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European Association of Urology

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 read with great interest the study by Kettunen *et al.* [1] on the conditional reprogramming (CR) method for generating patient-derived bladder cancer (BC) cell cultures and their feasibility for planning personalized treatment strategies.

Conditionally reprogrammed cells (CRCs) yield long-term cultures of primary cells from both normal and cancer tissues without changing their genotypes; the authors successfully established four CR cultures from six BC patients. Measurement of the consistency between CR cultures and the corresponding parental tumors in terms of genomic, transcriptomic, and protein expression analyses revealed that two out of four CR cultures corresponded well to their parental tumors.

We would like to highlight several concerns. As mentioned by the authors, given the great differences in gene mutation types, clinical characteristics, and biological behaviors of BC, the study is limited by the small number of CR cultures (two CR cultures). Emerging evidence indicates that the clinical heterogeneity of different subtypes and different clinical backgrounds are important reasons for difficulties with BC treatments. A study based on 472 urothelial carcinoma cases revealed that *RB1* mutation rates were only 9–22% in high-grade BC [2]. By contrast, Kettunen *et al.* reported that the *RB1* gene in both their CR cultures (HG-T1 and SmCC-T4) was a mutant form [1]. Moreover, *TP53* mutation rates as high as 45–58% have been reported for high-grade BC [2], whereas all four BC patients described by Kettunen *et al.* were *TP53* mutant carriers [1]. Furthermore, the *TP53* mutation in HG-T1-CR was different to that in the corresponding tumor, suggesting that the CRCs may be from a minor subclone. Thus, two CRC lines established by Kettunen *et al.* could only reflect a few biological characteristics of BC.

Establishment of BC cell models targeted at different genetic backgrounds and clinical characteristics of different tumors is of great significance for the study of pathogenesis and precise treatment of BC. At the Human Genetics Resource Preservation Center of Hubei Province (the Zhongnan Hospital Biobank) [3], we have successfully cultured normal bladder epithelial cells and CRCs isolated from BC tissues in collaboration with Dr. Xuefeng Liu, one of the inventors of the CR technology [4]. We are currently establishing CRCs with diverse clinical and genetic backgrounds for distinct BC patients, which could provide a reliable research tool for studying BC with different clinical outcomes in the Chinese population.

Kettunen *et al.* also carried out drug sensitivity screening to identify novel drugs for the two CR cultures, which revealed that the SmCC-T4-CR cells had high sensitivity to statins [1]. We previously found that fatty acid metabolism could act as a key role in BC tumorigenesis, and simvastatin could induce cell cycle arrest and inhibit the proliferation of BC cells via the PPARγ signaling pathway [5]. Therefore, in our future research on consistency between BC CRCs and the corresponding specimens, we will use metabonomics (especially lipidomics) in addition to genomic, transcriptomic, and protein expression analysis. Finally, we would like to discuss the establishment and application of BC CRCs with more international researchers.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: We thank the grant from the Chinese Central Special Fund for Local Science and Technology Development of Hubei Province (2018ZYYD023).

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