

## Recent Advances in Application of Tissue Engineering to Cancer Biology

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Tissue engineering is an interdisciplinary field that applies the principles of engineering (materials science and biomedical engineering) and the life sciences (biochemistry, genetics, cell and molecular biology) to develop biological substitutes of human body parts to improve, replace or restore their biological functions [1]. Tissue engineering started as a research field dedicated to regeneration of skin, bone, and cartilage. More recently tissue engineering is being investigated for reconstruction of more complex, vascularised tissues, such as the liver or pancreas and development of novel 3D models of solid tumours [2].

Cancer biologists use monolayers of tumour cells for pre clinical drug testing. These 2D models of tumour cells lack *in vivo* tumour behaviour therefore are not ideal models for pre-clinical drug testing [3,4]. As a result of current 2D model inadequacies only 5% of cancer drug candidates enter clinical trials to receive approvals from U.S. Food and Drug Administration [5]. This represents a huge burden, both financially and clinically, as limited resources are devoted to compounds that will never demonstrate clinical benefit [6]. On the contrary 3D models of solid tumours closely resemble *in vivo* tumour microenvironment and metabolic characteristics [7]. 3D models of solid tumour consist of numerous cells grown in close contact in the presence of extra cellular matrix [8]. It is known that multicellular spheroids (a kind of 3D tumour model) show greater drug resistance than monolayer of tumour cells and closely resemble the drug resistance offered by solid tumours *in vivo* [9]. The reason for this is tumour cells when cultured in 3D in the presence of ECM change shape, lose polarity and form disorganized proliferative masses or aggregates similar to those seen in tumour progression *in vivo* [10,11]. Thus 3D tumour models are of increased biological significance and clinical relevance [12].

One of the major differences between 2D monolayers and 3D tumour models is the presence of extracellular matrix. Extra cellular matrix binds to cell surface adhesion molecules such as integrin and plays a vital role in development of tumours [12]. Naturally occurring as well as synthetic extra cellular matrix has been used to generate 3D tumour models. Among naturally occurring extra cellular matrix, matrigel, which consists of mainly type IV collagen and laminin has been extensively used [13]. Apart from matrigel, type I collagen gels has also been consistently used to develop 3D cancer models. It is suggested that cancer metastasis requires cancer cells to interact with a stromal environment that is often dominated by cross-linked networks of collagen. Therefore 3D gels of native type I or IV collagen are used to recreate an *in vivo* like environment for migrating cancer cells [14-17]. Another important factor in extra cellular matrix gels is their microstructure. Gel microstructure is often hard to control as it depends on a number of factors including crosslinking agent, temperature and pH. Due to these and other limitations of naturally derived gels synthetic hydrogel-like biomaterials and scaffolds have been developed. These synthetic gels and scaffolds mimic key features of extra cellular matrix. Synthetic hydrogel offer may salient features including consistent matrix morphology, degradation rates and mechanical properties [15].

Over time different kinds of synthetic hydrogels and scaffolds have been developed from a wide variety of polymers. Out of which, macromers or copolymers of polyethylene glycol are the most common.

The reason for this is the fact that polyethylene glycol readily forms a 3D polymeric network upon physical or chemical cross-linking. These 3D polymeric network can even be made biodegradable by insertion of functional unit that can be cleaved enzymatically [18]. Combination of Arg-Gly-Asp (RGD) and aligante has also been used to make extra cellular matrix gel. One of the unique features of this gel is its controllable mechanical properties. Due to this many recent studies have used this gel system [19]. A more recent alternative to use of hydrogel and scaffold is 3D cell culture system. These systems consist of carcinoma cell seeded scaffolds. The angiogenic characteristics of these systems are found to be similar to 3D *in vitro* model and *in vivo* tumor xenograft experiments, but different from those observed in routine 2D cell culture system suggesting that these 3D cell culture systems are promising 3D models of *in vivo* tumour xenografts [20]. All the above suggests that deep interdisciplinary linkages between tissue engineering and integrative cancer and tumour biology (Figure 1) [21].

Part of the reason for this is that existing methods for imaging and analysing cell function and protein distribution are not compatible with 3D tumour models [22]. Therefore new methods need to be developed that take into consideration differences between 2D and 3D tumour models. Despite of all these challenges it is clear that 3D tumour

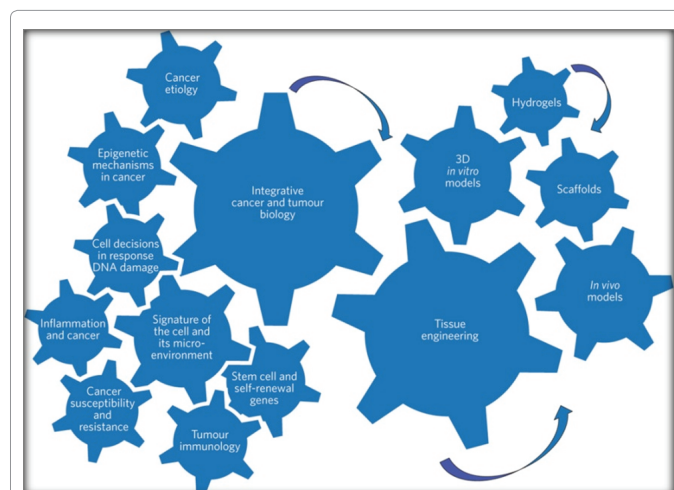


Figure 1: Deep interdisciplinary linkages between tissue engineering and integrative cancer and tumour biology [21].

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Received December 12, 2013; Accepted December 13, 2013; Published December 26, 2013

Citation: Lal S (2013) Recent Advances in Application of Tissue Engineering to Cancer Biology. J Biomim Biomater Tissue Eng 18: e102. doi: [10.4172/1662-100X.1000e102](http://dx.doi.org/10.4172/1662-100X.1000e102)

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models are superior to 2D models. 3D tumour models are not only ideal systems to model tumour cell behaviour and drug response but also novel candidates for elucidation of fundamental understanding of biological processes. Additionally, 3D tumour models are also ideal for studying the influence of biomechanical forces on tumour formation and homeostasis.

Conclusively, current 3D tumour model systems have limitations in mimicking the tumour behaviour *in vivo* but the innovation of new hydrogels, scaffolds and co-culture systems will help cancer biologist's leverage on the novelties of 3D tumour model systems for pre clinical drug testing and studying pathways responsible for the growth and metastasis of cancer.

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Citation: Lal S (2013) Recent Advances in Application of Tissue Engineering to Cancer Biology. J Biomim Biomater Tissue Eng 18: e102. doi: 10.4172/1662-100X.1000e102

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