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Advanced cell culture technology generation of in vivo-like tissue models

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Abstract

Human tissues are mostly composed of different cell types, that are often highly organised in relation to each other. Often cells are arranged in distinct layers that enable signalling and cell-to-cell interactions. Here we describe the application of scaffold-based technology, that can be used to create advanced organotypic 3D models of various tissue types that more closely resemble in vivo-like conditions (Knight *et al*., 2011). The scaffold comprises a highly porous polystyrene material, engineered into a 200 micron thick membrane that is presented in various ways including multi-welled plates and well inserts, for use with conventional culture plasticware and medium perfusion systems. This technology has been applied to generate numerous unique types of co-culture model. For example: 1) a full thickness human skin construct comprising dermal fibroblasts and keratinocytes, raised to the air-liquid interface to induce cornification of the upper layers (Fig.1) (Hill *et al*., 2015); 2) a neuron-glial co-culture to enable the study of neurite outgrowth interacting with astroglial cells to model and investigate the glial scar found in spinal cord injury (Clarke *et al*., 2016); 3) formation of a sub-mucosa consisting of a polarised simple epithelium, layer of ECM proteins simulating the basement membrane, and underlying stromal tissues (e.g. intestinal mucosa). These organotypic models demonstrate the versatility of scaffold membranes and the creation of advanced in vivo-like tissue models. Creating a layered arrangement more closely simulates the true anatomy and organisation of cells within many tissue types. The addition of different cell types in a temporal and spatial fashion can be used to study inter-cellular relationships and create more physiologically relevant in vivo-like cell-based assays. Methods that are relatively straightforward to use and that recreate the organised structure of real tissues will become valuable research tools for use in discovery, validation studies, and modeling disease.

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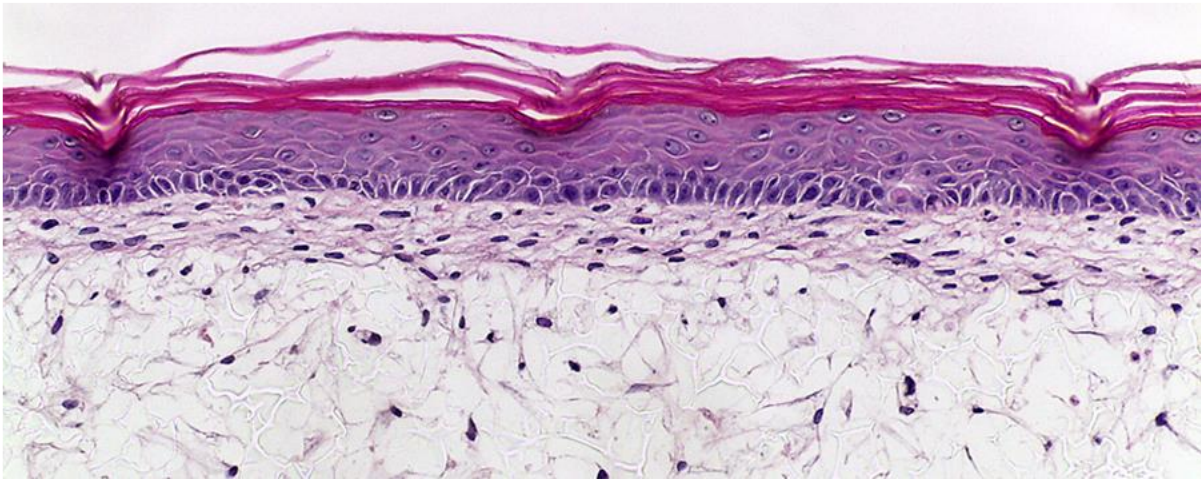

Fig. 1 *This figure showcases the potential of 3D cell culture technology and how it can be used to create tissue-like models. The histological image reveals the cellular structure of a human skin equivalent. The full thickness of the epidermis is shown resting on the underlying dermis. The model is built on the Alvetex® platform that consists of a porous polystyrene scaffold in which human dermal fibroblasts are seeded. These cells produce exogenous collagens to form the dermal compartment. Human keratinocytes are then seeded onto the surface of the dermal model that is subsequently raised to air-liquid interface where they differentiate, stratify and form a mature epidermis. The layers of cells in the 3D culture model replicate those in the real tissue, including the formation of the skin barrier and the surface stratum corneum (Figure courtesy of S.Bradbury, Durham University)*

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