of this project will be presented at a public (virtual) symposium and poster session held on April 1, 2021.

Additionally, this project was presented as an oral presentation at the American Institute of Chemical Engineers meeting in November, 2020. We also plan to present this work as an accepted poster at the American Association for Cancer Research (AACR) annual meeting in April 2021.

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

With data collection for our drug panel validation completed, our (*Zangle*) next immediate task is to finish writing the manuscript detailing these results (**Milestone 1**). The depth of the data we have collected in this project far exceeds that of previous studies of QPM. Our analysis has already revealed key performance criteria that will inform future clinical applications, for example, demonstrating the importance of defining the time of response. Defining the roles of the four parameters we can pull out of QPM data on cell growth in response to therapy is an exciting step and key to future applications.

Along with this, we (*Zangle/Bernard*) are now turning our system to cells derived from primary samples (**Task 3**). We have begun testing plating and cell culture conditions based on the key expertise of our collaborator Welm. The immediate next step here will be validating these results with QPM. During this step, we will also acquire data on the early stages of primary cell growth that has broader relevance for optimizing other functional precision medicine assays. Beyond this initial work, we will ramp up 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.

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 year, we have measured 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.

In the future we will use this instrument to test many different therapies so we can provide options for the most appropriate treatment. Then we will then see how well our approach does with cancer cells collected directly from patients with advanced or metastatic breast cancer who have been treated at the Huntsman Cancer Institute. We will 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.

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 1-2 of this project, into a method that can help patients within the next five years.

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 and validation work done in years 1-2, 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

In early experiments comparing QPM to CTG, we stopped imaging at 24 h. However, we noticed that this timeframe was not sufficient for all compounds to demonstrate a full response. For example 4-hydroxytamoxifen shows a roughly 24 h delay before the start of impacts on cell growth (**Figure 5a**). We hypothesize this delay is related to drug mechanism. We have therefore moved to 72 h experiments for initial characterization of QPM drug responses. These results will help us to find the optimal timeframe for acquisition to improve our diagnostic accuracy in predicting drug response. For example, in future applications, we will consider imaging ‘early’ responding drugs during incubation with ‘late’ responding drugs to minimize the time required for measuring drug response by QPM while optimizing data collection.

Additionally, we have added time of response as a new parameter to be extracted from QPM data. We have noted that this parameter is highly variable from drug to drug and linked to measurement of cell-to-cell heterogeneity (**Figure 5**). We therefore believe this parameter is key for interpreting QPM results with a drug panel that spans multiple mechanisms of action.

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

The move to a 72 h QPM assay reduces the number of imaging experiments that can be performed. We have therefore limited the panel of compounds so that data can be collected by running two 96-well plates while still spanning a wide range of drug mechanisms (**Table 2**). We have also reduced the number of cell lines for initial testing in **Task 2** to 3 (**Table 1**), covering a range of receptor statuses. This tradeoff, however, is crucial given the importance of time of response to interpreting QPM results and the impact of differential drug mechanisms. As noted above, we plan to optimize future applications of QPM based on the response times we have measured with the data from year 2.

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. We feel she is capable of performing the necessary work.

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.

Polanco, E.R., Griffin, J., and Zangle, T.A., “Fabrication and bonding of refractive index matched microfluidics for precise measurements of cell mass,” *Polymers*, 2021, 13. 496.

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

Nothing to Report.

Other publications, conference papers and presentations.

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,” Accepted to American Association for Cancer Research Annual Meeting, April 10-15, 2021.

Polanco, E.R., Moustafa, T., Bodily, T., and Zangle, T.A., “Measurement of cancer cell drug response with quantitative phase imaging,” American Institute of Chemical Engineers (AIChE) 2020 Annual Meeting, November 16-20, 2020

Website(s) or other Internet site(s)

Nothing to Report.

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 second year we developed:

- Validation data for the QPM instrument as described above and in the original project proposal.
- A dataset consisting of repeated 72 h dose response experiments with three breast cancer cell lines to a panel of 9 FDA-approved chemotherapies. These data will be used to demonstrate the capabilities of QPM for multi-modal analysis of cancer cell therapy response and to benchmark QPM for application to clinical 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: 4
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: Byeong-Il Kang, Ph.D.
Project Role: Postdoctoral fellow
Researcher Identifier (e.g. ORCID ID): ORCID: 0000-0001-6208-501X
Nearest person month worked: 1
Contribution to Project: Dr. Kang expanded cell lines for use with the QPM drug screen and performed initial validation of the cell assays.
Funding Support: N/A

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.