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A Critical Review on Human Prostate Cancer Xenograft Models, Methodological Challenges and Paradigm Shift for Advanced Therapies

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Abstract
Human prostate cancer remains a leading cause of male morbidity worldwide, with post-treatment complications such as fibrosis, erectile dysfunction, and urinary incontinence continuing to impose significant clinical burdens. The development of effective regenerative and therapeutic biomaterials therefore relies on preclinical models that accurately recapitulate the human prostate tumour microenvironment. Among available in-vivo platforms, rat prostate xenograft models established using human prostate cancer tissue offer important advantages, including suitable anatomical scale, dynamic tissue remodeling capacity, and compatibility with injectable biomaterial scaffold testing. Nevertheless, substantial methodological, ethical, and translational challenges continue to limit their reproducibility and clinical relevance. Reported tumour engraftment success varies markedly depending on tissue source and implantation site, with subcutaneous xenografts achieving approximately 40–60% take rates, while highly vascularized sites such as the renal capsule demonstrate engraftment efficiencies approaching 90–95%. This variability highlights the influence of pre-analytical handling, tumour heterogeneity, immune compatibility, and host micro-environmental factors on experimental outcomes. This critical review synthesizes current conceptual methodologies governing human prostate cancer tissue acquisition, preparation, preservation, xenograft induction, and in-vivo disease monitoring in rat models. Emphasis is placed on ethical governance, biosafety considerations, and adherence to the principles of Replacement, Reduction, and Refinement. The review further evaluates the implications of these challenges for regenerative medicine, particularly the development and assessment of injectable biomaterial scaffolds aimed at restoring prostate tissue structure and function following cancer therapy. Emerging alternatives, including patient-derived organoids, three-dimensional bio-printed tumour–stroma constructs, and prostate-on-chip platforms, are discussed as complementary strategies for improving translational fidelity, while reducing reliance on animal models.

Keywords: *Xenograft models, Biopsy preservation, Rat prostate model, Tumour microenvironment, Injectable scaffolds*

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I. Introduction

1.1 Global Burden of Prostate Cancer and Post-Treatment Morbidity

Prostate cancer is one of the most frequently diagnosed malignancies among men and represents a significant contributor to cancer-related morbidity and mortality worldwide (Madu & Lu, 2010; Shen & Abate-Shen, 2010). While early detection and advancements in surgical, chemotherapeutic, and radiotherapeutic interventions have improved patient survival rates, a large proportion of survivors continue to experience long-term complications following treatment (Beltran et al., 2019; Chang et al., 2014). These include urinary incontinence, erectile dysfunction, pelvic fibrosis, tissue atrophy, and chronic inflammation, which collectively diminish quality of life and impose sustained healthcare burdens (Centenera et al., 2013; Tan et al., 2009).

In recent years, regenerative medicine approaches have emerged as promising strategies for restoring damaged prostate tissue following cancer therapy (Basak et al., 2022; Germain et al., 2023). Injectable biomaterial

scaffolds, hydrogels, and bioactive polymer composites particularly chitosan-based materials derived from marine waste sources such as crab shells have demonstrated substantial potential in modulating fibrosis, promoting angiogenesis, and enhancing tissue remodeling (Abdolahi et al., 2022; Gengenbacher et al., 2017). However, the translational success of such innovations is fundamentally dependent on the availability of disease-relevant preclinical models that accurately replicate the human prostate tumour microenvironment and post-treatment tissue degeneration (Ittmann et al., 2013; Risbridger et al., 2018; Sailer et al., 2023).

1.2 Need for Clinically Relevant Prostate Cancer Models

Traditional in vitro prostate cancer models rely heavily on immortalized cell lines cultured in two-dimensional (2D) monolayers. While these systems offer convenience and reproducibility, they fail to capture the complexity of tumour–stromal interactions, extracellular matrix architecture, immune modulation, and mechanical cues that define in-vivo prostate cancer pathology (Farhat et al., 2021; Rauner et al., 2025). Consequently, results obtained from such simplified systems often translate poorly into clinical outcomes (Day et al., 2015; Gengenbacher et al., 2017).

Animal models, particularly rodents (Fig. 1), provide an intermediate platform in which tumour growth, angiogenesis, immune interactions, and tissue remodeling can be studied under physiologically relevant conditions (Adamiecki et al., 2022; Ittmann et al., 2013). Among these, xenograft models based on the transplantation of human prostate cancer tissues into immunocompromised rodents have gained prominence (Hidalgo et al., 2014). These models preserve critical aspects of tumour heterogeneity, androgen responsiveness, and extracellular matrix composition that are otherwise lost in conventional cell culture systems (Davies et al., 2018; Risbridger et al., 2018; Sailer et al., 2023).

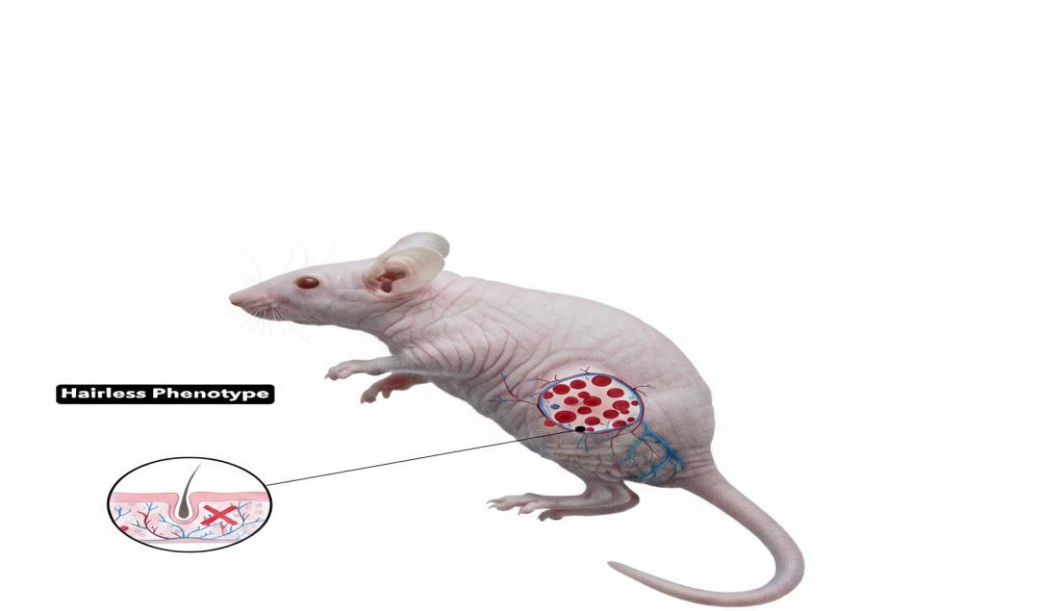

Figure 1: Hairless Rat Model

1.3 Rationale for Rat Prostate Xenograft Systems

Although murine models dominate oncological research, rats offer several anatomical and physiological advantages for regenerative studies. The rat prostate is larger and more accessible for surgical manipulation, imaging, and biomaterial implantation compared to that of mice. Additionally, the regenerative dynamics of rat connective tissues exhibit closer resemblance to human wound-healing kinetics, making them particularly suitable for evaluating injectable scaffolds aimed at restoring prostate tissue integrity.

Human prostate cancer xenografts in rats represent a powerful methodological bridge between clinical pathology and experimental regenerative engineering. They enable the assessment of tumour-induced fibrosis, stromal remodeling, vascular disruption, and post-treatment tissue degeneration key targets for biomaterial-based therapeutic interventions.

1.4 Methodological Complexity and Reproducibility Challenges

Although xenograft rat models of prostate cancer offer valuable biological insights, their application is constrained by notable technical, ethical, and translational challenges (Hidalgo et al., 2014; Jin et al., 2023). Factors such as inconsistencies in the quality of human biopsy specimens, pronounced tumour heterogeneity, cellular stress induced during tissue preservation, immune system incompatibilities, and non-uniform disease induction methodologies contribute significantly to poor reproducibility between research groups (Ittmann et al., 2013; Risbridger et al., 2018). In addition, the manipulation and propagation of human-derived cancer tissues pose biosafety risks and demand rigorous ethical regulation, particularly in studies involving repeated in-vivo passaging (Day et al., 2015; Gengenbacher et al., 2017).

Moreover, the absence of standardized protocols governing biopsy acquisition, tissue handling, xenograft implantation, and longitudinal disease assessment continues to limit the robustness and translational relevance of these models (Adamiecki et al., 2022; Jin et al., 2023). Such methodological variability is especially detrimental in regenerative medicine investigations, where even minor alterations in the tissue microenvironment can substantially affect biomaterial integration, host responses, and overall therapeutic efficacy (Basak et al., 2022; Risbridger et al., 2018).

1.5 Aim and Scope of the Review

This critical review systematically evaluates the core methodological frameworks underpinning preclinical prostate cancer research, with particular emphasis on four interconnected areas. These include the ethical acquisition and regulatory governance of human prostate cancer biopsy specimens, preanalytical handling and tissue preservation strategies, approaches for inducing human prostate cancer pathology in rat xenograft models, and in-vivo monitoring techniques used to confirm tumour establishment and progression (Ittmann et al., 2013; Adamiecki et al., 2022; Jin et al., 2023).

The review further examines how limitations across these methodological stages influence the reliability and translational relevance of injectable biomaterial scaffold development for prostate tissue regeneration, where experimental outcomes are highly sensitive to variations in the tissue microenvironment (Basak et al., 2022; Germain et al., 2023). In this context, emerging experimental platforms including patient derived prostate organoids and microfluidic prostate on chip systems are discussed as promising alternatives that more accurately recapitulate human tissue architecture, cellular heterogeneity, and dynamic tumour stromal interactions (Risbridger et al., 2018; Farhat et al., 2021; Sailer et al., 2023).

By synthesizing current evidence and critically identifying persistent technical and conceptual limitations, this review seeks to establish a coherent foundation for advancing translational prostate cancer research at the interface of oncology, biomaterials, and regenerative medicine (Gengenbacher et al., 2017; Day et al., 2015).

II. Ethical, Regulatory, and Biosafety Considerations

2.1 Human Tissue Procurement and Consent Frameworks

The use of human prostate cancer biopsy material in preclinical research is regulated by internationally accepted ethical principles, including the Declaration of Helsinki and Good Clinical Practice guidelines. These frameworks require that human tissues are obtained solely from patients undergoing medically justified diagnostic or therapeutic interventions, such as transrectal ultrasound guided biopsy, transurethral resection, or radical prostatectomy, and not for research purposes alone (Ittmann et al., 2013; Day et al., 2015). The secondary use of such specimens for research must be clearly articulated within the informed consent process, specifying the scope of the research, potential risks, duration of tissue storage, and the procedures by which participants may withdraw consent at any stage (Jin et al., 2023).

Prior to sample collection, ethical approval is required from institutional hospital based research ethics committees as well as relevant national regulatory authorities. In low and middle income countries, disparities in research infrastructure, biobanking capacity, and regulatory enforcement can hinder harmonization of ethical practices, highlighting the importance of transparent documentation, traceable audit systems, and robust governance frameworks for tissue repositories (Gengenbacher et al., 2017; Adamiecki et al., 2022).

2.2 Animal Welfare and the 3Rs Principle

The experimental induction of human prostate cancer pathology in rat models is generally classified as a procedure of moderate to high severity under most institutional animal care and use regulations. As a result, investigators are required to demonstrate clear scientific justification that alternative in vitro or in silico approaches are insufficient to address the proposed research objectives (Day et al., 2015; Adamiecki et al., 2022). Ethical implementation of prostate cancer induction studies in rats is guided by the principles of Replacement,

Reduction, and Refinement, collectively referred to as the Three Rs (Table 1), which form the foundation of contemporary laboratory animal welfare frameworks (Gengenbacher et al., 2017).

Replacement prioritizes the use of non-animal methodologies wherever scientifically appropriate, including prostate organoids, three dimensional tumour stroma coculture systems, and microfluidic prostate on chip platforms. These approaches are capable of modelling selected aspects of tumour biology, cell matrix interactions, and biomaterial responses while substantially reducing dependence on whole animal experimentation (Risbridger et al., 2018; Farhat et al., 2021; Sailer et al., 2023). Reduction aims to limit animal numbers without compromising statistical robustness, commonly achieved through rigorous power calculations, longitudinal non-invasive imaging strategies, and experimental designs that enable multiple endpoints to be assessed within the same animal over time (Olkowski et al., 2023; Adamiecki et al., 2022).

Refinement focuses on minimizing pain, distress, and overall disease burden through careful optimization of experimental endpoints, adoption of minimally invasive monitoring techniques, appropriate analgesic support, and the establishment of predefined humane euthanasia criteria (Day et al., 2015; Gengenbacher et al., 2017). Collectively, adherence to the Three Rs not only ensures compliance with animal welfare regulations but also improves data quality, experimental reproducibility, and the translational relevance of prostate cancer xenograft research (Hidalgo et al., 2014; Jin et al., 2023).

Table 1: Application of the Three Rs (Replacement, Reduction, and Refinement) in Human Prostate Cancer Induction Models in Rats

Principle	Definition	Application in Prostate Cancer Xenograft Studies	Methodological Implication	Key References
Replacement	Use of non-animal alternatives wherever possible	Use of prostate organoids, three dimensional tumour stroma culture systems, and microfluidic prostate on chip platforms to model tumour biology prior to in-vivo experimentation	Reduces animal use by enabling early screening of biological hypotheses and injectable biomaterial scaffolds before rat based studies	Rauner et al., 2025; Farhat et al., 2021; Mahadik et al., 2025
Reduction	Minimization of the number of animals used while maintaining scientific validity	Application of statistical power calculations and longitudinal imaging approaches to obtain multiple outcome measures from the same animals over time	Ensures efficient animal utilization while preserving statistical robustness and experimental reliability	Gengenbacher et al., 2017; Olkowski et al., 2023
Refinement	Modification of experimental procedures to minimize pain distress and suffering	Implementation of minimally invasive monitoring techniques optimized experimental endpoints appropriate analgesic protocols and clearly defined humane euthanasia criteria	Improves animal welfare while enhancing data quality reproducibility and translational relevance	Day et al., 2015; Zaky et al., 2025

2.3 Biosafety and Dual-Use Risks

Human derived cancer tissue is regarded as a potential biological hazard because of the risk of blood borne pathogens, oncogenic viruses, and unidentified microbial contaminants. Consequently, experimental work involving human prostate cancer specimens must be conducted in facilities that comply with biosafety level 2 containment standards, including restricted laboratory access, validated decontamination procedures, and fully traceable waste management systems (Day et al., 2015; Gengenbacher et al., 2017). In addition, the transplantation of human cancer tissue across species boundaries introduces further concerns related to zoonotic transmission and dual use risk, thereby requiring formal review and ongoing oversight by institutional biosafety committees (Hidalgo et al., 2014; Jin et al., 2023).

Reported tumour engraftment success in human prostate cancer xenograft models, which ranges from approximately 40 to 60 percent in subcutaneous implantation settings and may reach up to 95 percent in highly vascularized sites such as the renal capsule, highlights an important yet frequently underrecognized biosafety consideration (Ittmann et al., 2013; Risbridger et al., 2018). High engraftment efficiency reflects sustained tissue viability, active proliferative capacity, and preservation of biological function within the host animal. While these attributes are essential for ensuring translational relevance, they also intensify biosafety and dual use concerns by demonstrating the continued pathogenic potential of transplanted human cancer tissue in-vivo (Hidalgo et al., 2014; Jin et al., 2023).

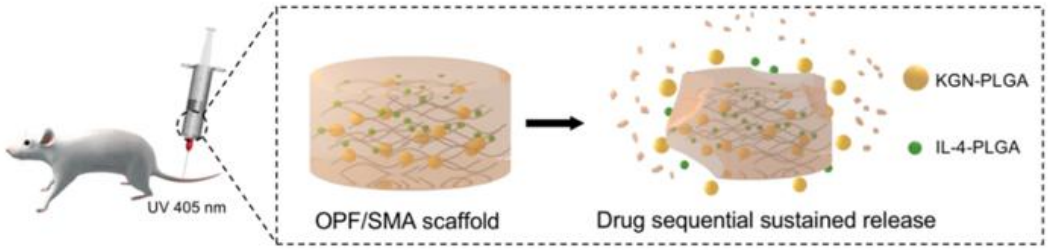

Figure 2: Schematic illustration of an OPF/SMA hydrogel scaffold loaded with dual drug PLGA microspheres for sequential sustained release. Adapted from Cheng et al. (2022).

Human prostate cancer specimens are designated as biosafety level 2 materials because of the potential presence of blood borne pathogens, oncogenic viruses, and patient specific microbial contaminants (Day et al., 2015; Gengenbacher et al., 2017). Reports describing elevated tumour engraftment success, particularly in studies using patient derived xenograft models that retain key histological and molecular features, indicate that transplanted tissues preserve not only malignant phenotypes but also associated biological risks (Hidalgo et al., 2014; Risbridger et al., 2018). As a result, laboratories achieving high levels of engraftment efficiency are required to implement stringent containment measures, including restricted facility access, validated decontamination procedures, and fully traceable waste management systems, in order to minimize occupational exposure and prevent unintended environmental dissemination (Jin et al., 2023; Day et al., 2015).

Table 2: Reported Success (Take) Rates and Case Data for Human Prostate Cancer Xenograft Models

Study / Model	Host / Species	Type of Xenograft	Key Outcome / Success Value	Notes	Key References
Subcutaneous and orthotopic prostate cancer xenografts	Immunodeficient rodents	Orthotopic implantation of human prostate cancer cells	Tumour take rates typically range from 60–70% within 6–8 weeks	Tumour growth is measurable using non-invasive imaging, with histopathology confirming adenocarcinoma phenotype	Inoue et al., 2017; Hidalgo et al., 2014
Aggregated engraftment rates across solid tumours	Immunodeficient rodents	Patient-derived xenografts (PDX)	Take rates vary by tumour aggressiveness, with higher success observed in poorly differentiated malignancies	Prostate cancer PDXs demonstrate higher engraftment success in advanced or treatment-resistant disease	van de Merbel et al., 2021; Jin et al., 2023
Implantation site comparison	Immunodeficient rodents	Subcutaneous vs subrenal capsule PDX	Subcutaneous implantation shows approximately 40–60% take rate, while subrenal capsule implantation approaches 90–95%	Highly vascularized implantation sites enhance tumour survival and reduce latency periods	Ittmann et al., 2013; Hidalgo et al., 2014
Renal capsule xenografts of human prostate tumours	Immunodeficient rodents	Renal capsule grafts of primary prostate cancer tissue	Moderate to high engraftment efficiency with preserved histological features	Xenografts retain genomic integrity and prostate specific antigen expression	Davies et al., 2018; Wang et al., 2005
Large scale prostate cancer PDX collections	Immunodeficient rodents	Serially transplantable prostate tumour PDX cohorts	Establishment of multiple stable PDX lines spanning primary and metastatic disease	Demonstrates feasibility of generating representative PDX repositories for translational research	Risbridger et al., 2018; van de Merbel et al., 2021

In addition, the transplantation of viable human cancer tissue across species boundaries introduces further concerns related to zoonotic adaptation and the potential for dual use misuse. Although there is currently no direct evidence of zoonotic transmission resulting from prostate cancer xenograft research, the sustained maintenance of human malignant tissue within immunocompromised rodent hosts presents theoretical risks that justify careful institutional oversight (Hidalgo et al., 2014; Jin et al., 2023). These concerns are particularly relevant in investigations involving serial passaging or prolonged tumour maintenance, where cumulative exposure and biological adaptation may increase uncertainty and risk over time (Ittmann et al., 2013; Risbridger et al., 2018).

Importantly, the observed association between high tumour engraftment success and biosafety risk underscores the need for proportionate regulatory scrutiny. Experimental models demonstrating superior engraftment efficiency, including renal capsule implantation or orthotopic prostate models, warrant more rigorous review by institutional biosafety committees than lower efficiency systems (Hidalgo et al., 2014; Gengenbacher et al., 2017). Such an approach aligns with responsible research and innovation principles by ensuring that advances in methodological performance are accompanied by appropriate ethical and safety governance (Day et al., 2015). Within this framework, reported xenograft success rates should not be interpreted solely as markers of experimental robustness, but also as indicators prompting enhanced biosafety management. Incorporating engraftment efficiency metrics into biosafety risk assessment strategies enables a more comprehensive evaluation of human prostate cancer xenograft studies, particularly as these models are increasingly applied in regenerative medicine and biomaterial scaffold research (Risbridger et al., 2018; Basak et al., 2022).

III. Methodological Principles in Human Prostate Cancer Biopsy Collection

3.1 Clinical Pathways for Tissue Acquisition

Human prostate cancer tissue used for preclinical investigations is typically obtained from three main clinical sources, namely diagnostic needle biopsy, transurethral resection, and radical prostatectomy specimens (Ittmann et al., 2013; Kato et al., 2021). Of these sources, radical prostatectomy material offers the most extensive representation of tumor heterogeneity, stromal interactions, and extracellular matrix organization, making it particularly valuable for studies aiming to preserve native tissue architecture and biological complexity (Risbridger et al., 2018; Davies et al., 2018). In contrast, diagnostic biopsy samples are generally more accessible but are constrained by limited tissue volume, sampling bias, and reduced representation of tumor stroma interactions, which may compromise their translational relevance in advanced modeling applications (Ittmann et al., 2013; Jin et al., 2023).

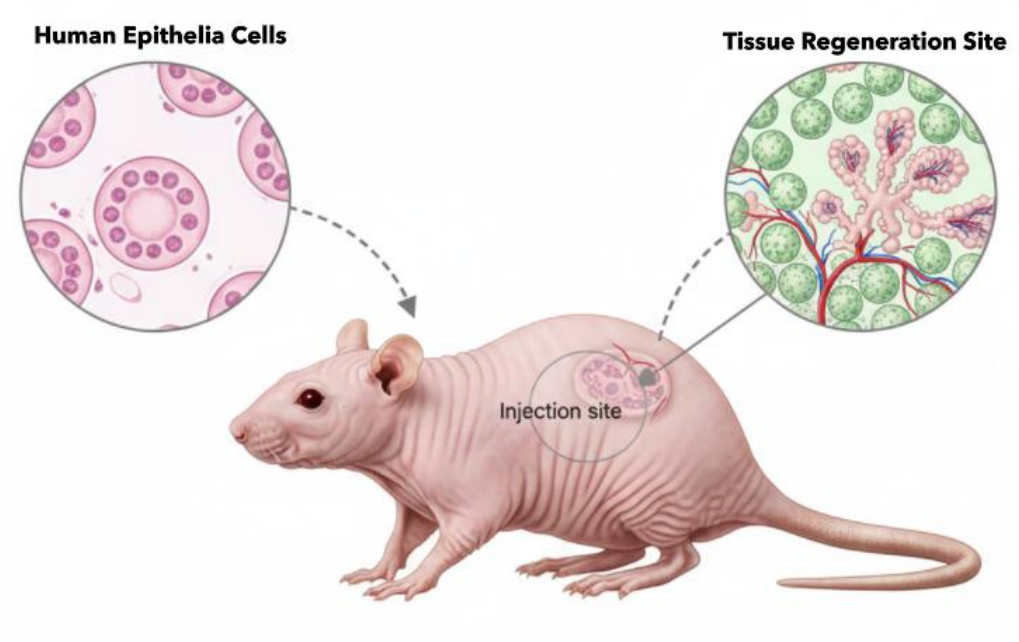

Figure 3: Xenograft methodology for prostate tissue repair

Table 3: Clinical Pathways for Human Prostate Cancer Tissue Acquisition

Clinical Pathway	Source of Tissue	Typical Clinical Indication	Type of Tissue Obtained	Research Relevance	Key Limitations	Key References
Transrectal Ultrasound-Guided Needle Biopsy (TRUS biopsy)	Prostate needle core samples	Initial diagnosis of suspected prostate cancer	Small localized tumour cores	Useful for molecular profiling and early-stage tumour characterization	Limited tissue volume sampling bias and reduced stromal content	Kato et al., 2021; Madu & Lu, 2010
Transperineal Prostate Biopsy	Systematic or targeted	Diagnostic confirmation	Multiple tumour-	Improved tumour localization and	Limited preservation of	Adamiecki et al., 2022;

	needle cores via perineum	and tumour mapping	containing cores	reduced infection risk compared to transrectal approach	tissue architecture and stromal complexity	Basak et al., 2022
Radical Prostatectomy	Entire prostate gland	Curative treatment for localized prostate cancer	Whole-organ tumour and surrounding stroma	Gold standard for preserving tumour heterogeneity extracellular matrix integrity and tumour microenvironment	Restricted to surgically eligible patients with localized disease	Risbridger et al., 2018; Davies et al., 2018
Transurethral Resection of the Prostate (TURP)	Prostate tissue chips	Relief of urinary obstruction often in advanced disease	Fragmented tumour and benign tissue	Enables investigation of obstructive and advanced disease states	Tissue fragmentation and thermal artefacts affecting viability	Centenera et al., 2013; Jin et al., 2023
Metastatic Lesion Biopsy	Bone or soft tissue metastases	Advanced or castration-resistant prostate cancer	Secondary tumour tissue	Enables study of late-stage disease progression and therapy resistance	Does not reflect primary prostate microenvironment	Beltran et al., 2019; Chang et al., 2014
Autopsy-Derived Prostate Tissue	Post-mortem prostate specimens	Research and pathological studies	Extensive tumour tissue	Allows large-scale histopathological and anatomical analysis	Post-mortem degradation and limited functional viability	Pistollato et al., 2020; Elmore et al., 2021

The clinical routes for obtaining human prostate cancer tissue summarized in Table 3 illustrate that no single acquisition pathway is universally optimal, as each source presents specific methodological advantages and constraints that directly influence translational relevance (Ittmann et al., 2013; Kato et al., 2021). Diagnostic needle biopsy specimens, including those obtained through transrectal or transperineal procedures, are widely accessible but typically yield small tissue volumes with pronounced sampling bias and limited stromal content, thereby restricting their utility in studies that require preserved tumour architecture and tumour stroma interactions (Jin et al., 2023; Risbridger et al., 2018).

Radical prostatectomy specimens represent the most biologically informative tissue source, as they maintain tumour heterogeneity, stromal organization, and extracellular matrix integrity, making them particularly suitable for xenograft establishment and regenerative medicine investigations (Davies et al., 2018; Risbridger et al., 2018). However, access to such material is largely confined to patients with localized disease eligible for surgical treatment, which introduces an inherent selection bias (Ittmann et al., 2013). Tissue obtained from transurethral resection procedures and biopsies of metastatic lesions enables the study of more advanced disease stages but is often compromised by tissue fragmentation, thermal damage, or loss of the native microenvironment, limiting functional interpretation (Adamiecki et al., 2022; Jin et al., 2023). Autopsy derived samples may provide substantial tissue quantities but are subject to post mortem degradation, reducing their suitability for functional and regenerative applications (Gengenbacher et al., 2017).

Accordingly, the selection of a tissue acquisition pathway should be carefully matched to the specific aims of the study, with balanced consideration of biological fidelity, ethical and regulatory constraints, and the requirements of downstream experimental platforms (Basak et al., 2022; Sailer et al., 2023).

3.2 Determinants of Tissue Quality

The biological quality of human prostate cancer tissue plays a decisive role in determining its appropriateness for translational and regenerative research applications. Critical parameters include tumour grade, most commonly evaluated using the Gleason scoring system, which influences tumour aggressiveness, growth kinetics, and engraftment potential, as well as androgen receptor status, which regulates hormonal sensitivity and treatment response (Shen & Abate Shen, 2010; Wang et al., 2021). In addition, stromal composition and preservation of extracellular matrix structure are essential considerations for investigations focused on tissue remodeling, cell matrix interactions, and biomaterial scaffold integration (Risbridger et al., 2018; Davies et al., 2018).

Further determinants such as intratumoral hypoxia, overall cellular viability, and the degree of necrosis have a direct impact on xenograft establishment, tumour take rates, and experimental reproducibility across studies (Ittmann et al., 2013; Hidalgo et al., 2014). Inadequate control, characterization, or reporting of these variables can introduce systematic bias, compromise data interpretation, and ultimately reduce the translational relevance of prostate cancer model systems used in preclinical research (Basak et al., 2022; Sailer et al., 2023).

Table 4: Determinants of Human Prostate Cancer Tissue Quality

Determinant	Description	Impact on Research Quality
Gleason Score	Indicates tumour grade and aggressiveness	Influences growth behavior and model relevance
Androgen Receptor Status	Reflects hormonal responsiveness	Affects tumour progression and treatment response
Stromal Composition	Proportion of stroma and extracellular matrix	Determines tissue remodeling and scaffold integration
Cellular Viability	Proportion of live tumour cells	Affects engraftment success and reproducibility
Necrosis Level	Extent of non-viable tissue	Reduces functional and translational applicability

3.3 Pre-Analytical Variability

Errors arising during preanalytical handling represent one of the most frequent sources of experimental artefact in prostate cancer research. Variables including prolonged ischemic intervals, temperature instability, mechanical stress during tissue manipulation, and enzymatic degradation can substantially disrupt cellular metabolism and alter tumour associated signalling pathways prior to experimental application, thereby compromising biological fidelity and downstream reproducibility (Ittmann et al., 2013; Kato et al., 2021; Risbridger et al., 2018; Jin et al., 2023).

IV. Preparation and Preservation of Prostate Cancer Biopsies

4.1 Tissue Stabilization Concepts

Immediately following surgical excision, prostate tissues undergo rapid metabolic collapse due to oxygen deprivation and nutrient withdrawal. Conceptually, preservation strategies are therefore designed to maintain:

- Membrane integrity
- Oncogenic signalling cascades
- Extracellular matrix microstructure

Short-term stabilization methods are typically used for immediate experimental application, whereas long-term storage requires cryogenic approaches.

4.2 Cryogenic Preservation Challenges

Cryopreservation enables the long term storage of large collections of patient derived prostate cancer specimens, thereby supporting longitudinal investigations and facilitating inter laboratory collaboration (Kato et al., 2021; Jin et al., 2023). Despite these advantages, the freezing and thawing process is frequently associated with ice crystal formation, osmotic stress, and cryoprotectant related toxicity, all of which can reduce cellular viability and induce phenotypic alterations in tumour tissue (Risbridger et al., 2018; Hidalgo et al., 2014). These drawbacks are particularly consequential for regenerative medicine applications, where preservation of native cell matrix interactions and microenvironmental integrity is essential for accurate evaluation of biomaterial performance and tissue remodeling responses (Basak et al., 2022; Sailer et al., 2023).

4.3 Impact of Preservation on Tumour Microenvironment

Emerging evidence suggests that prolonged storage alters:

- Matrix stiffness
- Collagen cross-linking
- Cytokine gradients

Such changes can profoundly influence tumour growth dynamics and the performance of injectable biomaterial scaffolds, thereby confounding translational outcomes.

V. Rationale and Conceptual Framework for Xenograft Induction in Rats

5.1 Why Human-Derived Xenografts?

Patient derived xenograft models maintain the genomic landscape and phenotypic diversity of primary prostate tumours with substantially greater fidelity than immortalized cell line systems, which often undergo genetic drift and loss of clinical relevance over time (Hidalgo et al., 2014; Risbridger et al., 2018). Preservation of this intratumoral heterogeneity is critical for investigating complex biological processes such as fibrosis development, angiogenic signaling, and tissue remodeling responses that occur following tumour related injury (Basak et al., 2022; Sailer et al., 2023). As a result, patient derived xenografts provide a more representative platform for evaluating biomaterial scaffold interactions within a biologically relevant microenvironment, particularly in the context of regenerative and translational prostate cancer research (Davies et al., 2018; Jin et al., 2023).

5.2 Host-Tumour Microenvironment Interactions

Successful establishment of prostate cancer xenografts is strongly influenced by the degree of compatibility between the implanted tumour tissue and the host microenvironment. Processes such as neovascularization, immune escape mechanisms, and recruitment of host stromal components act in concert to support tumour survival and sustained growth following transplantation (Hidalgo et al., 2014; Ittmann et al., 2013). In rat based xenograft models, these interactions are further shaped by the hormonal environment and species specific growth factor signaling pathways, which can modulate tumour behavior and affect experimental outcomes (Risbridger et al., 2018; Sailer et al., 2023).

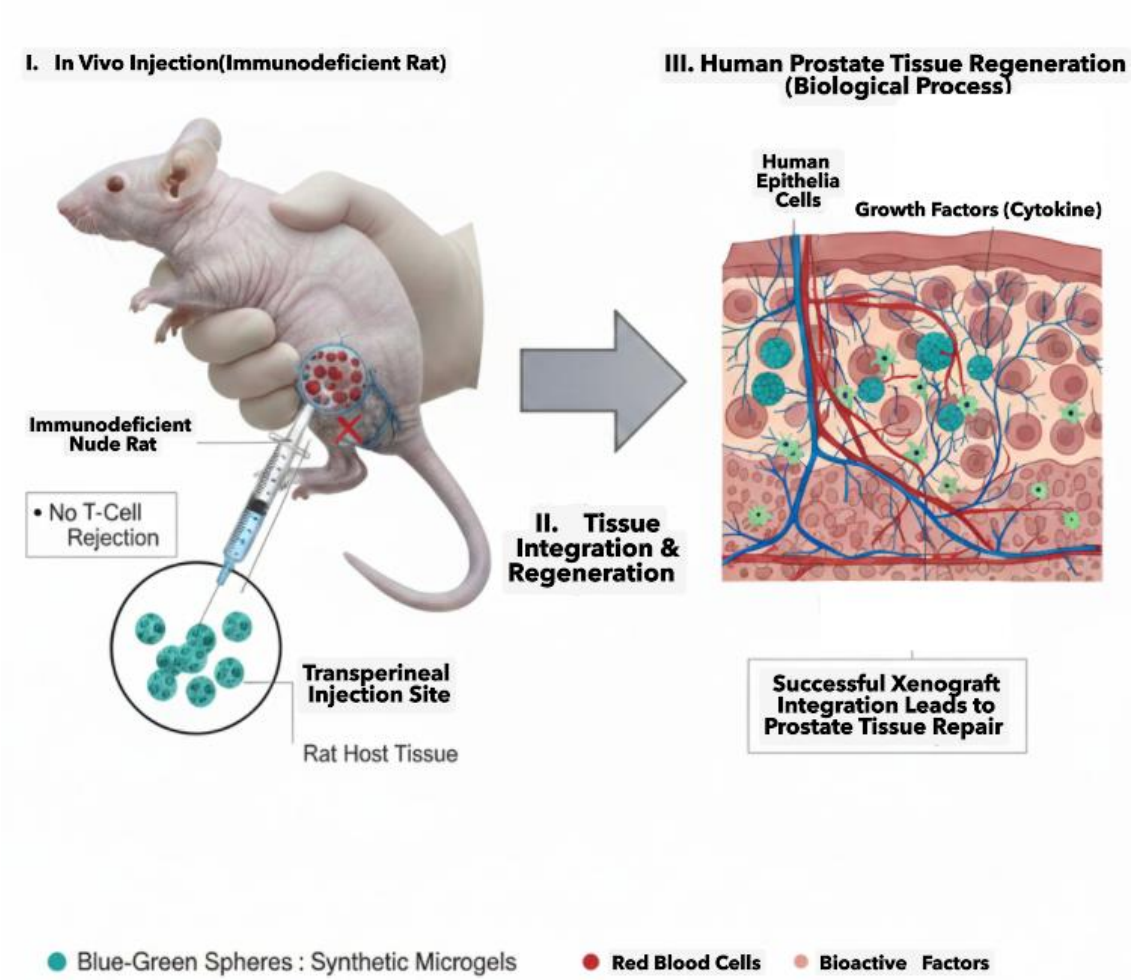

Figure 4: Xenograft Modeling of Human Prostate Tissue Regeneration using Synthetic Microgel Scaffolds via Transperineal Injection in Immunodeficient Rats

This figure illustrates the xenograft methodology for prostate tissue repair. (I) Synthetic blue-green microgels are delivered via transperineal injection into an immunodeficient nude rat, which lacks T-cell rejection. (II) Over time, the scaffold facilitates tissue integration and the signaling of bioactive factors. (III) The resulting biological process shows successful human epithelia regeneration, supported by rat host vasculature and cytokine-mediated growth factors.

VI. In-vivo Monitoring of Prostate Cancer Progression

6.1 Clinical Observation Metrics

Animals bearing prostate cancer xenografts are routinely monitored for behavioral and physiological signs indicative of disease burden, including changes in grooming behavior, impaired mobility, progressive weight loss, and abnormalities in urinary function. These observable and non-invasive indicators serve as sensitive early markers of tumour associated distress and are widely used to inform timely implementation of humane endpoints in accordance with animal welfare guidelines (Zaky et al., 2025; Ruddat et al., 2005). In addition, longitudinal

assessment of these parameters complements imaging based and pathological evaluations by enabling continuous evaluation of disease progression without increasing procedural burden on the animal (Olkowski et al., 2023).

Table 5: Clinical Observation Metrics for Monitoring Prostate Cancer Progression in Rat Models

Observation Metric	Description	Significance
Body weight change	Monitoring of weight loss or gain over time	Indicator of systemic disease burden and overall health
Behavior and mobility	Assessment of grooming, activity level, and posture	Reflects pain, distress, or functional impairment
Urinary function	Observation of urine output or retention	Indicates prostate-related obstruction or dysfunction
Physical appearance	Changes in fur condition or body condition score	Provides early signs of disease progression or distress

6.2 Imaging-Based Assessment

Advanced imaging modalities including ultrasound, magnetic resonance imaging, and positron emission tomography allow repeated and non-destructive assessment of tumour burden, vascular development, and tissue structural changes over time. These longitudinal approaches are especially advantageous in preclinical prostate cancer studies because they permit continuous monitoring of disease progression and therapeutic response without requiring early animal sacrifice (Lee & Kim, 2025; Bidkar et al., 2024). Such imaging strategies are particularly well suited for evaluating the regenerative performance of injectable biomaterial scaffolds, as they enable dynamic visualization of tissue remodeling and scaffold integration within the host environment across extended experimental timelines (Skidmore et al., 2024; Agarwal et al., 2023).

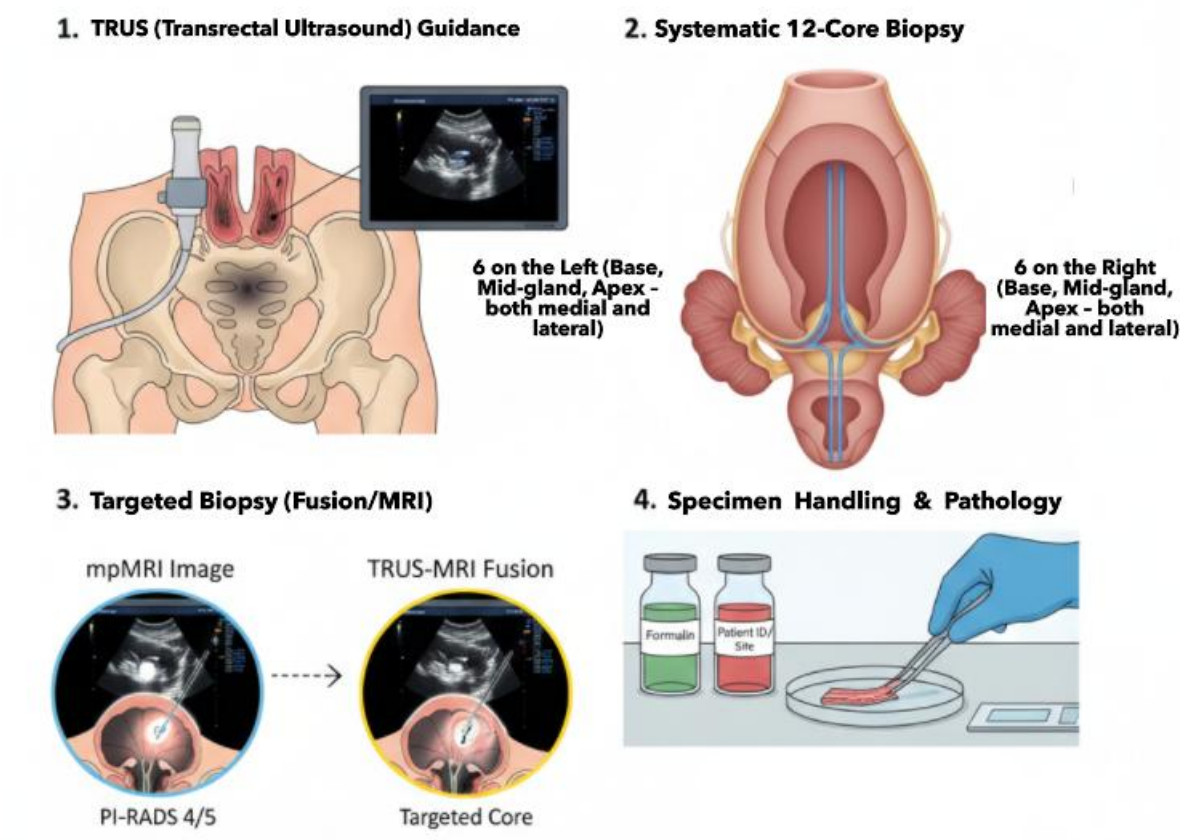

Figure 5: Workflow of transrectal ultrasound guided and MRI fusion prostate biopsy with pathological processing.

Table 6: Imaging Modalities for In-vivo Assessment of Prostate Cancer Progression in Rat Models

Imaging Modality	Primary Assessment Capability	Relevance to Regenerative Studies	Key References
Ultrasound	Tumour size, prostate morphology, gross tissue changes	Enables real time, low cost monitoring of tumour growth, scaffold placement, and gross tissue responses without sacrificing animals	Adamiecki et al., 2022; Olkowski et al., 2023
Magnetic Resonance Imaging (MRI)	Soft tissue contrast, tumour architecture, fibrosis	Provides high resolution evaluation of tissue remodeling, stromal changes, and biomaterial scaffold integration	Lee & Kim, 2025; Centenera et al., 2013
Positron Emission Tomography (PET)	Metabolic activity and tumour viability	Allows functional assessment of tumour progression, angiogenic activity, and therapeutic or regenerative response	Bidkar et al., 2024; Agarwal et al., 2023

VII. End-Point Validation and Histopathological Assessment

End point validation represents a critical step in confirming the successful establishment and progression of prostate cancer pathology in rat models, as well as in differentiating malignant transformation from benign hyperplasia or inflammation driven tissue changes. At predefined experimental endpoints, excised prostate tissues are subjected to detailed histopathological examination to evaluate tumour distribution, depth of invasion, stromal remodeling, and tissue degeneration, thereby confirming biological relevance and disease fidelity (van de Merbel et al., 2021; Elmore et al., 2021).

Routine histological staining techniques enable assessment of glandular organization, fibrosis, and overall tissue architecture, while immunohistochemical analyses facilitate the detection of tumour associated markers, cellular proliferation indices, and angiogenic activity that collectively define malignant progression (Miyahira et al., 2023; Carnevali et al., 2024). In the context of regenerative medicine research, histopathological evaluation also provides indispensable insight into host biomaterial interactions, scaffold integration, and tissue repair dynamics, supporting objective assessment of therapeutic efficacy (Mahadik et al., 2025; Bhoir & De Benedetti, 2025).

Together, these end point analyses enhance confidence in disease modeling accuracy, strengthen the interpretability of experimental outcomes, and reinforce the translational credibility of preclinical prostate cancer studies employing xenograft and regenerative strategies (Colonna, 2025; Elmore et al., 2021).

Table 7: End-Point Validation and Histopathological Assessment in Prostate Cancer Rat Models

Assessment Method	Purpose	Research Relevance	Key References
Histological staining	Evaluation of tissue architecture, tumour presence, and fibrosis	Confirms disease establishment, tumour localization, and extent of tissue degeneration	Huang et al., 2016; Garcia López, 2013
Immunohistochemistry	Detection of tumour, proliferation, and angiogenic markers	Differentiates malignant tissue from benign hyperplasia or inflammatory changes	Zhao et al., 2022; Angel et al., 2023
Molecular analysis	Assessment of gene and protein expression profiles	Validates tumour phenotype, treatment response, and regenerative signaling pathways	Madu & Lu, 2010; Shen & Abate-Shen, 2000
Biomaterial–tissue interface analysis	Examination of scaffold integration and host tissue response	Determines effectiveness of regenerative interventions and quality of tissue repair	Bidkar et al., 2024; Tamura et al., 2024

VIII. Implications for Injectable Biomaterial Scaffold Development

Injectable biomaterial scaffolds have emerged as a promising therapeutic approach for restoring prostate tissue architecture and functional integrity following tumour related injury or cancer treatment. Human prostate cancer xenograft models offer a disease relevant microenvironment in which the regenerative effects of these scaffolds on fibrosis regulation, angiogenic responses, and tissue remodeling processes can be systematically investigated (Kwon & Joung, 2025; Flores Islas et al., 2026). Unlike studies conducted in healthy animal systems, xenograft based models incorporate tumour driven alterations in extracellular matrix composition, vascular integrity, and inflammatory signaling pathways, thereby enabling a more physiologically representative evaluation of scaffold behavior and performance (Tavares et al., 2024).

As a result, prostate cancer xenograft systems provide critical insight into biomaterial tissue interactions under pathological conditions, supporting more accurate assessment of regenerative outcomes and enhancing the translational relevance of scaffold based therapeutic strategies intended for clinical application (Kwon & Joung, 2025; Flores Islas et al., 2026).

IX. Emerging Alternatives and Future Directions

Advanced in vitro and microengineered experimental platforms are increasingly being recognized as credible alternatives to animal based prostate cancer models, particularly in efforts aimed at ethical refinement and improved translational precision. Prostate organoids generated from patient derived tissues retain essential characteristics such as tumour heterogeneity, androgen dependent behavior, and epithelial stromal interactions, thereby enabling investigation of disease progression and therapeutic response in a patient specific context. Their scalability and compatibility with high throughput screening approaches make organoid systems particularly attractive for early phase evaluation of biomaterials and regenerative interventions (Mostafa et al., 2025).

Three dimensional bioprinted tumour stroma constructs further enhance model sophistication by enabling controlled spatial arrangement of malignant cells, stromal fibroblasts, endothelial populations, and extracellular matrix components. These platforms allow precise modulation of matrix stiffness, formation of vascular like structures, and establishment of biochemical gradients, offering mechanistic insight into tumour microenvironment interactions that are difficult to dissect in whole animal systems (Gjyrezi et al., 2020). In parallel, prostate on chip microfluidic technologies recreate dynamic physiological conditions such as fluid flow, nutrient exchange, and paracrine communication, permitting real time observation of tumour behavior and treatment responses under tightly regulated conditions (Mostafa et al., 2025).

Despite these advantages, such platforms do not yet fully recapitulate systemic interactions, including immune surveillance and endocrine regulation, which play central roles in prostate cancer biology and treatment resistance. As a result, future research is expected to favor integrated experimental strategies in which advanced in vitro systems are employed to reduce and refine animal experimentation rather than replace it entirely, thereby accelerating translational progress while upholding ethical responsibility and scientific rigor (Gjyrezi et al., 2020).

X. Conclusion

Human prostate cancer xenograft models in rats constitute a powerful yet technically complex platform for advancing regenerative medicine research. This critical review has examined the interconnected methodological factors that shape the reliability and translational relevance of these models, including ethical pathways for human tissue acquisition, intrinsic determinants of tissue quality, and challenges associated with preparation, preservation, and in-vivo disease induction. Variability arising from clinical tissue sources, pre-analytical handling conditions, and tumour heterogeneity exerts a substantial influence on experimental outcomes and must be systematically controlled to ensure reproducibility and interpretability across studies (Tan et al., 2009; Chang et al., 2014).

The review further emphasizes the necessity of rigorous adherence to ethical and regulatory principles, particularly the application of Replacement, Reduction, and Refinement, as a means of minimizing animal burden while preserving scientific validity. Comprehensive disease monitoring strategies that integrate clinical observation, advanced imaging modalities, and detailed histopathological validation are essential for accurately defining tumour progression and for objectively assessing the regenerative impact of therapeutic interventions (Elmore et al., 2021; Chang et al., 2014).

Importantly, the convergence of xenograft based approaches with emerging alternatives such as patient derived prostate organoids, three dimensional bioprinted tumour stroma constructs, and prostate on chip systems offers a complementary experimental framework. This integrative strategy enhances mechanistic insight, while supporting ethical refinement through reduced reliance on animal models (Rauner et al., 2025; Tan et al., 2009). When applied within a clearly defined ethical, biosafety, and methodological framework, human prostate cancer xenograft models in rats remain an indispensable translational tool for the development and evaluation of injectable biomaterial scaffolds aimed at restoring prostate tissue structure and function following cancer therapy.

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