Effect of Drug Resistance in Breast Cancer Models

Ryan Zhang, Alazar Izkinder

Abstract

Several mathematical models have appeared for usage in simulating the effects of treatment cycles on breast cancer. While effective in modeling the theoretical and sometimes experimental data of the treatment, the models may fall short of real therapy due to the lack of resistance measuring. To demonstrate the potential for resistance modeling in breast cancer models, we first analyzed an existing model and then applied the resistance to the relevant equations. We showed that resistance can be modeled in multiple drugs, and highlighted the potential for combination therapy modeling, with each therapy having a unique resistance level. We also demonstrate the importance of drug schedules and the need for a potent itinerary that takes advantage of resistance decays and slow resistance growths, ideally to avoid any significant resistance effects at all. While research is not complete, continued efforts can be made to better fit the parameters of the added resistance and identify more experimental data.

Background

The effects of breast cancer are characterized by widespread and uncontrollable growth of cells in the tissues of the body, starting from breast cells. The disease progression ranks from I-IV in a person and is the most common form of cancer in women. The severity of breast cancer has made it an important area of study in cancer, and most traditional treatment methods can be applied to it. These include drug therapy, including chemotherapy which involves deadly chemicals used to kill the cancer, ICI (Immune Checkpoint Inhibitors, or Fulvestrant) drugs which block immune checkpoint inhibitors, and hormone therapy. In addition to this type of therapy, there is radiation therapy, such as mammosite brachytherapy, and direct surgery, which for breast cancer includes but is not limited to lumpectomies and single/double mastectomies.

These treatments are very experimental and are constantly being innovated. One such method to explore these treatments is with mathematical models, which simulate the effects of the treatment on important proliferators or inhibitors of breast cancer. These models should be complex, and able to account for the effects of various treatments and intertwining treatment schedules at the same time. The usage of drug therapy is one treatment that is particularly well modeled, due to its chemical nature. Its models can also incorporate schedules and doses, which is another reason why the use of mathematical models for this treatment is especially effective.

Of breast cancer cases, 70% are oestrogen receptor positive. One model that effectively models this type of breast cancer is a paper by Wei He et all, which specifically covers 3 types of drug

therapy. These are ER deprivation ER-, (a hormone therapy), the introduction of an ICI, and the usage of palbociclib. The paper not only models each one's effect but them combined. The constructed model involves 14 variables, and, although a huge simplification from the biological model, effectively models the effects of these treatments on breast cancer [1].

We chose to do our research on the paper as a foundation because it was the cutting edge in breast cancer modeling research. It mentions how their model differs from other existing models because it is experimentally calibrated and validated. In addition, it provides necessary tools, such as Matlab code, to build upon, as well as detailed explanations of how they obtained their parameters, built their mathematical model, and tested it for accuracy, such as with sensitivity tests.

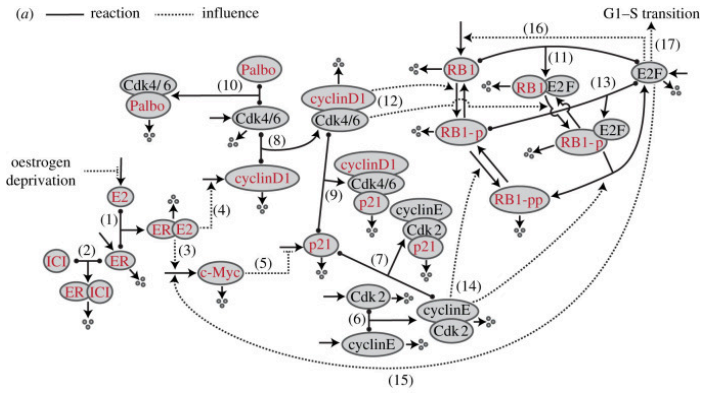
Another reason is that resistance is a key focus of this paper. Acknowledging the development of resistance, the paper comments on how the model can be used for this very purpose, and that this is one of the key factors in the recurrence of cancer [1]. The model includes some work on resistance to palbociclib, although does not show its combined effects with resistant ICI or ER- therapies.

In our research, we attempt to model the introduction of resistant ICI and see its effects when paired with resistant palbociclib. Our hope is that this can create potential treatment schedules that could be revealed through mathematical modeling. In addition, we could also model resistance to ER- and pair it with the others. We must also acknowledge that real systems are far more complicated than our resistance models, and likely involve thousands of moving parts which cannot be completely modeled.

Reading [1]

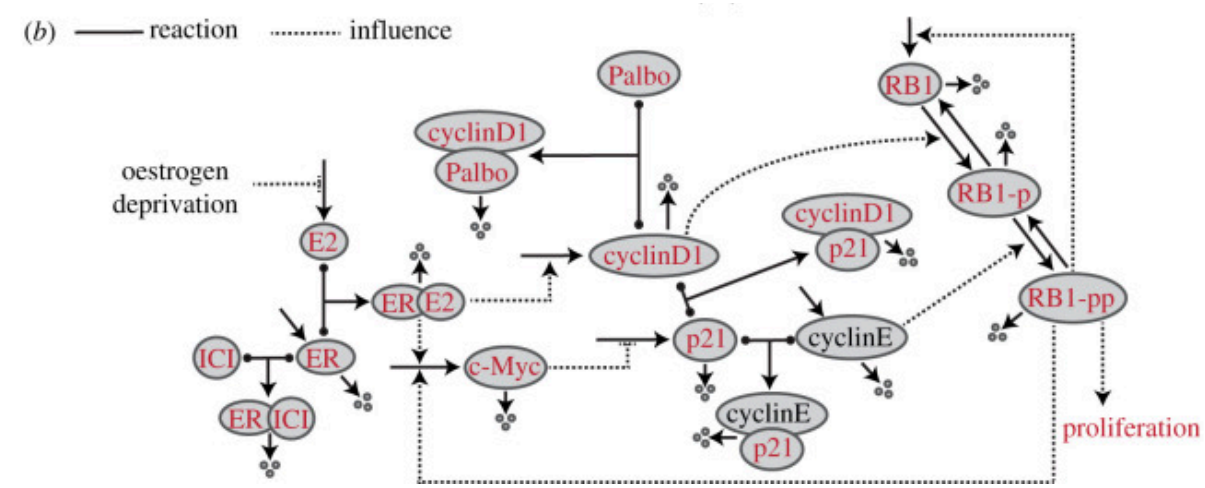
The research involved in this paper heavily relies on the models created by another paper, *Mathematical modeling of breast cancer cells in response to endocrine therapy and Cdk4/6 inhibition* by Wei He et all. As such, it is of importance that necessary parts of this paper be properly analyzed and understood for the purposes of this research. While this section will involve lots of coverage on important parts, it will not be a full overview and so reading of the original paper is recommended.

The paper begins by creating a model for the breast cancer system, starting from ER and going to RB1-pp. The model uses two important factors: experimental data, which was obtained from others, and parameters obtained from a genetic algorithm fitting the equations to the aforementioned experimental data. These will also be important tools in our own research.



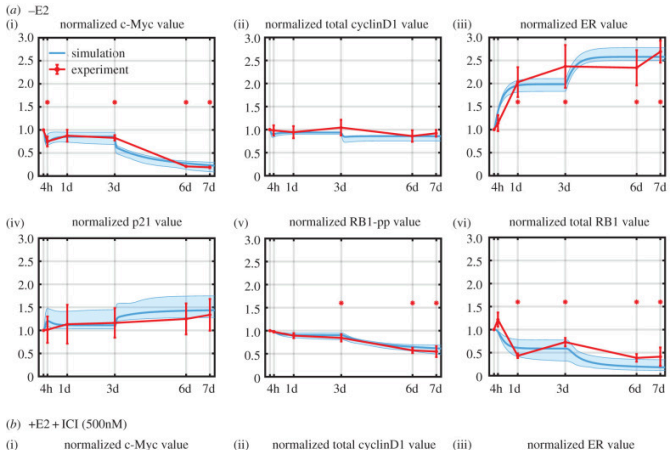
The equations were determined based on the biological model, which is shown to the left. The general model follows the proliferation starting from the binding of E2 and ER.

While the figure on the top is the biological model, the one below is the mathematical model. It simplifies the biological model greatly, allowing for more streamlined simulation. The three treatments are the introduction of ICI, which binds with ER and therefore removing it from the proliferation cycle, oestrogen deprivation with inhibits the production of E2, and Palbociclib, which effectively binds with cyclinD1, helping neutralize it. In this model, RB1-pp represents proliferation of the cancer.



To explain the model, the three main parts of the proliferation, or increase of normalized cell count, are the binding of E2 and ER, which then leads to the activation of cyclinD1 synthesis which finally brings the activation of RB1-pp synthesis. Each of these involve several interactions, but these 3 are the main areas which the treatments target.

After creating the model on Matlab, the model simulation vs experimental data graphs were generated. This is the result:

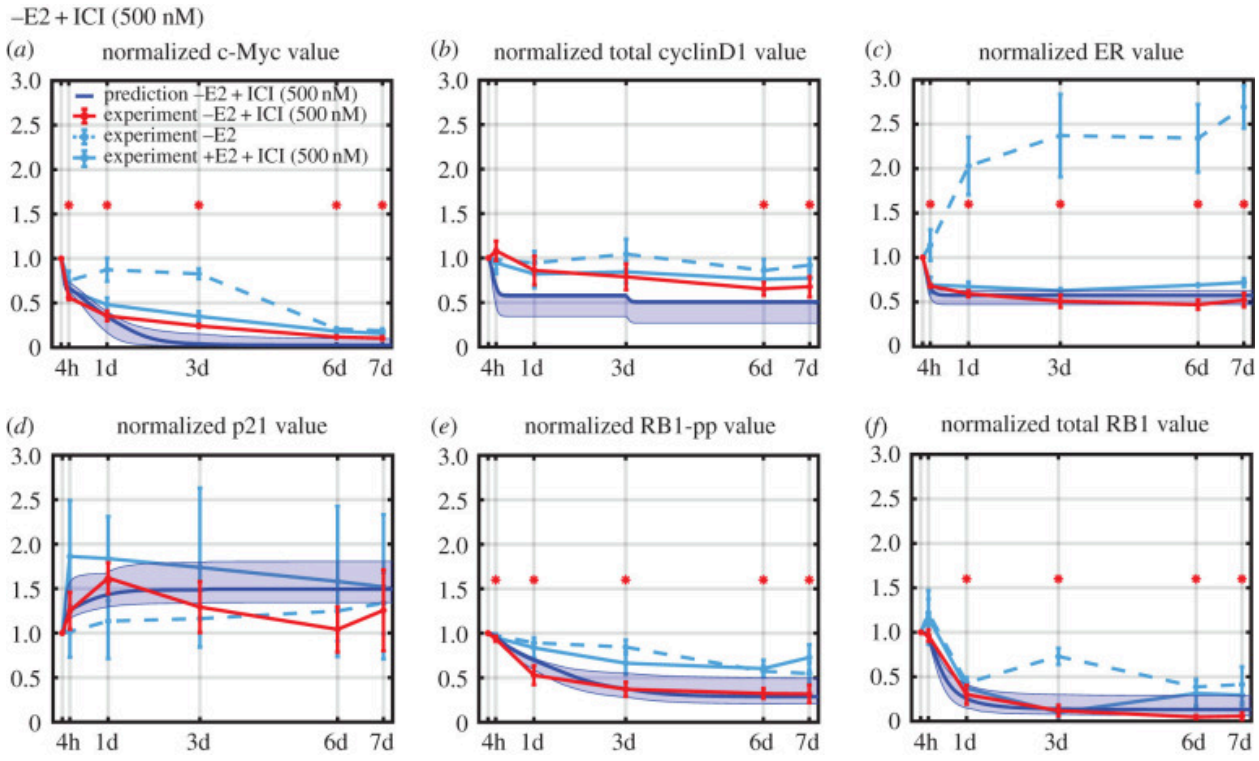


The resulting graphs show very accurate simulation results which accurately reflect experimental results. One aspect of our research is to obtain experimental results that reflect resistance in ICI, which we will

then use in a similar way to compare simulation vs experimental results.

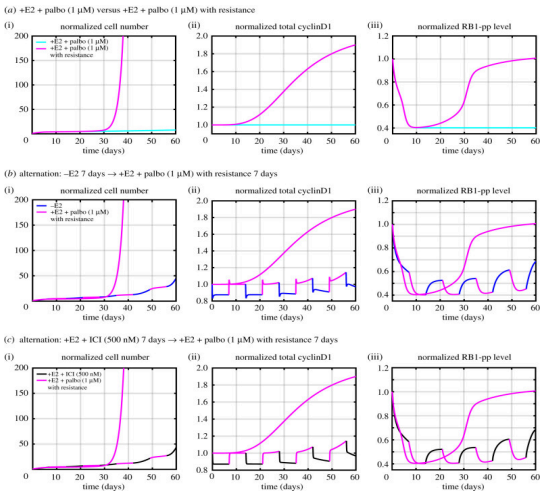
The reflection of the experimental results with the simulation results is in part due to the genetic algorithm, which our research will also use in the future to acquire proper parameters for modeling ICI resistance.

The paper goes on to discuss the addition of palbociclib, which the paper focuses on, but our research does not. Importantly, the effects of combined therapy was also tested during the paper, and the results are shown below:



In our research, we also plan to show combination therapies, where we will compare nonresistant therapies to resistant ICI. In addition, we will need to obtain experimental data on combination therapies involving resistant ICI. This will likely involve obtaining data or all the therapies, resistant and non resistant, and their interactions and combinations with the others.

The key aspect of the paper was their modeling of resistance to palbociclib, their introduced drug. They mention that the addition of the drug was for the purposes of testing resistance. To test resistance, they introduced another term to the CyclinD1 equation and added a resistance variable. These were made using a hill function to model the slow growth of resistance and its capping at a certain point.



They then set the parameters and ran the same graphs again, this time obtaining results far off from the nonresistant experimental data.

The graphs all demonstrate how resistance leads to expanded proliferation. However, they also model the effect of a combined therapy involving a drug treatment schedule involving alternating ICI and palbociclib. This takes advantage of resistance going down over time while the drug is not active.

$$\frac{dres}{dt} = par1_{res} \times palbo - par2_{res} \times res$$

However, this drug treatment schedule assumes no ICI resistance, resulting in the stark contrasts seen in the graph. In our current and future research, we will see how introducing ICI resistance changes these graphs, and a better-adapted drug treatment schedule could account for this resistance, possibly involving all three mentioned therapies.

Methods

M.1 - Code Editing

We obtained the code from the paper, and edited it to include new Matlab code for the modeling of ICI resistance. For the equation used, we took the same equation as the original, and used it for ER. Thus, we added our new term to dER/dt because it reflects the addition of their Palbociclib resistance term to dCyclinD1/dt.

This way, since it is parallel to the original paper, it should model in a similar way resistance to a treatment like the palbociclib resistance modeled. Below is the added equation to Matlab:

```
% ER and ICI
dER = k_ER - kd_ER * ER... % translation and degradation
    - kb_E2ER * E2 * ER + kub_E2ER * E2ER...  % bound unbound with E2
    - kb_ICIER * ICI * ER + kub_ICIER * ICIER... % bound unbound with ICI
    + res3 * ( (res^res5) / (res4 ^ res5 + res^res5) ); %resistance equation
```

We added the term at the end similar to the paper, and used a hill function. In the term, "res" is the equation of resistance itself, res5 is the Hill coefficient, res4 is a constant which affects where the hill function plateaus, and res3 affects the magnitude of the effects of the resistance.

In addition to this, we also added the resistance equation itself as a differential equation, to reflect the change in resistance as the drug dosage goes up and down, and as time passes. It was written similarly to how the resistance to palbociclib was written to make use of the parallel structures. Below is how we wrote it:

$$\frac{dres}{dt} = par1_{res} \times \text{ICI} - par2_{res} \times res$$

Here, par1 represents the rate at which resistance grows concerning the amount of ICI, and par2 represents the rate at which resistance decays involving the current amount of resistance.

M.2 Parameter Estimation

During this stage of the research, we have not yet included resistance to palbociclib like the paper did, and are focusing on reproducing the resistance in the paper except for ICI. However, the greatest challenge was choosing the parameters to use for the ICI resistance model. The original paper had several parameters for Palbociclib resistance, but these could not be applied in the same way or magnitude. As such, we experimented with different parameters to attempt to recreate the graphs from the original paper.

The original paper used these values for their parameters
res1 = 1e^-4
res2 = 1e^-3
res3 = 0.819
res4 = 0.06
res5 = 4.87

These won't fit for ICI, however, so we edited them to make them fit better with ICI's numbers. The results of this is below:

```
% resistance
res1 = 1/((2.71828)^2); %e^-2
res2 = 1/((2.71828)^0.5); %e^-0.5
res3 = 5; % Resistance Coefficient
res4 = 0.15;
res5 = 12; %Hill Coefficient
```

In the future, parameter estimation can be mathematically perfected with the use of a genetic algorithm that will use either experimental data or the curve of the paper's palbociclib graph.

Other methods could potentially be used as well, or parameters could be found directly from another paper that studies ICI resistance.

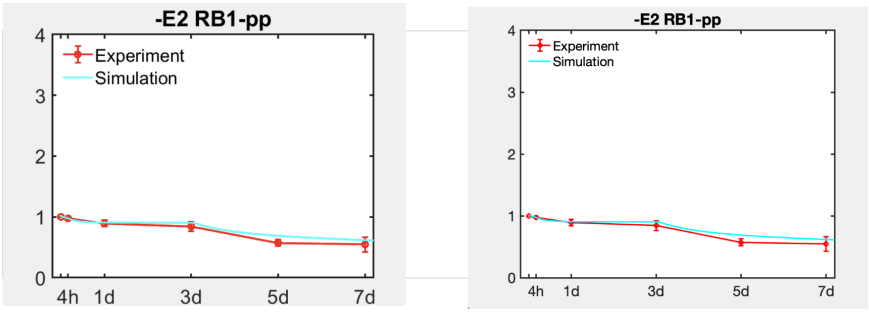
M.3 Combinational Resistance

We did not reimplement the resistance of cyclinD1 to palbociclib to the model as the paper did. Our research focused on ICI resistance for now. However, the addition of palbociclib resistance will certainly be important for creating the graphs we want to use for comparisons and building schedules.

Results

R.1 - Control

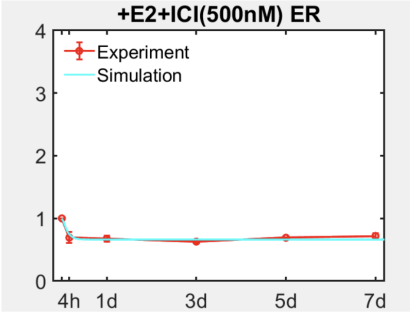
While the actual graphs are not exactly similar, they demonstrate increased proliferation and decreased effectiveness of the treatment. First, we confirmed that E2- was not affected by modifications to ICI. This is for confirmation the resistance is affecting the right parts of the system and not spilling over into the wrong parts. The results are below:

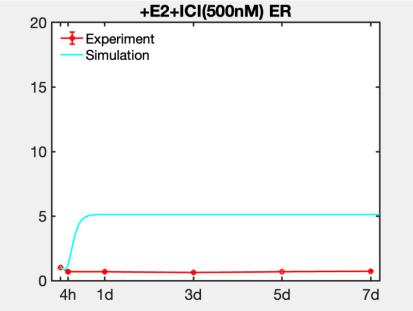


R.2 - ICI Resistance Results

The localized effect of resistance to ICI is what we focused on for now, but in the future we plan on also modeling resistance to oestrogen deprivation. The unchanged graph does not stray very far from the non-resistant experimental results and are practically the same as the original paper's graph looked.

The most direct chemical affected by ICI resistance is ER, which is what it binds with. With resistance to ICI, ER should go up. This was reflected in our experiment:

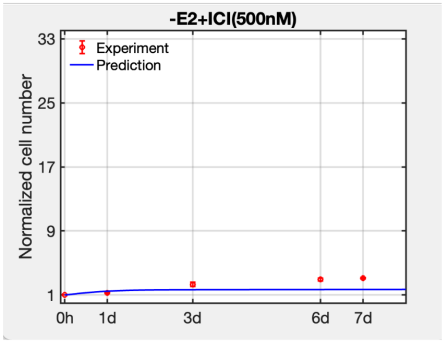


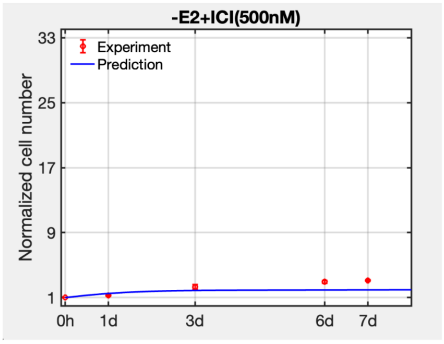


Our set parameters lead the E2 to plateau around 5, but these values could be further fine-tuned depending on what experimental data shows.

R.3 - Combination Therapies

Although we did not model oestrogen deprivation resistance yet, we attempted to model the impact of just ICI resistance on the model for combined -E2 and ICI therapy. It did not make much of a difference, although still increased normalized cell number by a marginal difference (around 0.5).





The result confirms that if one of the therapies does not have resistance, suppression of proliferation is still very effective even with that one alone. This means that a three-way drug treatment schedule could be extremely effective in mitigating resistance, as only one of the drugs may be needed to suppress proliferation as a whole.

R.4 - Palbociclib Combination

We did not experiment with palbociclib resistance as the paper did, but we suspect that the combination of two resistant drugs will not have much effect on the proliferation unless a good drug schedule is adopted. As such, more research in this area is recommended and is what we will likely focus on in the future.

As suggested earlier, this drug schedule will likely need to also involve -ER in order to be effective. Therefore, resistance will also need to be introduced properly to -ER to test the effects of resistance to all three and what schedule is needed. This will also need to be experimentally validated. In addition, ER- may also prove more challenging to model, as it uses an inhibitory mechanism instead of directly binding with a proliferating chemical such as ER or CyclinD1.

Discussion

Our research shows that ICI can be modeled similarly to palbociclib in how resistance affects the system. Specifically, it showed the increase in ER similar to how CyclinD1 increased in the paper. In addition we showed that the normalized cell count steadily increases with the resistance while staying flat without, and demonstrated that one therapy is very effective alone, drowning out the effects of the resistance on ICI almost entirely. Lastly, we also commented on the potential improvements in parameter estimation for the ICI resistance.

In addition to current research, future work is quite abundant. While the foundation is clear, there is a lot of work to be done in three main areas. The first is to properly tune the parameters and to obtain experimental data for both individual resistant ICI treatment and also combined resistance ICI treatment with both resistant and nonresistant ER-, as well as with Palbociclib. Fortunately, the paper discusses how it is easy to expand on the existing data in the model with little new data and still create a very functional model.

The second main area of future research is to model the effects of different combinations, first with just ICI alone, and then combined with some, or all of the other discussed therapies, resistant and non-resistance. This will reveal which ones are most potent, and which resistances are fastest growing/slowest decaying. It will also reveal whether resistance makes a significant difference in ICI and ER- therapy or not.

Finally, we will utilize these results to build a drug treatment schedule and model the alternation between the two or maybe all 3 therapies to see if it effectively combats the growth of resistance and takes advantage of resistance decay. To do this, the timeframe will likely need to be expanded beyond 7 days. Our hope is that this schedule takes advantage of the resistance decay times enough to effectively act like a resistance-free treatment and avoid the worst effects of the resistance buildup.

The main goal of this research is to build on what the original paper suggested was one of the main concerns with breast cancer, its resistance development, and test the model's ability to reflect resistance in some or all drugs at the same time. Same as in the original paper, more research after we are complete with the above will be needed to confirm the practical viability of the model and its long-term potential.

In addition, the oversimplification may get too amplified as the original paper already used many simplifications to ensure the model did not get too complex to build. Adding on top of the model may prove challenging as these simplifications may eventually complicate the results of adding resistance on top of the model's interactions. It could also be noted that resistance to ICI and ER- may prove to be insignificant or impractical to measure, in which future research may also be impeded.

There are also difficulties in the modeling or resistance that will need to be further investigated. There are different kinds of resistance, intrinsic and acquired, and each will need to be modeled differently. For our research, we assumed it is acquired, but this may not necessarily be the case, or perhaps is only sometimes the case. Also, there is no uniform model for resistance, meaning that testing resistance is not easy, and finding reliable experimental data is difficult. Experimentally testing for resistance is also not easy and involves several techniques, including Fresh Cell Culture Tests, Cancer Biomarker Tests, Positron Emission Tomography, and many others. Testing for specific therapies with non-resistant cells and all the combinations needed for future works to have reliable experimental data will be difficult to do on a large scale and reliability will always be a concern.

References

[1] He W, Demas DM, Conde IP, Shajahan-Haq AN, Baumann WT. Mathematical modelling of breast cancer cells in response to endocrine therapy and Cdk4/6 inhibition. J R Soc Interface. 2020 Aug;17(169):20200339. doi: 10.1098/rsif.2020.0339. Epub 2020 Aug 26. PMID: 32842890; PMCID: PMC7482571.