Reviewer's report

Title: Gene expression profiling revealed novel mechanism of action of Taxotere and Furtulon in prostate cancer cells

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Reviewer: Lukas Bubendorf

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General

The authors present a study on the molecular changes that occur upon treatment of the prostate cancer cell lines PC-3 and LNCaP with Taxotere and Capecitabine. These drugs have been shown to be effective in some patients with late-stage prostate cancer. The Affymetrix gene chip analyses reveal that both drugs induce changes of a large number of genes involved in a variety of cellular functions including cell cycle, proliferation, apoptosis and differentiation. The understanding of the complex molecular pathways involved may be of value for further research to optimize the therapy of this disease. The experimental design of the study is solid and straightforward, the experiments were carefully conducted, and the data are clearly presented. Overall, I believe that the results could be of interest to both clinicians and researchers involved with prostate cancer.

The study suffers from a problem common to most gene chips studies: the wealth of information makes it difficult to identify the molecular key events and distinct these from secondary downstream events (such as change of proliferation and apoptosis). I am afraid to note that the first goal of the study, which was to identify novel genes with key roles in the effects of Taxotere and Furtulon, has not fully been reached. The fact that both drugs affect almost all critical cellular functions makes it almost impossible to find the golden needle in the haystack (if there is such a needle). The fact that some functions are even altered in both ways makes things even more complex (e.g. upregulation of both TIMPs and MMPs).

It is not surprising to me that drugs that inhibits tumor growth leads to a change of expression of genes involved in proliferation and/or apoptosis. Therefore, these changes are by no means specific to Taxotere and/or Capecitabine but just reflect their effect on cell growth.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The authors have already tested effect of Taxotere on gene expression using Affymetrix chips in a previous study (Ref 11). It should be clarified to what extent there is overlap of the data between the two studies. Is the current study an extension of the previous study by including Furtulon and LNCaP?

In the present study, Furtulon was chosen as another drug to be analyzed. Was there a mechanistic hypothesis or clinical data to suggest that Taxotere and Furtulon may have synergistic effects in prostate cancer?

It is briefly mentioned that the results of the Western Blot analyses were in direct agreement with the microarray and real-time RT-PCR data. Since protein expression is critical, it would be worthwhile to supplement figure 2 with the corresponding Western Blots.
It should be clarified whether all genes with expression changes >2 are shown on the tables, or whether a selection of genes is presented. I wonder how the expression of prominent genes such as Ki67 and Bcl-2 responded to treatment. Although Ki67 has been analyzed by RT-PCR (table 1), no data are shown. It would at least be surprising and worth reporting how and to what degree the expression Ki67 was affected by the treatment.

**What next?:** Accept after minor essential revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No