Reviewer's report

Title: ROS generation via NOX4 and its utility in the cytological diagnosis of urothelial carcinoma of the urinary bladder

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Reviewer: Christian Schwentner

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This is a very impressive article not only investigating the the pathobiological role of NADPH oxidase (NOX)4-mediated generation of reactive oxygen species (ROS) in urothelial carcinoma (UC) of the urinary bladder but also demonstrated the utility of ROS labeling in urine cytology. As such this is the first study elucidating the role of NOX-4 in BC. The abstract is concise and appropriate. The same applies for the introduction. The array of methods used herein is really comprehensive (Western-blot, cell culture, RT-PCR, siRNA, animal experiements..). There is absolutely nothing I would add to that. Finally, fluorescent labeling of ROS-(hydrogen peroxide and superoxide anion) positive cells in voided urine samples was used to improve of the sensitivity of urine cytology in bladder cancer. Hence, translational and basic research is shown at the same time underlining the value of this discovery.

The results are clear and the role of NOX in BC is well-described. Inhibition obviously changes BC-growth which is quite interesting.

Moreover, it was shown that ROS was not present in normal urothelium. A very important finding for diagnostics.

Finally, the authors convincingly showed that sensitivity and specificity of cytology could be clearly improved.

The discussion is ample although the results are just too extensive to be discussed in detail.

Tables and figures are well-illustrated.

Minor-essential reviews: Pls do a final check for typos and spelling errors and proof-reading by native speaker.

Otherwise a great piece of work. This work really augments our diagnostic armamentarium for BC.

Level of interest: An exceptional article

Quality of written English: Needs some language corrections before being published
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

Nothing to disclose.