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Patient-derived xenografts: A platform for accelerating translational research in prostate cancer

Alastair H. Davies [a, b], Yuzhuo Wang [a, b], Amina Zoubeidi [a, b, *]

[a] Vancouver Prostate Centre, Vancouver, BC, Canada
[b] Department of Urologic Sciences, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

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ABSTRACT

Recently, there has been renewed interest in the development and characterization of patient-derived tumour xenograft (PDX) models. Numerous PDX models have been established for prostate cancer and, importantly, retain the principal molecular, genetic, and histological characteristics of the donor tumour. As such, these models provide significant improvements over standard cell line xenograft models for biological studies, preclinical drug development, and personalized medicine strategies. This review summarizes the current state of the art in this field, illustrating the opportunities and limitations of PDX models in translational prostate cancer research.

1. Introduction

The use of preclinical model systems is central to each step of translational cancer research, ranging from the fundamental biological understanding of the disease to the development of new treatment paradigms. With regard to drug development, the advent of cancer cell line culture techniques in the 1970s fuelled the rapid acceleration and expansion of preclinical testing of anticancer agents both *in vitro* and *in vivo* (Venditti et al., 1984). Currently, xenografts developed by growing cell lines subcutaneously in immunodeficient mice is the ubiquitous platform for preclinical drug development and screening. However, the harsh reality is that about 85% of anticancer therapies fail in early clinical trials, despite significant efficacy in *in vivo* models (Arrowsmith, 2011; Ledford, 2011).

The randomized, phase 3 SYNERGY trial in patients with metastatic, hormone-refractory castration-resistant prostate cancer (CRPC) treated with a standard chemotherapy regimen of docetaxel and prednisone with or without custirsen, an antisense oligonucleotide designed to inhibit production of the cytoprotective protein clusterin, led to unexpected disappointing results (Chi et al., 2015). The addition of custirsen to standard chemotherapy failed to significantly improve survival. Preclinical studies, however, suggested that inhibition of clusterin could be beneficial as treatment with custirsen slowed tumour growth and resensitized treatment-resistant cell lines and tumours to chemotherapy (Sowery et al., 2008; Zellweger et al., 2001; Gleave and Miyake, 2005). Also, a small randomized phase II trial testing the combination of custirsen with docetaxel/prednisone showed an increase of sensitivity of tumours to combination therapy, leading to a 50% reduction in the rate of death in patients receiving custirsen (Chi et al., 2010). Why, then, was there not a benefit in the phase III setting? The observations described above confirm, once again, a failure in the translational process and an urgent need to develop more relevant preclinical models of prostate cancer.

Preclinical models, unfortunately, seldom mirror drug efficacy and outcomes in clinical trials (Johnson et al., 2001). Although the underlying cause of this poor predictive value is not fully understood, emerging evidence suggests that the process of generating cell lines yields major alterations in biological properties, including gain and loss of genetic information as well as modifications in invasive capabilities and the reliance on specific growth and survival pathways (Gillet et al., 2011; Hausser and Brenner, 2005;

* Corresponding author. Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, 2660 Oak Street, Vancouver, BC, V6H 3Z6, Canada.
E-mail address: azoubeidi@prostatecentre.com (A. Zoubeidi).

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Daniel et al., 2009). In addition, cell line models are not representative of the complex heterogeneity evident in the clinic, partly due to increased homogeneity after long-term *in vitro* culturing. Finally, these model do not possess the tissue architecture of the original tumour and, consequently, do not accurately recapitulate the complex interactions between the tumour cells and various components of their microenvironment (reviewed in (Choi et al., 2014)).

In an attempt to circumvent these issues, there has been increasing interest in the application of more advanced preclinical models, including PDX as well as genetically engineered mouse (GEM) models and short-term primary cultures or organoids (Fig. 1). PDX models are not new; studies conducted in the 1980s demonstrated a high degree of correlation between clinical response in lung cancer patients treated with cytotoxic therapy and PDX models generated from these patients (Fiebig et al., 1985). In recent years, there has been a renewed interest in developing and utilizing PDX models to improve the drug discovery process. Indeed, a recent phase II clinical trial integrated PDX models to better assess the efficacy of cabozantinib in CRPC patients (Varkaris et al., 2016). Utilizing more relevant preclinical models to test anticancer agents before the implementation of clinical trials can possibly reverse the failures of phase III trials and open a new era of translational research.

2. Methodological aspects of prostate cancer PDX models

The process of generating PDX models in mice from fresh primary or metastatic human prostate tissue has been extensively described in the literature (Wang et al., 2005a; Priolo et al., 2010; van Weerden et al., 1996; Zhao et al., 2010). Briefly, tumours maintained as tissue structures are procured by surgery or biopsy. These tumours are subsequently implanted as small pieces or single-cell suspensions, either alone or in some studies coated with Matrigel or mixed with mouse seminal vesicle mesenchyme (SVM), into immunodeficient mice. Tumour take *in vivo* can be measured by serum level of prostate-specific antigen (PSA), which is not produced by mice and thus must be synthesized and secreted into the blood by the grafted human tumour tissue (Priolo et al., 2010). Table 1 provides a summary of approaches used to generate prostate cancer PDX models.

Defining the most appreciate host mouse strains to develop PDX models is an important consideration. It is generally assumed that more severely immunocompromised models are better suited for PDX generation due to higher engraftment rates. Indeed, NOD/SCID mice and NOD/SCID/IL2γ-receptor null (NSG) mice are routinely employed for developing prostate cancer PDX models. However, one study found no significant difference in engraftment rate between nude (nu/nu) mice (which lack T cells) and NOD/SCID mice (which lack both T and B cells), suggesting the type and extent of immunodefiniency in the murine host does not affect tumour take (Priolo et al., 2010).

A more substantial difference between methods is the site of implantation. The most common site of implantation is on the dorsal region of mice (subcutaneous implantation), although several approaches have implanted primary tumours in the subrenal capsule (SRC; subcapsular implantation) and anterior prostate (orthotopic implantation) in an effort to increase engraftment success rates. The various sites (subcutaneous, subcapsular, and

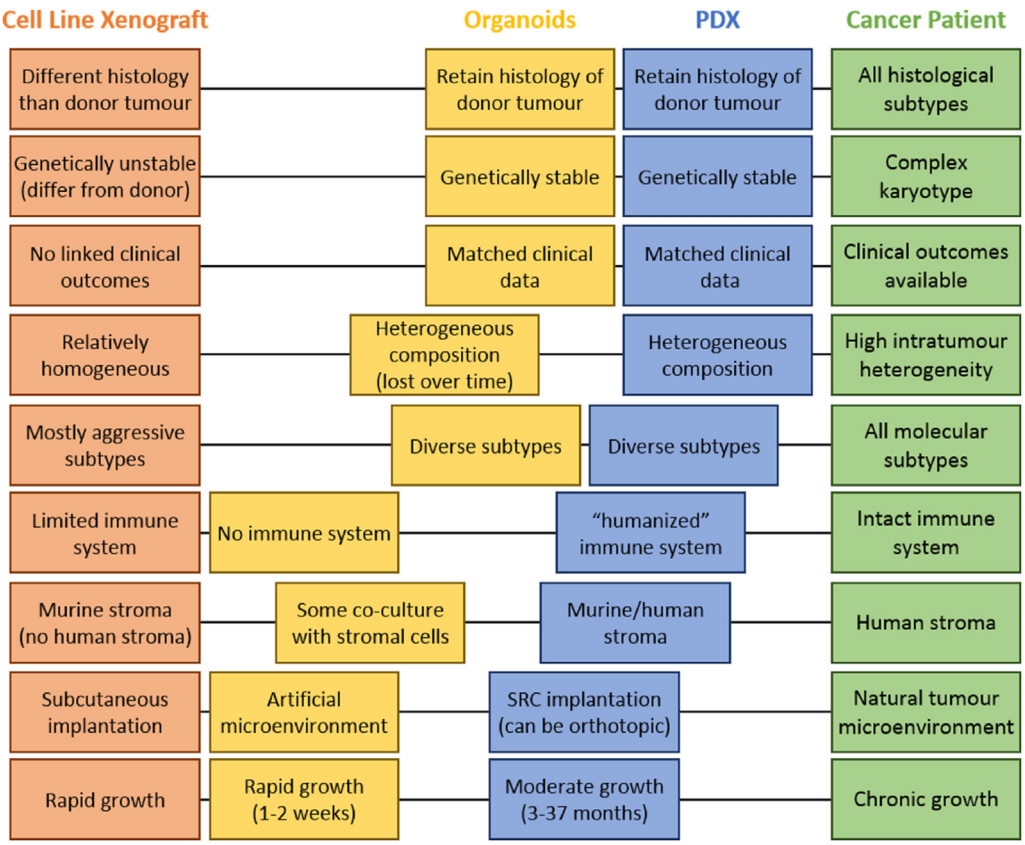

Fig. 1. Comparison of preclinical models utilized in prostate cancer translational research. A "tumour model abacus" illustrates the strengths and weaknesses of patient-derived xenografts in modeling human prostate cancer, as well as a comparison to cell line xenografts and three-dimensional organoid cultures.

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