Author’s response to reviews

Title: Anti-oncogenic and Pro-differentiation Effects of Inhibition of Monoamine oxidase A on High Grade Prostate Cancer Cells

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Author’s response to reviews:

Dear Editor,

We submit for your consideration our manuscript: “Anti-oncogenic and Pro-differentiation Effects of Inhibition of Monoamine oxidase A on High Grade Prostate Cancer Cells.” We investigated the effects of inhibition of monoamine oxidase A (MAO-A), one of the most highly overexpressed proteins in high grade prostate cancer, using a primary cell culture as an experimental model. Gene expression profiling and Significance Analysis of Microarrays identified 156 genes whose expression was significantly increased by clorgyline, an irreversible inhibitor specific for MAO-A, over the time course of 96 h. Strikingly, more than half of these genes are reportedly suppressed by at least one known oncogene (beta-catenin, Src, ERBB2, Ras, E2F3, MEK and Myc). In addition, genes downregulated # 2-fold by clorgyline were significantly enriched with those upregulated by key oncogenes including beta-catenin and ERBB2, indicating an anti-oncogenic effect of MAO-A inhibition. Another remarkable effect of MAO-A inhibition was the induction of androgen receptor (AR) and classic AR target genes such as prostate-specific antigen together with other secretory epithelial cell-specific genes, suggesting that clorgyline promotes differentiation of cancer cells. Moreover, clorgyline downregulated EZH2, a critical component of the Polycomb Group (PcG) complex that represses the expression of differentiation-related genes. Indeed, many genes in the PcG repression signature that predicts prostate cancer outcome were upregulated by clorgyline, suggesting that the differentiation-promoting effect of MAO-A inhibition may be mediated by EZH2. Our results suggest that inhibitors of MAO-A, already in clinical use to treat depression, may have potential application as therapeutic drugs against prostate cancer by inhibiting oncogenic pathway activity and promoting differentiation.

Please note that neither the submitted paper nor any similar paper, in whole or in part, other than an abstract or preliminary communication, has been or will be submitted to or published in any other primary scientific journal and that all of the
authors are aware of and agree to the content of the paper and their being listed as an author on the paper. None of the authors has any financial or other interests with regard to the submitted manuscript that might be construed as a conflict of interest.

Thank you for your consideration of our work. If I can be of further assistance, please do not hesitate to contact me.

Sincerely,

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