Genuine 3D Cell Culture, Simply and Routinely

Reprocell.com
Culturing cells in three dimensions (3D)

The goal of three-dimensional (3D) cell culture is to eliminate the stress and artificial responses that cells experience as a result of cell adaptation to flat, 2D growth surfaces and to create suitable surroundings for optimal cell growth, differentiation and function. Genuine 3D cell culture allows individual cells to maintain their normal 3D shape and structure with minimal exogenous support and interference. Cells are freely able to form complex interactions with adjacent cells and to receive and transmit signals, enabling a more natural environment to foster the creation of native architecture found in tissues.

Could the limitations of 2D cell culture be holding you back?

Finding experimental systems that model and provide useful information about in vivo biological processes is one of the most challenging tasks in scientific research. Cell culture enables the growth of cells outside the body in a controlled laboratory environment. Although convenient, culturing mammalian cells results in flat mono-layer cultures. This is dramatically different to the 3D in vivo environment cells experience in the body.

In order to enable survival in 2D culture, cells are forced to make dramatic changes to their morphology. Gene expression mediated changes to the cytoskeleton result in a flattened cell morphology. These changes can impair cellular functions. Cells grown in the laboratory do not always grow and function in a realistic fashion. This has major implications for research and discovery. For example:

- Inaccuracy of predictive assays in the drug discovery process
- Modification of normal behaviour of cells in response to external stimuli
- Generation of potentially inaccurate / misleading data
- Misunderstanding of complex biological phenomena
- Poor planning and direction of future research programme

Alvetex enhances the biological relevance of your cell culture research

By accurately recreating the complex cellular organisation and environment experienced by cells within their native tissues, Alvetex enables more accurate investigation into the study of cell function and behaviour than ever before possible within conventional 2D model systems.

Cells maintain their natural 3D shape and structure within Alvetex, freely interacting with adjacent cells and laying down extra-cellular matrix which often leads to the formation of “mini slabs” of tissue-like structures. Using Alvetex, the cell biologist can create in vitro models which more accurately mimic the tissue environment, gaining a much deeper insight into the complexities of cell function and behaviour.

Typical mammalian cells are around 10-25 μm in size and are rarely further than 0-50 μm from another cell or 100-200 μm from a source of nutrients via a blood capillary. Alvetex is made of the same poly-styrene as used in traditional 2D cell culture plastic-ware. Alvetex has been designed to enable cells to reproduce natural shape and form to enable the cell biologist to maintain the integrity of the micro-scale in vivo cell environment within simple in vitro models.

The Effects of Changing the Growth Environment on Cells

**In vivo 3D environment**: typically cells maintain a 3D ellipsoidal structure and organisation

**In vitro 2D environment**: cells adopt flattened morphology in a mono-layer

Alvetex Scaffold

Cells grown within Alvetex Scaffold maintain their natural shape and 3D organisation. **A**: 3D cell culture of human pluripotent stem cells within Alvetex Scaffold. **B**: 3D cell culture of liver hepatocytes grown within Alvetex Scaffold.
Summary: changing cell culture environment impacts on cell behaviour

<table>
<thead>
<tr>
<th>General dimensions and physical differences</th>
<th>Traditional 2D Cell Culture</th>
<th>Alvetex 3D Cell Culture</th>
<th>Normal in vivo Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum distance of cell from the source of nutrients</td>
<td>0</td>
<td>0-100 μm</td>
<td>0-200 μm</td>
</tr>
<tr>
<td>Resemblance to in vivo cellular environment</td>
<td>Low</td>
<td>High</td>
<td>N/A</td>
</tr>
<tr>
<td>Appearance of cell morphology</td>
<td>Flattened</td>
<td>3D shape</td>
<td>3D shape</td>
</tr>
<tr>
<td>Potential for 3 dimensional cell to cell interactions</td>
<td>Very low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Ability to form complex 3 dimensional cellular structures</td>
<td>Very low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

| Upon initial seeding of cells onto plasticware | | | |
| Degree of cellular stress placed upon cell structure | High | Low | N/A |
| Changes to protein and gene expression | High | Low | N/A |
| Cell surface area in contact with plasticware | at least 50% | 0-50% | N/A |

| Post seeding phase | | | |
| Degree of cellular stress placed upon cell structure | High | Low | N/A |
| Changes to protein and gene expression | High | Low | N/A |
| Cell surface area in contact with plasticware | at least 50% | 0-50% | N/A |
| Opportunity for enhanced in vitro cell functionality | Low | High | N/A |

Alvetex is a unique micro-scale environment to support genuine 3D cell growth

The structure of Alvetex provides cultured cells with an environment and physical space in which to grow in three dimensions. The architecture of Alvetex, as viewed by a scanning electron microscope, illustrates voids that are interconnected by pores creating a material with > 90% porosity. Emulsion templating is used to control the size of the voids, optimising the porosity of the material for 3D cell culture. The matrix structure has been designed to enable cells to reproduce an environment that is more consistent with the in vivo cellular environment.

Alvetex viewed by scanning electron microscope to highlight its porous structure. 
A: a 200 μm thick Alvetex Scaffold disc. 
B: a 200 μm thick Alvetex Strata disc. 
C: Close up of Alvetex Scaffold voids with dimensions of approximately 42 μm in diameter and interconnects of approximately 13 μm in diameter. 
D: Close up of Alvetex Scaffold voids with dimensions of approximately 15 μm in diameter and interconnects of approximately 5 μm in diameter.
Alvetex’s unique scaffold dimensions are ideally suited to 3D cell culture

<table>
<thead>
<tr>
<th>Alvetex Feature</th>
<th>Benefits of using Alvetex for 3D cell culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same polystyrene as existing cell culture plasticware</td>
<td>• Easily switch between 2D and 3D protocols</td>
</tr>
<tr>
<td></td>
<td>• Inert — no effect on cell growth or function — no new experimental variables</td>
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<tr>
<td></td>
<td>• Stable — does not degrade, no change throughout long-term studies</td>
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<tr>
<td></td>
<td>• Can be pre-coated with ECM proteins</td>
</tr>
<tr>
<td>Consistent scaffold structure — extremely low batch to batch variability</td>
<td>• Reproducible, consistent results, low batch to batch variability</td>
</tr>
<tr>
<td></td>
<td>• Genuine and homogeneous 3D cell growth</td>
</tr>
<tr>
<td>Entire scaffold is only 200 μm thick</td>
<td>• No cell is ever more than 100 μm away from nutrients and gasses — mimics in vivo conditions</td>
</tr>
<tr>
<td></td>
<td>• Cells can feed and excrete via passive diffusion — mimics in vivo conditions</td>
</tr>
<tr>
<td>&gt; 90 % Porosity</td>
<td>• Cells can easily penetrate scaffold and lay down ECM to more closely mimic in vivo conditions</td>
</tr>
<tr>
<td></td>
<td>• Cells and media move freely through the matrix</td>
</tr>
<tr>
<td></td>
<td>• Nutrients and waste exchanged by passive diffusion</td>
</tr>
<tr>
<td></td>
<td>• Partial cell retrieval is possible</td>
</tr>
<tr>
<td>Alvetex Scaffold void dimensions approximately 42 μm</td>
<td>• Typically up to 75 cells may occupy a single void</td>
</tr>
<tr>
<td>Alvetex Strata void dimensions approximately 15 μm</td>
<td>• Highlight behavioural differences between non-invasive (eg. epithelial) and invasive (eg. Fibroblast) cell types</td>
</tr>
</tbody>
</table>

Alvetex 3D cell culture leads to the creation of mini-slabs of tissue

Cells grow and divide occupying the 3D space within the porous Alvetex scaffold. Cells form complex interactions with one another, behaving in a manner that far more closely mimics normal growth in tissues than is possible using traditional 2D techniques. Cells are free to migrate throughout the matrix, functioning as they would within their natural environment, laying down extracellular matrix and forming organised and complex in vivo-like structures.

Alvetex derived cell cultures can be processed just like normal tissue samples and prepared for histology using standard procedures including fixation, embedding, thin sectioning and counter staining.

3D growth of cultured cells form 200 μm thick ‘slabs of tissue’. A: Naked Alvetex Scaffold before cell seeding viewed under scanning electron microscope to show the highly porous scaffold. B: Cells have grown throughout Alvetex Scaffold to the point where the scaffold is no longer visible. C: Hepatocytes form a thick multilayer on top of Alvetex Strata with maximal cell-cell contact as would be found within in vivo tissue.

Tissue processing and staining highlight the complex organisation of cells growing throughout Alvetex Scaffold. D: Resin sections of Alvetex Scaffold showing skin keratinocytes stained with Toluidine Blue. E: Paraffin sectioned skin keratinocytes counter stained with H&E viewed by bright field microscopy.
The geometry and shape of a cultured cell is significantly affected by the physical environment in which it grows. Using Alvetex to culture cells, it is possible to maintain natural 3D cell morphology and to replicate the conditions for growth and development that occur within living tissues.

Unlike cells grown on conventional 2D substrates where cell morphology is much more varied in appearance, consisting of clumps and individual flattened cells, cells grown in Alvetex exhibit a morphology that is much more consistent with that found within the *in vivo* environment. The appearance of cells is more homogeneous with a high degree of 3D organisation.

Cells grown on conventional 2D surfaces (*A* and *B*) adopt a typical flattened morphology covering a large surface area in horizontal x–y plane (*A*) and have a reduced height in the vertical z plane (*B*). In comparison, cells maintained in Alvetex Scaffold (*C* and *D*) retain a more cuboidal morphology and 3D cell structure, particularly in the z-plane.*


Scanning electron microscopy image comparing the cell morphology and organisation of HepG2 liver cells grown in Alvetex Scaffold versus 2D culture. *A*: Structure of cells in 2D is very heterogeneous with poor organisation. *B*: Cells in Alvetex Scaffold grow homogeneously and develop a 3D form characteristic of liver tissues in the body.
Maintaining \textit{in vivo} cell structure in Alvetex results in improved function

By maintaining the shape and structure of cells and enabling a high level of cell-to-cell interaction, Alvetex enables a much deeper understanding of how cells function \textit{in vivo}.

Enabling cells to maintain their natural morphology and 3D organisation leads to improved cell function and responsiveness which is much more representative of the natural \textit{in vivo} environment. Alvetex delivers data of unmatched biological relevance. Factors such as cell viability and responsiveness have been demonstrated to be enhanced when growing cells in Alvetex in comparison to 2D mono-layer cultures.

Example 1: Improved Cell Function and Responsiveness

Assessment of HepG2 cells grown on 2D and 3D substrates. Cell viability was determined using a MTT assay and showed greater numbers of viable HepG2 cells in Alvetex Scaffold than on 2D substrates. Similarly, the secretion of albumin from 3D HepG2 cells was elevated compared to standard 2D cultures. In both cases, these data have been normalised to total protein per well to take into account differences in cell numbers. Overall, these results indicate the superior performance of HepG2 cells in 3D culture compared with their 2D counterparts.

Example 2: Increased Cell Viability

Cell viability of rat primary hepatocytes determined by quantification of live/dead cell staining of hepatocytes maintained for 24 hours on 2D plasticware or Alvetex Scaffold. Cells showed greater than 74% viability when grown on Alvetex Scaffold compared to 2D monolayer culture.*

Example 3: Increased Metabolic Responses

Metabolic responses to model toxicants were significantly enhanced using Alvetex Scaffold. Primary rat hepatocytes were cultured for 3 days in either 2D or 3D culture, Cytochrome p450 expression was induced in cells using a cocktail of model toxicants.*

Example 4: Increased Cell Sensitivity

Primary hepatocytes cultured on 2D plasticware versus Alvetex Scaffold were exposed to a range of acetaminophen (APAP) concentrations for a period of 20 hours and their viability was determined by a standard MTT assay. In general, these data demonstrate that rat primary hepatocytes cultured in 3D using Alvetex Scaffold show increased sensitivity to the model toxicant, acetaminophen.*

* Data generated during a collaborative project between Reinnervate Ltd and LGC Standards — data now published in the following journal: Title: Rat primary hepatocytes show enhanced performance and sensitivity to acetaminophen during three dimensional culture on a novel polystyrene scaffold designed for routine use. Maaike Schutte, Bridget Fox, Marc Baradez, Alison Devonshire, Jesus Minguéz, Maria Bokhari, Stefan Przyborski, Damian Marshall. Assay and Drug Development Technologies DOI: 10.1089/adt.2011.0371

(Reinnervate Ltd. was acquired by REPROCELL Inc. in 2014, and merged with BiopTA Ltd. to form REPROCELL Europe Ltd. in 2016.)
Changes in cellular morphology and function limit the value of cells grown in 2D cell culture. 3D culture systems enable cells to form more complex structures. Various models have been developed to create 3D skin constructs in vitro, including raft cultures. These methods are often technically challenging, involve multiple steps, show poor reproducibility and are difficult to practise routinely. Alvetex provides an alternative method for 3D growth of keratinocytes, enabling reproduction of natural in vivo structures including the development of the stratum corneum, an essential component of the epidermal barrier. Skin constructs generated on Alvetex can then be used for drug and allergen penetration studies as well as assessment of barrier function.

Imaging reveals the integrity of in vivo-like structure and organisation of cells grown in Alvetex

Co-culturing a Full Thickness Skin construct on Alvetex

Histology images showing a full thickness skin construct grown by co-culturing human dermal fibroblasts inside Alvetex Scaffold and human keratinocytes on top, thus replicating both the dermal and epidermal compartments. Note that the presence of a stratum corneum is also evident.

Validation of dermal and epidermal structure in full-thickness human skin equivalents. A: Representative photomicrographs of haematoxylin and eosin (H&E) stained Alvetex Scaffold seeded with human dermal fibroblasts after culture in Media A for 18 days. B & C: Representative photomicrographs showing H&E stained 35 day full-thickness human skin equivalents at 20× and 10× magnification respectively.*

Alvetex can easily be coated with ECM proteins

Alvetex can be coated with extracellular matrix (ECM) proteins and other reagents commonly used to treat cell culture substrates, notably: Collagen I; Collagen IV; Fibronectin; Laminin; Poly-D-lysine; Poly-L-lysine; Poly-D-lysine and Laminin; Poly-L-orthinine and Laminin; Matrigel™; PuraMatrix™.

A: Scaffold pre-loaded with Collagen IV. B: Coating Alvetex Scaffold with fibronectin. C: Coating Alvetex Strata with Collagen I (2mg/ml shown). The ECM proteins form a web of fibres spanning voids into which cells can grow and migrate in 3D. Depending on the ECM concentration used, this coating can either encourage cell invasion into the scaffold or create a barrier between two co-cultured cell populations.

Cells can be explanted directly into Alvetex

Cells can move into Alvetex directly from pieces of primary tissue or cell aggregates, migrating freely into the scaffold and spreading throughout its structure. Depending on cell type and characteristics, cells may proliferate as well as migrate. By enabling cells to be explanted in this way, Alvetex creates the opportunity for many different applications including tumour cell biology, separation of alternative cell types and establishing and maintaining 3D cultures de novo directly from primary sources, etc.

Examples of cells from tissue pieces placed on top of Alvetex Scaffold migrating into the structure of the scaffold. A: A neural aggregate generated on a low-adherence plate before transfer to Alvetex Scaffold shows extensive neurite elongation within the thickness of the scaffold. B: cells from an embryonal carcinoma aggregate readily invade Alvetex Scaffold.

Freshly-obtained intact tissues can also be maintained directly on Alvetex Strata for improved adherence and stability during imaging.

Time lapse imaging of spinal cord tissue slice maintained on Alvetex Strata demonstrates minimal tissue drift over a period of 24 hours. (Images courtesy of Kieran McDermott, University of Cork.)
Transfection of various cell types using Alvetex 3D culture

In collaboration with Mirus Bio, methods have been developed that enable the transfection of cells grown in Alvetex 3D culture.

Common cell types (CHO-K1, HeLa, HepG2, MCF-7 and NIH-3T3) were seeded at optimised cell densities in 12 well Alvetex Scaffold 3D plates and adapted to 3D culture conditions for 48 hours. After adaptation, cells were transfected with a novel Mirus Bio formulation combined with a plasmid encoding firefly luciferase at the reagent-to-DNA ratios indicated beneath the bars. Luciferase activity was measured 24 hours post-transfection using a conventional assay. High expression was detected in all cell types demonstrating the efficiency of the Mirus Bio TransIT® 3D Transfection Reagent (MIR 5804) when used with Alvetex Scaffold 3D culture plates.

Fibroblasts grown in 3D using Alvetex Scaffold were successfully transfected with a GFP construct and imaged using confocal microscopy. In brief, cells were transfected with the new Mirus Bio Transfection Reagent for 3D transfection at a reagent-to-DNA ratio of 3:1 using a GFP-expressing plasmid. Cells were seeded at 48 hours prior to transfection, and the cultures were fixed 24 hours post-transfection. Cells were imaged using a confocal microscope (Zeiss LSM510). The data shows a 40 μm integrated stack of multiple images as viewed from above the intact 3D culture. The position of all the cell nuclei are visualised with Hoechst 33342 (blue) and the positively transfected cells express GFP (green).
Advancing from single cell mono-cultures and co-cultures in conventional 2D models, Alvetex Scaffold provides the next step towards replicating the in vivo environment by providing the architecture necessary for 3D cell culture in vitro. Alvetex’s extremely high porosity allows cells to penetrate, grow and proliferate throughout the material for highly effective and reproducible 3D cell culture. Cells are freely able to form complex interactions with adjacent cells and receive and transmit signals, enabling a more natural environment to foster the native architecture found in tissues.

As well as being able to study single cultures in 3D, Alvetex Scaffold provides a support that enables the co-culture of more than one cell type. The structure of tissues is often comprised of discrete layers of distinct cell types. Growing different cell types in 3D, inside and on the surface of Alvetex Scaffold, enables users to recreate such tissue structures in vitro. A variety of cell co-culture scenarios can be set up to study different cell-cell interactions, according to the requirements of the cells and the dynamics under investigation.

Key Benefits and Applications

- Study interactions between distinct cell types in 3D culture
- Recreate in vivo tissue morphology
- Recreate specific niche environments for disease modelling or drug testing
- Customise co-culture setup to suit the cell types involved

Several alternative approaches for co-culture design can be utilised. Alvetex Scaffold is a versatile technology that enables users to create co-culture models in many different ways.

Key to image parts:

**Alvetex Scaffold in standard multi-well plate**

A ‘clip’ holds Alvetex at the bottom of the well

**Alvetex Scaffold in well insert in standard multi-well plate**

Cell type A growing in 3D within Alvetex Scaffold

Cell type B growing in 3D within Alvetex Scaffold

Mix of cells A & B in 3D within Alvetex Scaffold

Alvetex Scaffold

Cells growing in 2D

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**Assembly option 1**

3D co-culture in multi-well plate or well insert

**Description:** Different cell types cultured together within the same scaffold

**Application:** Emulate the structure of a tissue comprised of more than one cell type
Co-culture of glial and neural cells to model brain tissues. Brightfield micrograph showing the structure of a human stem cell-derived neurosphere co-cultured for 7 days with U118-MG glial cells on Alvetex Scaffold presented in the 12-well insert in 12-well plate format.

Enhanced cell function with hepatocyte and endothelial cell co-culture. The activity of CYP3A4 in upcyte hepatocytes cultured on a 2D plate and on Alvetex Scaffold presented in both a 12-well plate and 6-well insert formats. Hepatocytes were grown as mono-cultures and also co-cultured with upcyte micro-vascular endothelial cells for 10 days. For further details please visit www.medicyte.com.

“Alvetex should enable the routine and reproducible creation of 3D cell cultures in the laboratory and extend the concept of 3D culture beyond the simple, reconstituted extracellular matrices to complex cellular structures.”

H. Steven Wiley, Lead Biologist at the Environmental Molecular Sciences Laboratory (EMSL) at Pacific Northwest National Laboratory (Richland, WA, USA) and award judge of The Scientist Magazine Top Ten Life Science Innovations 2010.
Visualisation of the structure of 3D cultures in Alvetex Scaffold is made possible using scanning electron microscopy (SEM). Samples are prepared in the same manner as would normally be used for tissues. In this example, skin cells have penetrated throughout the scaffold and some have stratified on the surface (lower right corner).

The ultrastructure of cells grown in Alvetex Strata can be analysed by standard transmission electron microscopy (TEM). At high magnification, cellular structures such as these specialised bile canalicular cell protrusions are readily visualised.

Immunocytochemistry used to visualise the expression of specific protein markers. In this example, cell cultures have been fixed in 4% paraformaldehyde, embedded in paraffin wax and sectioned (10 μm). Antigen retrieval followed by immunocytochemical analysis with the proliferation marker Ki67 (green) and the nuclear stain DAPI (blue) was performed following standard immunocytochemical methods.

Unlike other 3D cell culture supports, Alvetex can easily be processed like a standard tissue sample. Frozen and paraffin embedded samples can be sectioned and stained to reveal the native cellular structures inside Alvetex. In this example, cells have been fixed in 4% paraformaldehyde, embedded in paraffin wax, sectioned (7 μm) before staining with H&E and cover-slipped.

Sectioning and Counterstaining

Immunocytochemistry

Scanning Electron Microscopy

Transmission Electron Microscopy

Alvetex is compatible with many downstream applications

- Tissue processing, fixation, embedding and sectioning
- Brightfield microscopy and photographic imaging
- Cryostat sectioning
- Fluorescence microscopy, confocal, laser capture
- Flow cytometry and cytopsinning
- Biochemical assays

- Histological staining, in situ hybridisation
- Electron microscopy – both SEM and TEM
- Immunocytochemistry
- Isolation of viable cells
- Extraction of nucleic acid and total protein
- And more . . .
It is possible to isolate some viable cells from Alvetex for downstream experiments such as flow cytometry, cytospinning and for sub-culture. Here, mesenchymal stem cells induced to form adipocytes were isolated from Alvetex Scaffold and 2D cultures. Cells were subsequently stained with Nile Red to detect the presence of lipid and analysed by flow cytometry.

Isolation of nucleic acid from rat primary hepatocytes grown in Alvetex and conventional 2D cultures. RNA quality was determined by the RIN (RNA Integrity Number) and showed that the quantity and quality of RNA isolated from cells grown on Alvetex Scaffold was the same if not better than that isolated from standard 2D cultures. Data generated in collaboration with LGC (unpublished).

<table>
<thead>
<tr>
<th>Sample</th>
<th>ng/µl</th>
<th>RIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D DMSO</td>
<td>82</td>
<td>9.3</td>
</tr>
<tr>
<td>3D DMSO</td>
<td>91</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Isolation of cells from Alvetex

Cell isolation and flow cytometry

With standard lysis protocols, total protein can be efficiently isolated from cells growing inside Alvetex. This allows for more biologically relevant protein expression analysis experiments to be carried out. Here we showed the increase over time of involucrin (Inv) expression in maturing keratinocytes by western blot analysis.

Biochemical assays

MTT cell viability assay of cultures grown on Alvetex Scaffold in 3D

Cells growing in 3D inside Alvetex can be studied using typical biochemical assays such as cell viability assays, apoptosis assays, cell proliferation assays etc. Here we show the measurement of cell viability using a standard MTT assay.

Unlock the potential of your in vitro cell culture with Alvetex and take your research to a whole new dimension.
A range of formats for all your applications

Alvetex is supplied as 200 μm thick discs that each provide a highly porous polystyrene scaffold in which cells can grow and interact in 3D. Compatible with conventional tissue culture plasticware, Alvetex is available in several multi-well plate and well insert sizes.

**Alvetex Scaffold**, our market leading product, is primarily designed for three dimensional culture of dissociated mammalian cells within the scaffold, forming three dimensional associations as they propagate and migrate.

**Alvetex Strata**, our second generation product, is primarily designed to support the growth of cells and intact tissues on the surface of the membrane. Mini-slabs of intact tissue or embryoid bodies can be maintained on the upper surface of Alvetex Strata, being fed from culture medium below or around.

Each product unit has been terminally sterilised by gamma irradiation and remains sterile until its blister pack is opened. Alvetex requires an ethanol wash prior to use to render it hydrophilic. Alvetex does not degrade during normal use.

### Alvetex well plate formats
- Ideal for 3D culture in the top half of the scaffold, or layered above
- Cells are fed from the top of the scaffold only
- Useful for when restricted cell penetration is required
- An option for use with expensive cells, reducing cell number (e.g. cell transfection)
- Allows high throughput applications in 3D

### Alvetex well insert formats
- Enables cells to be fed from above and below simultaneously
- Ideal for longer term 3D culture
- Growth of cells at the air/liquid interface
- Readily transfer 3D cultures to a fresh plate
- Enables co-culture studies (2D and 3D, or 3D and 3D)

### Alvetex well insert holder and deep Petri dish
- Reduces frequency of media changing as up to 95 ml of medium can be used to support a single 3D culture
- Ideal for maintaining long term 3D culture experiments of up to several weeks
- Facilitates the use of a magnetic stirrer to increase media circulation if required

### Alvetex perfusion plates
- Inter-changeable Luer-locks can be adapted to a range of tubing diameters
- Tissue fragments, 3D cultures in Alvetex well inserts and 2D cells can be maintained in the perfusion plate (for 2D cells, the plastic-ware may require coating with the appropriate cell culture reagent to promote cell adhesion)
- Unidirectional flow between separate wells allows the study of the interaction between cell populations grown in separate wells through the release of paracrine factors
Multiwell plate formats: Alvetex Scaffold

Alvetex Scaffold 12 Well Plate

Comprised of a single loose disc of Alvetex Scaffold and a polystyrene clip in each well of a 12 well plate. The clip holds the disc in position during transit and use, and can easily be removed for access to the Alvetex Scaffold and cells grown in 3D culture.

The 12 well plate format, a simple presentation of Alvetex Scaffold technology, is primarily suitable for short term culture experiments where the medium is replaced every 1-2 days.

![12 well plate clip](image1)

![Alvetex disc](image2)

![12 well plate](image3)

<table>
<thead>
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<tbody>
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<td>2 × 12 well plates</td>
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<td></td>
<td>AVP002-80</td>
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Units are individually sterile blister packed.

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Alvetex Scaffold 24 Well Plate

Comprised of a single loose disc of Alvetex Scaffold and a polystyrene clip in each well of a 24 well plate. The clip holds the disc in position during transit and use, and can easily be removed for access to the Alvetex Scaffold and cells grown in 3D culture.

The 24 well plate format, a simple presentation of Alvetex Scaffold technology, is primarily suitable for short term culture experiments where the medium is replaced every 1-2 days.

![24 well plate clip](image4)

![Alvetex disc](image5)

![24 well plate](image6)

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Units are individually sterile blister packed.
Alvetex Scaffold 96 Well Plate

Comprised of a black 96 well plate, clear plastic base, with Alvetex Scaffold at the bottom of each well. The Alvetex Scaffold has been heat welded to the base of the wells in a process which does not alter its physical structure.

Cells growing in 3D are exposed to culture medium from above only, and therefore predominantly reside in the top portion of scaffold.

Alvetex Scaffold 96 well plate technology is compatible with a wide range of \textit{in vitro} cell viability assays.

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Units are individually sterile blister packed.

Alvetex Scaffold 384 Well Plate

Comprised of a black 384 well plate, clear plastic base, with Alvetex Scaffold at the bottom of each well. The Alvetex Scaffold has been heat welded to the base of the wells in a process which does not alter its physical structure.

Cells growing in 3D are exposed to culture medium from above only, and therefore predominantly reside in the top portion of scaffold.

Alvetex Scaffold 384 well plate technology is compatible with a wide range of \textit{in vitro} cell viability assays.

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<td>Alvetex™ Scaffold 384 Well Plate (with lid)</td>
<td>AVP010</td>
<td>Made to order</td>
</tr>
</tbody>
</table>

Units are individually sterile blister packed.
Well insert formats: Alvetex Scaffold and Alvetex Strata

Alvetex 6 Well Insert Format

Comprised of discs of either Alvetex Scaffold or Alvetex Strata in individually sealed polystyrene inserts, designed to fit into most 6 well plates or our custom-made “Alvetex Well Insert Holder in Deep Petri Dish” (AVP015).

Note that plates and well insert holders are not supplied with the product and have to be sourced separately.

The presentation of Alvetex in well insert formats is versatile, enabling long term 3D culture as cells can receive nutrients from media above and below the membrane, sustaining optimal 3D cell growth.

---

Product | Product code | Presentation
---|---|---
Alvetex™ Scaffold 6 well inserts | AVP004-12 AVP004-48 AVP004-96 | 12 inserts 48 inserts 96 inserts
Alvetex™ Strata 6 well inserts | STP004-12 STP004-48 STP004-96 | 12 inserts 48 inserts 96 inserts

Inserts are individually sterile blister packed.

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Alvetex well inserts enable three different media fill options

1. Media in contact from below only
   - This enables 3D growth at the air/liquid interface.

2. Media in contact above and below
   - Independent compartments enable 3D growth with two different media constituents.

3. Media in contact above and below
   - Interconnected compartments enable optimal conditions for maximising cell growth and increased viability.
Alvetex 12 Well Insert Format

Comprised of discs of either Alvetex Scaffold or Alvetex Strata in individually sealed polystyrene inserts, designed to fit into most 6 well or 12 well plates, or our custom-made “Alvetex Well Insert Holder in Deep Petri Dish” (AVP015).

Snapping the extended wings off Alvetex 12 well inserts (along “break lines”) enables fitting into 12 well plates.

Note that plates and well insert holders are not supplied with the product and have to be sourced separately.

The presentation of Alvetex in well insert formats is versatile, enabling long term 3D culture as cells can receive nutrients from media above and below the membrane, sustaining optimal 3D cell growth.

 Inserts are individually sterile blister packed.
Alvetex Tools

Alvetex Well Insert Holder and Deep Petri Dish

Comprised of a single well insert holder in a deep Petri dish with lid. The well insert holder is capable of housing up to three Alvetex well inserts (either 6 or 12 well inserts). The Petri dish itself is not tissue culture treated.

The Alvetex Well Insert Holder and Deep Petri Dish enables users to grow their 3D cultures in larger volumes of media compared to an ordinary multiwell plate, facilitating fewer media changes. Capable of sustaining long term 3D culture experiments (3-4 weeks).

The well insert can be positioned at three different levels in the insert holder: high, medium and low. This feature allows cultures to be raised to the air liquid interface by moving the insert to a different level within the same holder.

Positioning the well inserts at different levels may also be used to conserve expensive media or allow for increasing media volumes for demanding cell types over the course of a long term experiment.

<table>
<thead>
<tr>
<th>Product</th>
<th>Product code</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvetex™ Well Insert Holder and Deep Petri Dish (with lid)</td>
<td>AVP015-2  AVP015-10</td>
<td>2 units  10 units</td>
</tr>
</tbody>
</table>

Units are individually sterile blister packed.
Alvetex Perfusion Plate

This product allows scientists to create cell based models that are another step closer to the environment experienced by cells and tissue in vivo. The systems can also be used to create complex co-cultures, multi-organ systems and to study paracrine effects.

Each unit contains an Alvetex Perfusion Plate with a lid and two Luer locks.

<table>
<thead>
<tr>
<th>Product</th>
<th>Product code</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvetex® Perfusion Plate</td>
<td>AVP011-2</td>
<td>2 units</td>
</tr>
<tr>
<td>(with lid and Luer locks)</td>
<td>AVP011-10</td>
<td>10 units</td>
</tr>
</tbody>
</table>

Units are individually sterile blister packed.

Note: Pump and tubing is not included.
Alvetex Kits

<table>
<thead>
<tr>
<th>Product</th>
<th>Product code</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvetex® Scaffold Plate Starter Kit</td>
<td>AVP-KIT-1</td>
<td>1 x 12 well plate 1 x 24 well plate 1 x 96 well plate</td>
</tr>
<tr>
<td>Alvetex® Scaffold Well Insert Starter Kit</td>
<td>AVP-KIT-2</td>
<td>6 x 6 well inserts 6 x 12 well inserts 1 x Alvetex Well Insert Holder in a deep Petri dish</td>
</tr>
<tr>
<td>Alvetex® Strata Well Insert Starter Kit</td>
<td>STP-KIT-2</td>
<td>6 x 6 well inserts 6 x 12 well inserts 1 x Alvetex Well Insert Holder in a deep Petri dish</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Product code</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kit: Alvetex® Perfusion Plate with Alvetex® Scaffold 6 well inserts</td>
<td>AVP-KIT-3</td>
<td>2 x Alvetex Perfusion Plates with Luer locks 12 x Alvetex Scaffold 6 well inserts</td>
</tr>
<tr>
<td>Kit: Alvetex® Perfusion Plate with Alvetex® Scaffold 12 well inserts</td>
<td>AVP-KIT-4</td>
<td>2 x Alvetex Perfusion Plates with Luer locks 12 x Alvetex Scaffold 12 well inserts</td>
</tr>
<tr>
<td>Kit: Alvetex® Perfusion Plate with Alvetex® Scaffold 6 well inserts</td>
<td>AVP-KIT-5</td>
<td>5 x Alvetex Perfusion Plates with Luer locks 48 x Alvetex Scaffold 6 well inserts</td>
</tr>
<tr>
<td>Kit: Alvetex® Perfusion Plate with Alvetex® Scaffold 12 well inserts</td>
<td>AVP-KIT-6</td>
<td>5 x Alvetex Perfusion Plates with Luer locks 48 x Alvetex Scaffold 12 well inserts</td>
</tr>
</tbody>
</table>

Alvetex defines the gold standard for 3D cell culture

Creating suitable surroundings for 3D cell growth, differentiation and function
Allowing cells to adopt a natural 3D shape and structure
Encouraging cells to form complex interactions with adjacent cells
Reducing stress and aberrant responses as a result of the growth substrate
Enabling a more natural environment to mimic native tissue structures
Consistent 3D cell culture growth within the matrix
High batch-to-batch reproducibility
Assay compatibility
Consumable, off-the-shelf product
Developed for routine use

“Alvetex is an example of innovation to move us closer to better models for mimicking in vivo behavior of cells with the control of in vitro conditions.”

Neil Kelleher (Award Judge of The Scientist Magazine Top Ten Life Science Innovations 2010) Northwestern University (Chicago, IL, USA).
Choosing the right Alvetex format based on assay type

The table below can guide your choice of the most suitable Alvetex format for your assay.

<table>
<thead>
<tr>
<th>Types of assay</th>
<th>Alvetex Scaffold</th>
<th>Alvetex Strata</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 well inserts</td>
<td>12 well inserts</td>
</tr>
<tr>
<td>Viability/Proliferation/Metabolic Activity Assays</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Toxicity Assays</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Gene Expression assays (qPCR/microarray)</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Protein Expression assays (e.g. western blot)</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Air-liquid Interface assays</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Cell Signalling assays</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Permeability assays</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Transfection assays</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Co-culture assays</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Invasion assays</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Migration assays</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Histology</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Immunostaining (IHC/IF)</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Confocal microscopy</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Live cell imaging</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Ex vivo tissue maintenance</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Live cell retrieval</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Suggested guidelines for the use of Alvetex formats for cell applications and assays:

- +++ = most suitable
- ++ = suitable
- + = least suitable
- N/A = not applicable

Ranking is based on Alvetex Scaffold disc format suitability, the likely cell yields and therefore signal generation, and whether exogenously added chemicals/cells can be contained to only one side of the membrane.

1 The growth of cells cannot be followed by traditional light microscopy as in 2D, but as with ex vivo tissues, 3D structures have to be evaluated using histology or confocal microscopy. Alternatively cell proliferation can be monitored using a viability assay such as the MTT.

2 The exact number of cells retrieved from Alvetex varies with the invasiveness of the cell line cultured, e.g. epithelial vs. fibroblastic. Although the three-dimensional structure of Alvetex precludes all 100% of the cells from being routinely retrieved, cells can be retrieved in adequate numbers for quantitative downstream processes, e.g. flow cytometry.

3 When designing co-culture, invasion or migration set-ups for Alvetex Strata, please keep in mind that some cell lines (e.g. epithelial) have a tendency to multilayer on top of the substrate rather than invade into it.

4 Alvetex Scaffold 384 well plates are made to order. Contact REPROCELL for details.
Testimonials

Don’t just take our word for it. Read the following testimonials to see how other scientists are using Alvetex™ 3D cell culture technology.

“I find Alvetex Scaffold convenient to use for studying cell migration in a 3D environment. This mobility can easily be monitored using confocal microscopy of live or fixed cells giving me a better resolution than when studying migration of these cells in Matrigel. I would certainly recommend Alvetex Scaffold to other scientists.”
— Dr. Patricia Muller, Beaton Institute for Cancer Research, UK

“We have been using Alvetex Scaffold for growing our prostate and colon epithelial cell lines in a 3D environment and comparing it to traditional 2D cell culture. We have found Alvetex Scaffold very easy to use and like the simplicity and repeatability of the experimental data. We found that preparation of samples for protein expression analysis as well as immunocytochemistry in 3D was simple and comparable to usual protocols. We have observed some striking differences between 2D and 3D prostate and colon cells surface marker expression and plan to use Alvetex Scaffold 3D culture as a complement to our standard 2D culture techniques.”
— Dr. Karel Soucek, Inst. of Biophysics, Czech Republic

“The ability to use Alvetex Scaffold to create a genuine 3D cell culture enabled us to provide a favourable environment in which our cells could grow, differentiate and proliferate. Using Alvetex Scaffold to culture immature stem cells enabled us to rise above the obstacles typically experienced when performing conventional 2D monolayer culture. The 3D polystyrene scaffolds offer cells a highly porous and uniform architecture to study the growth and differentiation of cells in new and exciting ways. Reinnervate has created a simple product that will further advance long-term 3D cell culture research and will ultimately lead to important new discoveries.”
— Prof. Ramin Beygui, Stanford University, USA

“Oncotest GmbH is a Contract Research Organization (CRO) based in Freiburg, Germany, focused on pre-clinical drug development in cancer therapeutics. We have performed extensive testing of Alvetex Scaffold for 3D tumour modelling. Tumour cell viability assays were very simple to perform and the results exceeded all of our expectations. Oncotest are particularly pleased at the ease of isolation of protein for downstream assays and potential biomarker validation. We are very excited about the forthcoming launch of the Alvetex Scaffold 96 well plate format and plan to incorporate this into our service offering.”
— Sumeer Dhar, Oncotest GmbH

“We have used the Alvetex system as an alternative approach to pre-clinical models, and are fully satisfied. We like the ease of use of this technology, and its flexibility that supports creative cell cultures such as co-culture. Moreover, Reinnervate* technical and scientific support is reactive and eager to assist us in the development and validation of novel in vitro models and settings.”
— Dr. Catherine Vaillant, Actelion Pharma, Switzerland

“After evaluating a range of different 3D cell culture systems (scaffolds and bead based systems) we established that the Alvetex Scaffold product was the most suitable for our needs. It was easy to work with, allowed additional biological coatings to be applied and should be straightforward to image cell growth on. Compared to bead based systems, there were lower shear forces and as a consequence better stem cell viability.”
— Dr. John Gardner, Roslin Cellab, UK

“Kirkstall has been working with many universities, most of whom were using ‘home grown’ scaffolds. However there was always an issue of availability and quality control with such scaffolds. Reinnervate* is one of the first companies to provide quality scaffold materials in volume production. We were particularly impressed by the large amount of experimental data that Reinnervate* had generated to demonstrate their ability to culture different cell types.”
— Dr. Malcolm Wilkinson, Kirkstall Ltd, UK

“The Alvetex Scaffold technology was a crucial factor in Tecan’s decision to partner with Reinnervate* Ltd. We found the evidence of real 3D cell culture, provided in several peer reviewed publications to be very compelling.”
— Dr. Kevin Moore, Tecan GmbH, Switzerland

“Reinnervate’s* expertise in 3D culture plates was backed by early results that show upcyte® hepatocytes, grown with a more native 3D morphology, in Alvetex Scaffold, seem to outperform their 2D counterparts.”
— Dr. Joris Braspenninck, Medicyte GmbH, Germany

“The importance of 3D cell culture is presently transforming how scientists conduct their studies. The timely development of Alvetex Scaffold makes such work easy to undertake in the laboratory, but more scientifically relevant too. Our experience to date has been very positive.”
— Prof. John Haycock, University of Sheffield, UK

“Alvetex Scaffold enhances the feasibility of creating 3D full thickness skin equivalent models with improved life span enabling us to advance our research to study more closely skin carcinoma invasion and early metastasis in a more relevant environment.”
— Dr. Penny Lovat, Newcastle University, UK

“Liver toxicity models need to be representative of the in vivo environment and applicable to high-throughput experimentation. Alvetex Scaffold helps to deliver on both of these accounts. I find that hepatocytes cultured on Alvetex Scaffold display a more realistic morphology, gene expression and function compared to 2D hepatocytes. I also find that Alvetex Scaffold supports analytical methods important for drug toxicity screening.”
— Adam Hayward, PhD student, University of Durham, UK

“We have been using the Alvetex Scaffold for growing or primary and metastatic melanoma cells in a 3D environment. I have found it extremely easy to use and certainly comparable to the ease of culturing cells in 2D. The preparation of protein extracts and immunocytochemical staining of cells grown within the Alvetex scaffold is very straightforward. This ease of use as well as the ability to use the Alvetex scaffold to culture cells in 3D for extended periods of time, has made Alvetex a regular addition to our set of research tools.”
— Dr. James Allen, University of Exeter, UK

“We use Alvetex for 3D imaging of neurospheres. We are now able to view 3D structure and able to localize the Spheres. We are also monitoring how cells migrate out of the spheres as Alvetex Scaffold makes such work easy to undertake in the laboratory, but more scientifically relevant too. Our experience to date has been very positive.”
— Dr. Penny Lovat, Newcastle University, UK

* Reinnervate Ltd was acquired by REPROCELL Inc in 2014, and merged with Biopta Ltd to form REPROCELL Europe Ltd in 2016.
“When cultured in Alvetex, my cells proliferated more evenly creating larger continuous domains compared to hydrogel type scaffolds. Normally hNSC cells form neuronal “bodies” without attachment. In hydrogels these bodies tend to be limited by size because of the hypoxia created by poor material transport of materials to the centre. The Alvetex Scaffold helps to overcome this problem.”

— Nándor A. Garamszegi, NAG Biosystems, USA

“We had more vigorous growth on the Alvetex Scaffold than in 2D. Moreover the cells tended to form more “anatomical structures” than in traditional 2D cultures. A biologically friendly scaffold where the background fluorescence of the scaffold makes it easy to use for confocal microscopy.”

— Monica Neagu, National Institute for Pathology, Romania

“We set out to compare the ECM gene expression of human NP cells grown on 3D Alvetex Scaffold, monolayer and alginate beads. We found that our NP cells, when grown on Alvetex 3D scaffold showed upregulation of Aggrecan compared to cells grown as monolayer. We can conclude that on the alvetex scaffold the NP cells can restore their phenotype.”

— Dessislava Markova, Jefferson University, USA

“Alvetex Scaffold is an example of innovation to move us closer to better models for mimicking in vivo behaviour of cells with the control offered by in vitro conditions.”

— Neil Kelleher (award judge of The Scientist magazine Top Ten Life Science Innovations), Northwestern University Chicago, USA

“Alvetex Scaffold should enable the routine and reproducible creation of 3D cell cultures in the laboratory and extend the concept of 3D culture beyond simple, reconstituted extracellular matrices to complex cellular structures.”

— H. Steven Wiley (award judge of The Scientist magazine Top Ten Life Science Innovations), Environmental Molecular Sciences Laboratory — Richland WA, USA

Alvetex 3D cell culture technology was pioneered in the laboratory of Professor Stefan Przyborski at Durham University, UK.

Professor Przyborski has over 30 years of research experience within the fields of cell and tissue biology with specialization in stem cell science, cell differentiation and the development of advanced technologies that enable the construction of human tissues in vitro.

Stefan’s interdisciplinary research at the boundaries of physical science and biology led to the development of Alvetex in the early 2000’s. He founded the company Reinnervate Ltd in 2002 with the purpose of commercializing and further developing Alvetex products and services.

The company, Professor Przyborski’s academic lab at Durham University, and scientists around the world who have used Alvetex in their research, have generated significant amounts of data which has been published extensively in peer-reviewed journals. This growing body of literature exemplifies the use of Alvetex in multiple applications with many cell and tissue types.

Alvetex was named among the winners of The Scientist magazine’s “Top 10 Life Science Innovations of 2010” and was voted one of the Top 100 Innovative Products of 2011 at the R&D 100 Awards. Several other awards have since followed. Alvetex is arguably the market leading physical scaffold product that supports robust and routine 3D cell culture.

In 2013, Alvetex was chosen by a research group at Massachusetts General Hospital (USA) for 3D culturing of murine osteocytes on the International Space Station (ISS) for the study of bone loss during space flight. These microgravity experiments took place onboard the ISS in 2015.

Recognizing the future of 3D cell culture applications and tissue engineered in vitro models for drug discovery and regenerative medicine, REPROCELL Inc. (Japan) acquired Reinnervate in 2014 and merged it with Biopta Ltd. (Glasgow, UK) to form REPROCELL Europe Ltd. in 2016.

Professor Przyborski currently serves as a Chief Scientific Officer of REPROCELL Europe, leading the research and development of new applications for 3D cell culture technologies and the generation of novel human tissue models that can be used in academia and industry for basic research, drug screening and safety assessment.

Stefan also holds an academic position in Department of Biosciences at Durham University as Professor of Cell Technology. He runs an active research laboratory consisting of postdoctoral and postgraduate researchers. His group is well funded and regularly publishes their work in peer reviewed journals. He is also the current President of the Anatomical Society which relates to the fundamental principle that ‘structure is related to function’ which underpins the bioengineered tissue models and assays he has developed.

Alvetex 3D cell culture technology continues to be developed, produced and distributed by REPROCELL worldwide. And with our own expertise and experience, REPROCELL also now offers worldwide 3D cell culture and bioengineered human tissue model services built around the Alvetex platform.
Useful References

Following is a selection from the growing list of scientific papers in which Alvetex has been used.


Notes