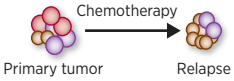
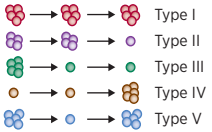
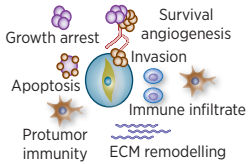
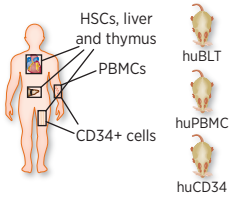
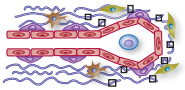
| | Source of heterogeneity | Implications for basic and translational research | Representation in current PDTX models | Future prospects |
|---|---|---|---|---|
| Cell-autonomous | **Genomic clonal dynamics**<br>  | Minor *KRAS* subclones predict resistance to EGFR targeted therapies in colorectal cancer.[4] Overall clonal diversity correlates with drug resistance in ovarian and oesophageal cancers.[16, 17] | Genomic clones reconstructed in a panel of 15 breast cancer PDTX models revealed ongoing clonal dynamics. Polyclonal engraftment was possible, but clonal selection was clearly evident.[5] | International collaborations such as the EuroPDX Consortium should facilitate sharing of expertise and eventually lead to increased engraftment with less pronounced clonal selection.[10] |
| | **Epigenetic/cellular clones**<br>  | Epigenetic 'attractor states' increase the phenotypic heterogeneity within the tumor and hence widen the pool of cellular clones able to contribute to treatment resistance.[20] | Colorectal and breast PDTX models show five distinct cellular clonal phenotypes.[6, 7] 'Type IV' quiescent clones were responsible for resistance to chemotherapy in colorectal cancer.[7] | PDTX models which better reflect the native tumor microenvironment should allow for more appropriate epigenetic clonal diversity. |
| Non cell-autonomous | **Stromal heterogeneity**<br>  | Pro- and anti- tumor properties are attributed to different populations of cancer associated fibroblasts (CAFs). Heterogeneous CAF or MSC populations could confer heterogeneity on the tumor bulk.[26] | Human stromal components are replaced by murine equivalents on PDTX passage. It is unclear how closely mouse fibroblasts mimic their human counterparts in supporting tumor growth. Human fibroblast cell lines are heterogeneous in their ability to promote treatment resistance.[26, 27] | Patient matched stromal components should be sourced whenever possible. Although human fibroblasts can be expanded *in vitro*, cell sorting may reduce engraftment efficiency of tumor cells and this should be considered. |
| | **Immune infiltrate**<br>  | The role of the immune infiltrate on tumour progression is highly complex. Checkpoint inhibitors and other immunotherapeutics are promising new treatment strategies in oncology. | Highly immunodeficient mice are used for PDTX implantation. The NSG strain is characterised by a lack of mature lymphocytes, the absence of functional NK cells, defective macrophages and defective dendritic cells.[33] | HuPDTX immune models remain a substantial technical challenge. But the implications for study of tumor biology are profound. |
| | **Dysregulated ECM**<br>  | Regulated ECM maintains tissue architecture and stem cell compartments. Loss of structure in cancer could contribute to oscillation between distinct transcriptional programs.[21] | Matrigel is currently used to increase engraftment efficiency. Growth factors present in this murine basement membrane extract could support preferential engraftment of specific cell types. ECM is tissue specific, however in PDTX models, ectopic implantation is commonly used.[23, 25] | The ECM is tissue specific and orthotopic models should be considered where possible. Synthetic human alternatives to Matrigel should be investigated. |