
ABSTRACT FACE PAGE

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11. **Is this the research presented in this abstract supported by IMAG MSM-related U01 funding? No**
12. **If the Presenting Author is a trainee, who is the trainee's primary research advisor? Ioannis Zervantonakis**

TRAINEE POSTER AND ORAL PRESENTATION COMPETITONS:

New to the meeting this year, we are holding *both* a trainee poster competition and a trainee oral presentation competition! If the presenting author is a trainee (i.e., a student at any level or a post doctoral trainee), he/she may enter his/her abstract in the trainee poster competition, the trainee oral presentation competition, or both competitions. Trainees may also submit more than one abstract to the meeting and enter more than one abstract in these competitions. Prizes will be given to the presenters of the top-ranked trainee oral presentation and the top-ranked trainee poster (judged during the meeting by the Program Committee).

13. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Poster Competition*? Yes**

*Note: Trainees who enter the poster competition are expected to stand by their poster during the scheduled poster sessions and present them to the judges.

14. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Oral Presentation Competition**? No**

**Note: The Program Committee will select the top four abstracts from trainees who elect to enter their abstract into the trainee oral presentation competition, these four trainees will be notified by Feb. 17th, and they will deliver their oral presentations (which will be judged) on the second day of the meeting after lunch.

A Predictive Model of Stromal Fibroblast-Mediated Drug Resistance in HER2+ Breast Cancer

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BACKGROUND: The tumor microenvironment can mediate tumor development and drug resistance through a myriad of mechanical (extracellular matrix) and chemical (growth factor/cytokine) signals. Drug resistance is a major challenge in patients with HER2 overexpressing (HER2+) breast cancer, which accounts for ~20% of all breast cancer cases [1]. Many of these patients (38-75%) do not respond to HER2 targeted therapies [2]. Fibroblasts are a prominent cell type found in the tumor microenvironment that are linked to poor patient prognosis and tumor drug resistance. A recent study has found that fibroblasts co-cultured with HER2+ tumor cells prevent tumor cell death and increase tumor cell proliferation in the presence of a HER2 inhibitor (Lapatinib). Fibroblasts confer this resistance through increased anti-apoptotic protein expression and PI3K/Akt/mTOR pathway activation in tumor cells; however, this resistance can be modulated by altering the number of tumor cells, number of fibroblasts, and drug concentration *in vitro*. A temporal model of tumor cell viability and death is developed to explain the effects of fibroblasts and Lapatinib on the dynamics of tumor cell growth.

METHODS: The dose-response characteristics of several HER2+ breast cancer cell lines (EFM192, HCC202, HCC1419, and HCC1954) was assessed *in vitro* in monoculture and co-culture with stromal fibroblasts derived from either primary tumor or metastatic sites (AR22, Wi38, 3T3). Dose response assays were conducted in 96-well plates. Tumor cells express nuclear-localized *H2BGFP* and Ethidium Bromide was used to identify dead cells. Cells were imaged every four hours for 96 hours using fluorescent microscopy. Tumor cells and fibroblasts were seeded in various tumor cell:fibroblast ratios (1:1, 1:2, 1:4) and drug doses ranging from 0.003 [nM] to 3 [μM]. The ODE-based model describes the impact of fibroblast cell count and drug concentration on the temporal viability of tumor cells. The model is trained using these experimental live and dead tumor cell data.

RESULTS: Lapatinib reduces tumor cell viability for all drug concentrations relative to the control (DMSO); however, co-culturing with fibroblasts "protects" tumor cells by reducing the cytotoxic effects of lapatinib at all drug concentrations. Greater fibroblast seeding density appears to increase the level of protection and tumor cell:fibroblast ratios of 1:1 and 1:2 convert drug dose that are cytotoxic in monoculture to cytostatic in co-culture. The model predicts the tumor cell dynamics for a variety of drug dose and fibroblast co-cultures. The model predictions are used to quantitatively determine which combinations of tumor cell density, fibroblast density, and drug dose prevent tumor cell death compared to monoculture.

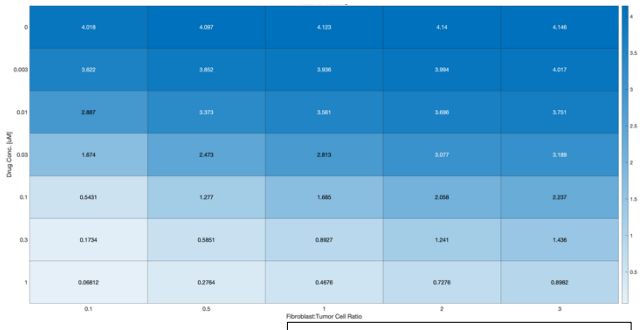

Figure 1: Predicted tumor cell viability after treatment with Lapatinib for 96 hours. Cell count is normalized to t=0.

CONCLUSIONS: Co-culturing HER2+ breast cancer cells with stromal fibroblasts reveals that fibroblasts protect tumor cells from the cytotoxic effects of HER2-targeted therapy. A computational model was developed to predict which conditions may protect these cells. A quantitative understanding of how stromal cells may protect tumor cells may lead to insight into why some patients develop drug resistance to HER2-targeted therapies; as patients respond to therapy, the microenvironment may adapt to favorable tumor cell and fibroblast conditions that yield these protective effects. Ultimately, a comprehensive understanding of this stromal influence may inform clinicians of when to switch to alternative or combination therapies to combat drug resistance.

REFERENCES:

1. Berns, K. et al. *Nature* **428**, 431-437 (2004).
2. Carey, L.A. et al. *Journal of Clinical Oncology* **34**, 542-549 (2016)

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