Author’s response to reviews

Title: A 3D-microtissue-based phenotypic high content screen of chemotherapeutic drugs that overcome tumour resistance to radiation therapy

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Author’s response to reviews: see over
Dear Editor,

In accord with the major scope of **BMC Cancer Journal** to publish the research articles on all aspects of cancer research, including prevention, diagnosis and treatment of cancers, with special Technical Advance section, herewith I submit the manuscript entitled:

*A 3D-microtissue-based phenotypic high content screen of chemotherapeutic drugs that overcome tumour resistance to radiation therapy* by Anastasov et al., for your consideration.

It has been demonstrated that two-dimensional (2D) monolayer cancer cell proliferation assay for anti-cancer drug screening is a very artificial model and cannot represent the characteristics of three-dimensional (3D) solid tumors. There are several methods and techniques used to culture cells on non-adherent surfaces in order to form 3D spheroids. Many spheroids generated from these techniques, however, suffer from problems such as low efficiency spheroids formation, limited culturing duration and extreme variations in spheroid sizes. Therefore, 3D spheroid assays have not been incorporated into mainstream drug development processes or specific biological and biochemical analysis due to the complex methodological requirements and unconfirmed reliability.

In the field of radiation oncology there is a pronounced stagnation in the development of new treatments, although combinations of radiotherapy and chemotherapy are predicted to be additive. Despite the number of preclinical studies suggesting potent radiation sensitizing effects of various chemicals, few have been tested in clinical studies so far. We ascribe some of the blame to the lack of convenient and relevant model systems. To overcome this roadblock in translational activity we have accomodated a novel 3D-microtissue approach to screen for radiation therapy potentiating effects. Such 3D-microtissue assay analysis can confirm the data gathered from colony forming assays (assumed to be a gold standard in radiation oncology analysis). In our manuscript we report the validation of both monotypic and heterotypic spheroid models and as a proof we show that the concurrent treatment of vinblastine and radiation proves to be very effective on mammary cancer cell growth.

The results from our study confirm that the assay operated using the 3D-microtissue models and high content imaging system is able to detect compounds that modulate tumour cell survival and growth delay after irradiation almost in real time analysis. Accomodating such 3D-microtissue platforms for high content screening activities is very reliable in the future drug discovery initiatives and can facilitate the identification of patient-relevant molecular targets as well as accelerate the timeline of efficient early stage treatment modalities.
All authors contributed substantially to the work, reviewed and agreed to its submission. Conflict of interest statement is included in the paper’s acknowledgements.

The data presented in the submitted paper is original and neither this paper nor any similar paper has been submitted to, or has been published in, any other scientific journal.

I hope you will find this research appropriate and suitable for the BMC Cancer Journal readership.

Sincerely,

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