To the Editor,

Please find enclosed my revised manuscript entitled “Iterative data multiplexing (IDM) supports elucidation of drug targets from functional genomics screening approaches.” for your consideration. In response to the reviewers’ extremely constructive comments, the manuscript has been substantially reworked. Their specific comments have been addressed as follows:

Reviewer 1:

1) “One aspect that is not covered within this review, and would be useful to the reader, is what methods are used for practical target validation”. The text has been reworked to include a detailed description of the practical approaches we use for target validation.

2) “I would also like to know what approaches they use for Off Target effects, as this is still hot in the field and most groups have different approaches”. The different approaches to elucidating OTEs have been discussed, including our preference.

Reviewer 2:

1) “The review is supposed to analyse some problems of the screens in general and not serve as a platform to tell about the screening facility at Beatson Institute and how one deals with sub-libraries of siRNAs. These parts need to be removed.” These sections have been completely omitted.

2) “The reasons of OTEs need to be described in more details as well as concrete current strategies to deal with them.” An extended section on approaches used to validate OTEs has been included.

3) “Use of patient or tumor cells for high-throughput screens need to be illustrated with the appropriate examples and discussed what benefit was obtained by using these and not more standard type of cells”. A section on the importance of predictive preclinical models has been included, and the benefits of translating these models for use in a screening environment. Substantial examples have been included/referenced.

4) “Concrete examples of complex screens to address the biology behind drug-insensitive tumors need to be discussed.” For succinctness, this section has been removed. We have some in-house examples of this, but they are only now approaching publication, so cannot be utilised as examples in this manuscript.

5) “A clear separation of ideas when talking about networks and pathway analysis and data multiplexing need to be made. In fact, these two are closely related, but manuscript nearly
completely lacks smooth logical transition as how data multiplexing contributes to the analysis of the entire pathway.” This has been addressed by restructuring of the manuscript with a clear indication as to where pathway analysis can be implemented within the IDM approach, and inclusion of a Figure to illustrate the overarching role of IDM in the analysis workflow.

I hope my addressing of the reviewers’ comments is acceptable. The revised manuscript has 3371 words (excluding references) and one figure.

I hope you will find this article of interest for publication in Cancer Research Frontiers.

Kind regards,

Emma Shanks