

UNDERSTANDING TUMOR-IMMUNE-DRUG INTERACTION THROUGH THE EFFECT OF HSP90 INHIBITOR ON IMMUNOCOMPETENT HUMAN UTERINE ADENOSARCOMA PATIENT-DERIVED TUMOROIDS UNDER VARIABLE OXYGENATION CONDITIONS

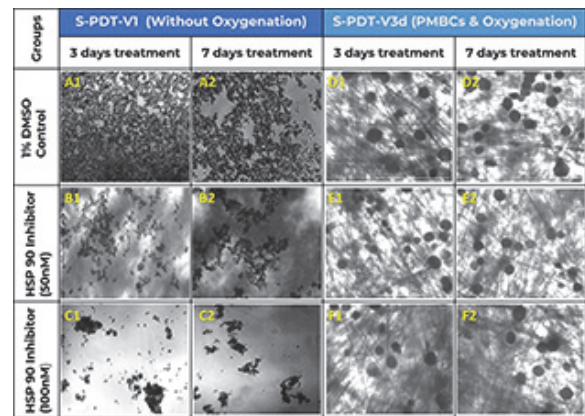
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Background Successful drug screening ultimately relies on highly representative therapeutic testing models. In addition to the regulation of the resident tumor cells, regulation of immune evasion involves tumor microenvironment (TME) parameters such as extracellular matrix (ECM), cell-matrix interactions, growth factors, cytokines, and oxygenation, all have an impact on the tumor and its treatment. Recapitulation of TME in terms of immune and oxygenation states allows for a comprehensive assessment of the impact of the drug. For a thorough evaluation of the drug effect under physiologically relevant conditions we investigated the role of heat shock protein 90 inhibitor (HSP90i) in Human Uterine Adenosarcoma Patient Derived Tumoroid that has immune and oxygen components of TME. We hypothesize that evaluating the drug's impact without the presence of immune system and oxygen status prevents omitting critical information of clinical relevance.

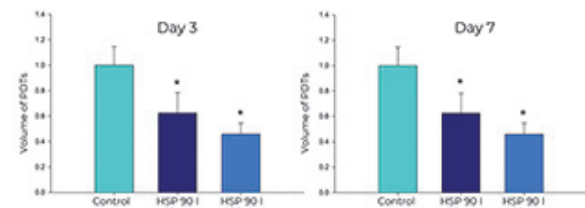
Methods Human Uterine Adenosarcoma models were prepared across two types of 3D immunocompetent PDT-Scaffold-based platforms: 1) S-PDT-V1(Matrigel based model without oxygenation) and 2) S-PDT-V3d (PBMCs with oxygenation). The previous is based on a static, apical oxygenation only set-up, the latter involves a dynamic, matrix-liquid-liquid interface via an in-well perfusion system with the aid of synthetic hemoglobin. The addition of activated peripheral blood mononuclear cells (PBMCs) adds an allogenic immune system to the model. Each model system has three treatment groups: a) Control, b) 50 nM HSP90i, c) 100 nM HS90i. Comparative histological assessment (tumoroid volume) was carried out via phase contrast imaging initially on Days 1, 3 and 7. Statistical analysis was done using One-way ANOVA for significance (* $p < 0.05$), $n = 3$

Results Tumoroid morphology results indicate an overall slower growth rate for tumoroids in dynamic models compared to static ones. The HSP90i reduces tumor volume in the S-PDT-V1 (figures A1-C2 and 2). When we treated the dynamic HSP90i within S-PDT-V3d, tumor volume reduction was not observed (figure D1-F2 and 3).

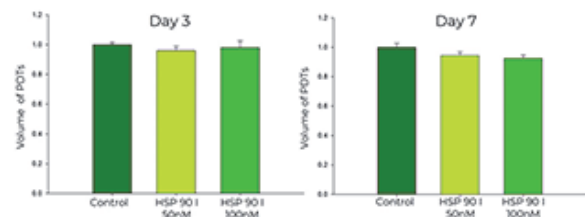
Conclusions To better evaluate the impact of drug treatment it is necessary to perform experiments under conditions that account for physiology of the tumor. The differences in effect of the same drug observed on our different model platforms suggests that a physiologically accurate model platform adds to understanding the drug's impact. The oxygenation status in an immunocompetent model provides a critical influence that would not have been observable otherwise. These model systems offer a new tool in the broader drug discovery process by enhancing our understanding of the complex tumor-immune-drug interactions.



Abstract 130 Figure 1 Impact of PBMCs and oxygenation on the efficacy of HSP90–1 treatment. A1-A2) Static, Control Group; B1-B2) Static, 50nM HSP90–1; C1-C2) Static, 100nM HSP90–1; D1-D2) Dynamic, Control Group; E1-E2) Dynamic, 50nM HSP90–1; F1-F2) Dynamic, 100nM HSP90–1. Human Uterine Adenosarcoma Sarcoma PDTs were treated with HSP90 Inhibitor at two different concentrations (50nM and 100nM) with and without oxygenation on S-PDT-V1 and S-PDT-V3d models to test the impact of oxygen on tumor volume.



Abstract 130 Figure 2 Effect of HSP90 Inhibitor treatment on S-PDT-V1. Matrigel-based Sarcoma S-PDT-V1 were established and treated with two different concentrations (50nM and 100nM) of HSP 90 Inhibitor for 3 days and 7 days. The effect of treatment was measured by change in tumor volume. Statistical analysis was done using One-way ANOVA followed by t-test for significance (* $p < 0.05$), $n = 3$. We observed similar rate of cell growth in the untreated samples in both model systems and HSP90 Inhibitor was effective in reducing tumor volume.



Abstract 130 Figure 3 Effect of HSP90 Inhibitor treatment on S-PDT-V3d. Matrigel-based Sarcoma PDTs were established on a Liquid-Liquid Perfusion Interface (LLPI) using a synthetic hemoglobin as a blood substitute. The PDTs were treated with two different concentrations (50nM and 100nM) of HSP 90 Inhibitor for 3 days and 7 days. The effect of treatment was measured by change in tumor volume. Statistical analysis was done using One-way ANOVA followed by t-test for significance (* $p < 0.05$), $n = 3$. We observed similar rate of cell growth in untreated samples in both model system, however the efficacy of HSP 90 Inhibitor in reducing the tumor volume was no longer observed in the PDTs on the LLPI system.

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