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Letter to the Editor

Reply to Mengxin Lu, Yi Zhang, Yu Xiao's Letter to the Editor, re: Kimmo Kettunen, Peter J. Boström, Tarja Lamminen, et al. Personalized Drug Sensitivity Screening for Bladder Cancer Using Conditionally Reprogrammed Patient-derived Cells. Eur Urol 2019;76:430–4

We want to thank Lu et al for their letter and interest in our recently published study on conditionally reprogrammed (CR) patient-derived bladder carcinoma (BC) cell cultures [1]. As discussed in the original article, our study is limited by a low number of patients and therefore should be considered a proof-of-principle methodological study rather than general characterization of BC with known high intertumoral heterogeneity. Lu et al also state that the frequency of *Rb* and *TP53* mutations (both present in the successful CR cultures) was higher than previously reported for large BC cohorts. Although this might imply that tumor cells with *Rb* and *TP53* mutations are more prone to survive after CR, these findings are more likely to be coincidental and further conclusions should not be drawn from two individual patients/cultures. Naturally our CR cells only model the tumors from which the cells originated (not BC in general) and from a methodological perspective it is more relevant that they carried mutations in the same genes as their parental tumors.

As pointed out by Lu et al, culture HG-T1-CR and its parental tumor predominantly carried different pathogenic *TP53* mutations, suggesting intratumoral heterogeneity and survival of a subclone in CR culture. Since separate tissue pieces from transurethral resection of bladder tumor were used for DNA extraction and CR culture, it is impossible to say with certainty which *TP53* mutation is predominant within the tumor. However, this CR culture still carried the majority of the mutations (134 out of 235) found in the parental tumor, indicating significant genomic similarities. Similar to other solid tumors (eg, lung and prostate carcinoma), intertumoral and intratumoral heterogeneity is one of the main challenges of BC research and diagnostics [2–4]. It is practically impossible to recapitulate the whole tumor in cell culture conditions, and processing of a large fraction of the tumor would hamper further tumor characterization, including clinical histopathological diagnostics.

While the high sensitivity of the neuroendocrine SmCC-T4-CR culture to statins is intriguing, it represents a single case and more studies are needed in the future. Therefore, we look forward to seeing first results from the project mentioned by Lu et al, especially with more detailed metabolomics/lipidomics data. However, from a broader perspective we feel that rather than trying to identify an individual new agent to treat BC, the drug sensitivity screening described in our study could be an effective strategy as it offers a means for truly personalized decision-making on medical treatment. We are pleased to hear that similar methodologies are under investigation in other laboratories. It is up to us and others to develop CR methodology further to minimize the culture time and maximize the survival of different tumor cell clones to preserve intratumoral heterogeneity under culture conditions.

Conflicts of interest: The authors have nothing to disclose.

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