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Platinum Priority – Editorial

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Identification of Potential Novel Candidates for Understanding Racial Differences in Prostate Cancer

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There has long been interest in the features and mechanisms responsible for the higher incidence of prostate cancer in the African population compared to patients of Caucasian origin. Studies performed in the USA in some cases have investigated not only the molecular background but also differences in the social status of patients that determine access to health care systems [1]. This is obviously an important factor to be studied in urological epidemiology in the context of different diets and exposure to carcinogens [2]. Interestingly, higher intake of calcium and magnesium is associated with aggressive prostate cancer in men of both African and American origin. The topic of the manuscript by Tonon and associates [3] in this issue of *European Urology* is, however, a different one; the authors investigated the molecular profile of aggressive prostate cancer in men of African Caribbean versus European ancestry. As expected, prostate cancer mortality is higher among African Caribbean than among French Caucasian patients. The authors' research and transcriptome analyses focused on androgen receptor signaling and DNA repair. After performing whole-genome and RNA sequencing, reliable results for 157 patients could be presented. Some interesting findings are evident in the context of established therapies and could represent a basis for future functional studies. PARP1 deletion in the African Caribbean population deserves discussion. PARP1 is involved in the regulation of several cellular processes in prostate cancer. For example, Pu and colleagues [4] demonstrated that PARP1 is a modulator of the epithelial-to-mesenchymal transition (EMT) in prostate cancer. Thus, PARP1 is implicated in the regulation of progression towards therapy resistance. EMT was also observed after chronic treatment with the chemotherapeutic agent docetaxel [5]. Targeting the EMT has not been successful so far, but several novel approaches are being developed.

There may be more implications of PARP1 loss in African Caribbean patients. Since genomic effects in DNA repair in prostate cancer are well documented, the use of inhibitors such as olaparib has considerable clinical relevance. Phase 1 and 2 studies with PARP inhibitors have been carried out [6]. Olaparib, nucaparib, and nirparib have been approved for clinical treatment. Those clinical studies opened the way for a personalized approach in advanced prostate cancer. Loss of PARP1 in a subgroup of African Caribbean patients is therefore important in answering the question of which signaling pathways are responsible for cancer development and progression and, consequently, how to optimize therapeutic intervention without PARP inhibition in those patients. At this stage it is difficult to assess the implications of *CDK12* truncating mutations in patients with prostate cancer as observed in the present study. Background information on the long noncoding RNA (lnc RNA) *PVT1* is more comprehensive at this stage. *PVT1* lncRNA is overexpressed in prostate cancer and contributes to prostate carcinogenesis [7]. Its specific function in inducing methylation of miR-146a has been elucidated. Moreover, *PVT1* is predictive of poor prognosis in prostate cancer. One could expect that further studies with *PVT1* in cancer models from African Caribbean patients will improve our understanding of its possible role in the regulation of proliferation and invasion [8]. lncRNAs are recognized as biomarkers for prostate cancer, and may also have an active role in the regulation of cellular events. Since more than 100 000 lncRNAs have been identified in the human genome, detailed studies in

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different patient groups may be very complex and difficult to perform. At present, their regulation is not well understood. For some lncRNAs, it is not known whether upregulation is causally associated with prostate carcinogenesis. To address this issue, it is important to develop patient-derived xenografts from African Caribbean patients. These xenografts may be a valuable addition to the collection recently described in the literature by a multinational consortium [9].

Collectively, the results presented by Tonon and colleagues have identified an interesting starting point for mechanistic studies on prostate cancer in patients of African origin. As mentioned above, multiple factors affect differences in the pathology, molecular properties, and therapy resistance of prostate cancer between Caucasian patients and men of African origin. One recent study demonstrated that interleukin-6 induces mRNA splice variant *MBD2* to promote stemness in tissues from African American patients [10]. This interesting topic may become the subject of collaborative investigations by experts in different clinical and preclinical specialties in the future.

Conflicts of interest: The author has nothing to disclose.

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