**Supplementary Results**

**The prostate cancer (PCa) PDX Program at MD Anderson Cancer Center**

When the tumor is large and/or involves multiple organs (cystoprostatectomy/pelvic exenteration specimens), in order to understand tumor heterogeneity, we process tumor samples from different areas of the same tumor for PDX development. These samples are established as independent PDXs uniquely identified according to a suffix (e.g., MDA PCa 144-2 and MDA PCa 144-4 are derived from areas 2 and 4 of specimen 144). With this approach, we have developed multiple PDXs from 13 human donor tumors: 2 independent PDXs from each of 7 donor tumors (counting the MDA PCa 2a and 2b cell lines), 3 independent PDXs from 1 donor tumor, 4 independent PDXs from each of 2 donor tumors, 5 independent PDXs from 1 donor tumor, 6 independent PDXs from 1 donor tumor, and 8 independent PDXs from 1 donor tumor. In total, we have developed 80 PDX lines from 47 PCa donors (Table 1, Table S1). The term “PDXs” is inclusive of MDA PCa 2a-T and 2b-Txenografts (T indicates a cell line–derived xenograft). We constantly monitor the growth rate of these PDXs and closely monitor these values over time as a quality control. The growth rate is generally slow during the first two or three passages, but stabilizes and remains constant in subsequent passages. We have listed growth rate values in Table S1-Addendum. This data is not listed for most archived models as they can no longer be grown.

Several of the PDXs reported in this manuscript are archived now and therefore are no longer able to be grown as PDX's in animals. However, this is a dynamic repository and the program up to date has a collection of clinically annotated 154 available PDXs derived from 99 PCa patients, including the non-archived models from the 47 human donor tumors described here.

**Morphological and immunohistochemical features of human donor tumors and PDXs**

In some PCa donor cases (indicated by asterisk(s) in Tables 1 and S1), diagnosis came from the original pathology report because there was no material available to review for this study. In four of these cases, there was either no material available for review or no malignant cells in the review material in the original report.

When we developed one or more PDXs from mixed adenocarcinoma and NEC, one or both morphological components present in the human PCa donor tissue were represented in the different PDXs. In the case of specimen 146, we developed four PDXs (MDA PCa 146-10, -12, -17, and -20) from different areas of the tumor. MDA PCa 146-10 and -17 were NEC, MDA PCa 146-12 was an adenocarcinoma, and MDA PCa 146-20 was a mixed adenocarcinoma and NEC (Fig. 1D and Table 1), indicating the extent of tumor heterogeneity. In the case of specimen 112, the corresponding PDX (MDA PCa 112) was an adenocarcinoma (Fig. S1 and Table 1). From specimens 144 and 181, we developed eight NEC PDXs and one NEC PDX, respectively (Fig. S1 and Table 1). In both of these cases, the adenocarcinoma component of the human donor was not represented in the corresponding PDXs.

Tissue from one sarcomatoid carcinoma with squamous differentiation developed into a squamous carcinoma, and a poorly differentiated carcinoma with neuroendocrine differentiation developed into a NEC, thus retaining most of the original morphology.

Finally, a donor tumor diagnosed as sarcomatoid carcinoma with squamous differentiation developed into a PDX diagnosed as adenocarcinoma with squamous differentiation, and a poorly differentiated carcinoma developed into a poorly differentiated carcinoma with morphology suggestive of neuroendocrine features.

**AR, ERG, and PTEN status in MDA PCa PDXs and in 15 paired human donor tumors and PDXs**

MDA PCa 2a-T and MDA PCa 180-30 had heterogenous PTEN deletion, whereas other PDXs derived from the same tumors had positive PTEN expression (Table S2). The poorly differentiated carcinomas with morphology suggestive of neuroendocrine features were AR-negative, ERG-negative, and PTEN-deleted or -heterogeneous. The squamous carcinoma was AR-negative, ERG-negative, and PTEN-heterogeneous,and theadenocarcinoma with squamous differentiationwas AR- and ERG-positive and PTEN-deleted.

As previously mentioned, MDA PCa 144 and MDA PCa 146 donor tumors were mixed, including adenocarcinoma and NEC components (1, 2). In the case of MDA PCa 144 donor tumor, eight tumor fragments from different areas were implanted into mice, and they all developed into independent PDXs. All MDA PCa 144 PDX lines have the same pattern of expression of ERG and AR, however the human donor tumor has two different patterns of ERG and AR expression, which is indicated by a representative line in Figure 2. Therefore, in this case, some cellular components of the human donor PCa of MDA PCa 144 were not represented in the corresponding PDXs. In contrast, the heterogeneous pattern of ERG and AR expression in the MDA PCa 146 donor tumor was reflected in the corresponding PDXs (Fig. 2). In addition to the 11 cases listed in Figure 2, we also studied 4 PDX–human donor pairs of archived PDXs, namely MDA PCa 76, MDA PCa 122, MDA PCa 137, and MDA PCa 160. In these cases, we also found concordance in most samples, with only a few differences, including a heterogeneous deletion in the human donor vs a deletion in PTEN on MDA PCa 76 and MDA PCa 160, and a positive in the human donor vs heterogeneous positive in ERG expression on MDA PCa 122.

**Copy number alterations in PDXs derived from different areas of the same human PCa**

MDA PCa 144-13 (but not MDA PCa 144-4) carries a deletion in chromosomes 1q32.3-q43 (a region encoding multiple genes) (Fig. S4) and gains in 8q12.1-q24 (an alteration frequently found in PCa [12]) and 10q24.32-q (regions encoding multiple genes) (Fig. S4).

Comparisons of copy number change analyses indicate that MDA PCa 146-12 differs from MDA PCa 146-10 and -20 in that it has losses in chromosomes 7p and 7q. Also, MDA PCa 146-10 and -12 differ from MDA PCa 146-20 in that they have gains in chromosome 8q and a deletion of ADAM3A chromosome 8p (Fig. S5).

NEC PDXs MDA PCa 150-1 and MDA PCa 150-3 showed many common gains and losses (e.g., two regions in chromosomes 5q and 10q encoding multiple genes including PTEN), with no obvious differences between the lines (Fig. S6).

The MDA PCa 155, MDA PCa 175, and MDA PCa 180 sets of PDXs share most gains and losses (Fig. S7). However, MDA PCa 155-12 (but not -16) has a focal loss of chromosome Xp, MDA PCa 175-6 (but not -2 or -10) has an amplification on MYC, and MDA PCa 180-30 (but not -11) has copy gains in chromosomes 1q, 2p, 3p, and X, the latter including AR.

**References**

1. Tzelepi V, Zhang J, Lu JF, et al. Modeling a lethal prostate cancer variant with small-cell carcinoma features. *Clin Cancer Res.* 2012;18(3):666-77.

2. Aparicio A, Tzelepi V, Araujo JC, et al. Neuroendocrine prostate cancer xenografts with large-cell and small-cell features derived from a single patient's tumor: morphological, immunohistochemical, and gene expression profiles. *Prostate.* 2011;71(8):846-56.