



Microscopy in Regenerative Medicine: Growing Tissue Engineered Skin

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Regenerative medicine is an exciting industry aiming to develop treatments that can replace or regenerate human tissues to restore normal function. The development of a tissue engineered skin to treat severe burns and acute skin wounds may help to save lives and provide significant benefit over current treatments. Light and electron microscopy are valuable techniques in the development of regenerative medicine products and can further the realisation of these products in everyday medical care.

Regenerative Medicine and the Skin

Regenerative medicine is a rapidly growing industry aiming to provide treatments that can replace or regenerate human tissues or organs to restore or establish normal function, Mason (2007). In the 1970s Rheinwald and Green demonstrated that living human skin cells from a small 1cm² patient biopsy, could be grown in a laboratory to produce enough cells to cover the entire body in approximately three weeks and then be transplanted back on to the patient. This research paved the way for the regenerative medicine industry and in particular the development of skin substitutes.

The skin consists of two principle layers, the outer epidermis and the underlying dermis. The epidermis comprises of layers of keratinocyte cells which continually differentiate and move from the inner layers to the surface of the skin where they are sloughed off every 2 - 3 weeks. The dermis provides the skin with structure and the majority of its viscoelastic properties. It is predominately comprised of an extracellular matrix made up of proteins and carbohydrate complexes such as entangled collagen fibres which provide tensile strength, elastin fibres which provide elasticity, and proteoglycans and glycosaminoglycans which attract water molecules to allow flexibility and movement. Fibroblasts are

the main cell type in the dermis and are responsible for maintaining the extracellular matrix by breaking down and secreting collagen and other extracellular matrix components in response to biochemical and mechanical signals. For example, biochemical signals are generated when the skin suffers an injury and stimulate the cells to repair the wound. Mechanical signals are generated in the soles of our feet when we walk around and stimulate the cells to make more extracellular matrix resulting in a thicker skin.

The basis of regenerative medicine or tissue engineered products is to use a naturally or synthetically derived matrix populated with living cells to form an artificial organ. The matrix material aims to be similar in structure and biochemical composition to the target organ. Typically a collagen based material is used as this is the most abundant component in the extracellular matrix. During the manufacture of tissue engineered constructs, the cells are responsible for remodelling the matrix to improve the structure by secreting both matrix degrading enzymes and new collagen fibres. The cells also secrete other extracellular matrix components which enhance the biochemical composition of the matrix so that it is similar to the composition of the target organ. Once in the body the matrix provides a structure into which the patients' cells can migrate and regenerate the organ by breaking down the tissue engineered matrix and secreting a new, patient derived matrix. Skin substitutes comprising of the epidermis only, dermis only and both skin layers have been developed to treat acute skin wounds such as burns and lacerations; and chronic wounds such as diabetic foot ulcers. However, for acute skin wounds, these products have yet to fulfil their potential and their routine use in everyday medical care has not been realised, Macneil (2007).

Current and Future Treatment of Skin Wounds

Minor skin wounds, such as a paper cut to a finger, can repair themselves through a normal wound healing process with minimal intervention such as a band aid. We have probably all observed this process in

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everyday life. For example, when we have a small cut on our skin, the bleeding will stop after a few minutes due to the formation of a fibrin clot or scab. Over time the scabs disappears as the fibroblast cells in the skin breakdown the clot and secrete collagen to form new skin. In comparison, major skin wounds, such as severe burns or lacerations caused by an accident, require human intervention to heal the wound and in extreme cases to save life. A current treatment for major wounds is skin grafting but in the future a tissue engineered skin graft may provide an alternative treatment which is more beneficial to the patient and clinicians.

Current Treatment - Skin Grafting

Skin grafting was first demonstrated in the 1870s by Reverdin who transplanted a patient's own skin from a healthy donor site to a wound site. Skin grafting has since become the gold standard treatment for major skin wounds and has high success rates but also has some limitations. For example, one of the most important factors in treating severe wounds is the ability to cover the wound as soon as possible. In the case of patients with burns covering large areas of the body this may be the difference between life and death. However, immediate skin grafting may not be possible as there may not be enough healthy donor graft skin. A temporary covering is then required to cover the wounds until sufficient skin for grafting is available. The removal of the temporary covering can sometimes be problematic as it can tear the healing skin and create new wounds. Additionally, the patients' condition must be stable enough to undergo the required surgical procedures and combat any infection that may occur in the donor graft site, which is in essence another wound. Finally, the clinician must decide whether to use a thin split thickness skin graft

(epidermis and thin layer of dermis) or thicker full-thickness skin graft (epidermis and full dermis). The advantages of split thickness skin grafts are that they create shallow donor sites which the body can repair through a normal wound healing process and can be taken from "low visibility" areas such as under the arms, thigh or groin. However, the healing of these donor sites is painful and from a cosmetic perspective the pigmentation, texture and structure of the graft often differs from the skin surrounding the wound. Contraction of the wound site can also occur causing scarring as the split thickness skin graft may not have sufficient structural integrity. In comparison, full thickness skin grafts are often taken from areas closer to the wound site and therefore have better cosmetic results. They also have more structural integrity which minimises contraction and scarring. However, full thickness skin grafts require a second operation to close the donor site and take longer to heal. In recent years, the cosmetic results of skin grafting have become more important due to the increasing incidents of skin carcinomas. Skin carcinomas often occur in highly visible areas such as the head, face and neck and treatment requires removal of the affected area followed by a skin graft to heal the excised area.

Future Treatment – Tissue Engineered Skin

There are many benefits that a tissue engineered skin could provide when treating major skin wounds. Firstly, off-the-shelf availability of a tissue engineered skin would allow immediate coverage of the wound and eliminate the need for healthy donor skin sites. Secondly, the tissue engineered skin would not

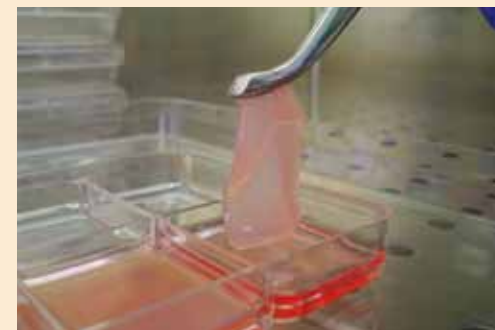


Fig 1. ICX-SKN, a tissue engineered skin.

require removal from the wound site as it would be broken down by the patients' cells. The tissue engineered skin matrix would provide a structure for the patient cells to migrate into and the biochemical composition of the tissue engineered skin could be designed to attract the cells and possibly accelerate wound healing. Finally, the number of operations required would be minimised which would be of benefit for both the patient and surgeon and could potentially reduce hospitalisation time and costs.

ICX-SKN produced by healthcare company Intercytex is a developmental tissue engineered dermal skin equivalent which aims to treat burns and acute wounds and provide an alternative skin graft for clinicians. ICX-SKN is manufactured in a laboratory by embedding living human dermal fibroblast cells (HDFs) in a fibrin matrix. This cell-matrix construct is supplied with a media containing essential nutrients to stimulate cell growth and collagen production. Over a seven week period, the cells multiply, breakdown the fibrin matrix and secrete a new collagen matrix. This process is described in detail by Flasz et al. (2007). By mimicking the normal wound healing process that occurs in the body, the ICX-SKN manufacturing process aims to produce a product with a naturally derived matrix structure and biochemical composition in order to be readily accepted by the body when implanted into the wound (Figure 1). Once in the body, ICX-SKN provides immediate coverage for the wound, mechanical support to prevent contraction and scarring and a structure for migration of the patients' cells. Over time, the patients' fibroblasts cells secrete enzymes to break down the ICX-SKN extracellular matrix and secrete new patient collagen. The patients' keratinocyte cells then multiply and migrate across the wound to form a new epidermis and complete the regeneration of the patients' skin. Phase I human clinical trials showed promising results in terms of the acceptance and integration of ICX-SKN into the body, Boyd et al. (2007).

A key challenge for the development and commercialisation of ICX-SKN is to qualify and quantify the interactions between the cells and the

matrix and the changes in biochemical composition and structure of the construct during manufacturing. This understanding will give insight into how to further improve the product and manufacturing process and how the construct interacts with the body during clinical trials. There are many assays that can provide quantitative data on the concentration of matrix components. However, repeatable and reproducible methods to firstly extract the matrix components into a form required by the assay for testing and secondly, to extract sufficient amounts of the matrix components so that the results fall in a suitable range for the assay, is challenging and can cause much variability in the results. For these reasons light and electron microscopy provide an important tool for producing images which can support quantitative data and can also provide additional data that may not be apparent from the quantitative results. The images in this article show the development of the ICX-SKN matrix and cells during its seven week manufacturing process and highlight the value of imaging in the development of tissue engineered products.

Imaging Techniques for Tissue Engineered Constructs

Tissue engineered constructs often have a high water content and less extracellular matrix than native human tissue. This presents several challenges when imaging. For example, traditional dehydration steps when preparing samples may lead to significant dehydration and misleading images when analysing the structure of the matrix. Various cryogenic SEM methods have been used to overcome this issue, however, care must be taken to avoid the formation of ice crystals during freezing. The low concentration of extracellular matrix in the samples requires trial and error of histological staining and antibody incubation times and section thickness to produce the best images. The methods used to produce the images presented in this article and the information gained from using each microscopy technique are outlined in the following sections.

Methods

Scanning Electron Microscopy (SEM)

Purpose: To observe changes in matrix structure and cell distribution.

Preparation method: Samples were fixed in 3% glutaraldehyde, washed in buffer and placed in 2.3M sucrose solution for 24 hours at 4°C. The samples were freeze fractured in slush liquid nitrogen, washed in distilled water and then dehydrated in increasing concentrations of acetone. The samples were critical point dried and sputter coated with gold. Cross-section images were acquired using an FEI Quanta 200F Field Emission Scanning Electron Microscope, 5kHz high vacuum mode.

Transmission Electron Microscopy (TEM)

Purpose: To observe changes in cell ultrastructure and cell life cycle.

Preparation method: Samples were fixed in 3% glutaraldehyde for 24 hours, washed in buffer and post fixed in 1% osmium tetroxide, washed in distilled water, dehydrated in increasing concentrations ethanol and infiltrated with resin over 24 hours. The samples were embedded in BEEM capsules and polymerised at 60°C for 48 hours. 90 nm ultra-thin cross-sections were cut and contrasted using methanolic uranyl acetate and lead citrate. Images were acquired using an FEI Tecnai BioTwin TEM operated at 100kV.

Histology

Purpose: To observe changes in biochemical composition of the matrix.

Preparation method: Samples were fixed in 10% neutral buffered formalin, processed in a Leica TP 1020 automatic tissue processor and embedded in paraffin wax. 8 µm cross-sections were cut and stained with Massons Trichrome (MT) and Hematoxylin and Eosin (H&E) to identify collagen, fibrin and cell nuclei.

Immunohistochemistry (IHC)

Purpose: To observe changes in collagen type I and type III concentration in the matrix over time.

Preparation method: The sections prepared for histology were also used for IHC to reduce the number of samples required for imaging. After cutting of the 8 µm cross-sections, the sections were dewaxed in xylene and then rehydrated in decreasing grades of alcohol followed by water. The sections were placed in the microwave in 1:100 Antigen Unmasking Solution in ultra-pure water. The samples were labelled with 1:200 dilution primary antibodies for collagen type I (Ab292, rabbit polyclonal, Abcam, UK) and collagen type III (Ab6310, mouse monoclonal [FH-7A], Abcam, UK) for 20 hours at 4°C. 1:100 dilution secondary antibodies conjugated to FITC (Goat Anti-Rabbit IgG, Jackson-Immuno, US) and TRITC (Goat Anti-Mouse IgG) were applied for 3 hours at room temperature for detection of collagen types I and III respectively. The cell nuclei were labelled using DAPI for 30 minutes at room temperature in the dark. A Leica Leitz DMRB fluorescent microscope was used for imaging.

Confocal Laser Scanning Microscopy (CLSM)

Purpose: To image ICX-SKN without using a dehydration process in order to maintain its native structure. To identify changes in cell and collagen type I distribution through the thickness of the ICX-SKN sample.

Preparation method: Samples were fixed in 4% paraformaldehyde and then washed in PBS followed by 2% NGS buffer. The samples were labelled with 1:200 dilution primary antibody for collagen type I (Ab292, rabbit polyclonal, Abcam, UK) for 20 hours at 4°C to detect cell actin filaments, secondary antibody for 20 hours at 4°C, conjugated phalloidin (A22287, Invitrogen, UK) for 20 hours at 4°C, and then DAPI for 30 minutes at room temperature in the dark. Images were acquired using sequential acquisition at intervals of 1 µm from the top surface of the ICX-SKN construct to a maximum of 40 µm depth. Images from the top surface of the samples were acquired by placing samples in an Iwaki glass bottomed culture dish to prevent mechanical compression of the constructs, Anderson (2007). The samples were then turned over and imaged from the bottom surface. A Leica SP2 confocal laser fluorescent microscope with Leica DMIRE2 inverted fluorescent microscope was used for imaging.

Results

Biochemical Composition

The histology images showed that the composition of the matrix changed from a fibrin matrix (Figure 2A) to a fibrin and collagen matrix over 3-4 weeks (Figure 2B) and then to a collagen only matrix after 4 weeks (Figure 2C). The IHC images showed that collagen type I and III fibres were present after 3 weeks (Figure 3A and 3B) but only collagen type I was present after 7 weeks (Figure 3C and 3D). This is similar to the events of a normal wound healing process in the body where the fibrin clot is broken down and the ratio of collagen type I to type III increases over time. The TEM images provided evidence that the fibroblast cells were responsible for these biochemical changes. In the first weeks of the manufacturing process, the cells had convoluted cell membranes and nuclei which increase the surface area for cellular processes (Figure 4A). Numerous cell organelles, such as mitochondria, endoplasmic reticulum, Golgi apparatus, secretory vesicles and lysosomes, were also observed (Figure 4B). It is known that procollagen molecules are assembled inside the cells in the endoplasmic reticulum and packaged into secretory vesicles in the Golgi apparatus which move to the cell membrane where the contents is discharged (Porter, 1964), and that lysosomes often contain digestive enzymes which could be used for the breakdown the fibrin matrix.

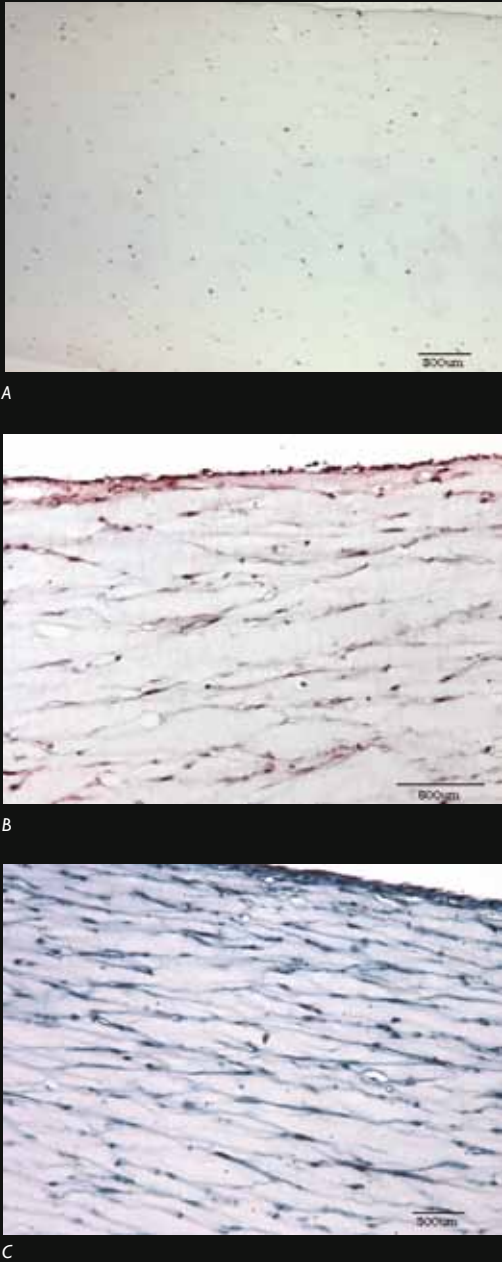


Fig 2. Masson's Trichrome stained cross-sections showing the change in matrix composition and HDF cell density over time. A) 1 day matrix, fibrin only (light purple) with few HDF cells (dark purple). B) 3 week matrix, fibrin (red) and collagen (blue). C) 7 week matrix, collagen only (blue) with many HDF cells (dark blue).

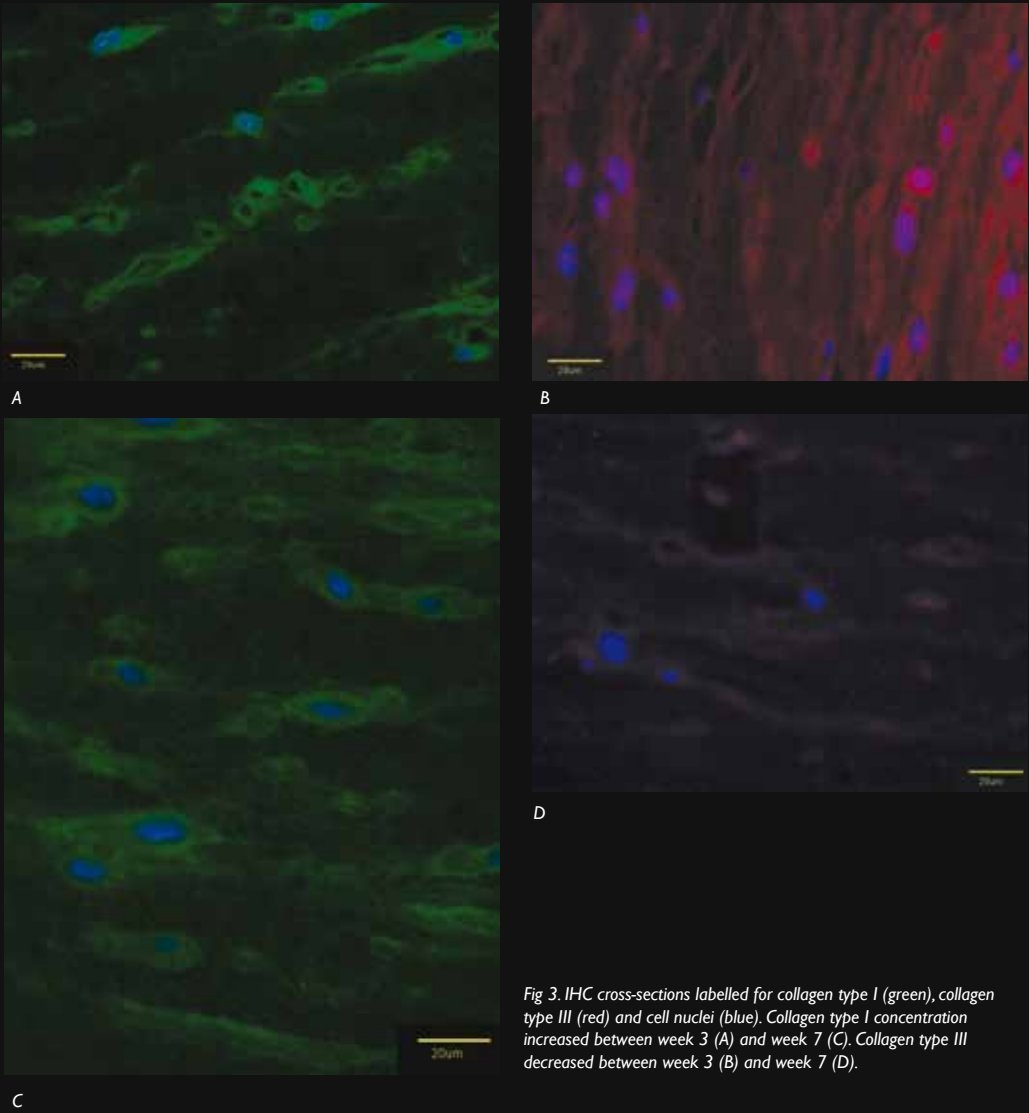


Fig 3. IHC cross-sections labelled for collagen type I (green), collagen type III (red) and cell nuclei (blue). Collagen type I concentration increased between week 3 (A) and week 7 (C). Collagen type III decreased between week 3 (B) and week 7 (D).

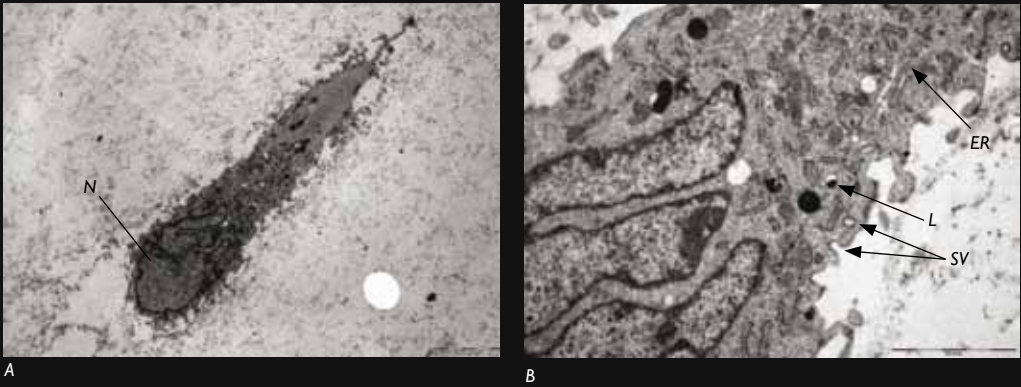


Fig 4. TEM cross-sections of a highly active HDF cell in the first week of manufacturing. A) Cell with convoluted nuclei (N) and plasma membrane. Scale bar 5000000 nm. B) Numerous endoplasmic reticulum (ER) and lysosomes (L). Secretory vesicles (SV) discharging content into extracellular space. Scale bar 2000 nm.

Viscoelastic Properties

Quantitative data showed that the viscoelastic properties of ICX-SKN increased during the manufacturing process. Imaging of the constructs provided evidence that these increases were due to the increasing amount of collagen I identified in the stacked CLSM images (Figures 5A-C) and thin collagen fibres spanning between the cells observed in the histology and IHC sections (Figures 6 and 3A-C). The light microscopy images also showed that there were high concentrations of collagen surrounding the cells. Higher magnification SEM images identified these concentrated areas as bundles of collagen fibres which also contribute towards the increase in viscoelastic properties (Figures 7A and 7B). The SEM images also showed that the structure of the fibrin matrix was different from the collagen matrix as the fibrin matrix appeared to comprise of aggregates of fibres compared to the finer, more structured collagen matrix (Figure 7C). Finally, it is also known that collagen type I has a higher tensile strength than collagen III and the IHC images showed an increasing ratio of collagen type I compared to collagen type III over time (Figure 3).

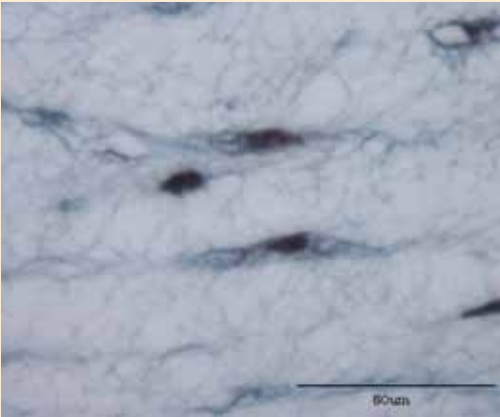


Fig 6. Masson's Trichrome stained cross-section of 7 week construct. Thin collagen fibrils (blue) spanning between cells (dark blue) contributing to the increase in viscoelastic properties.

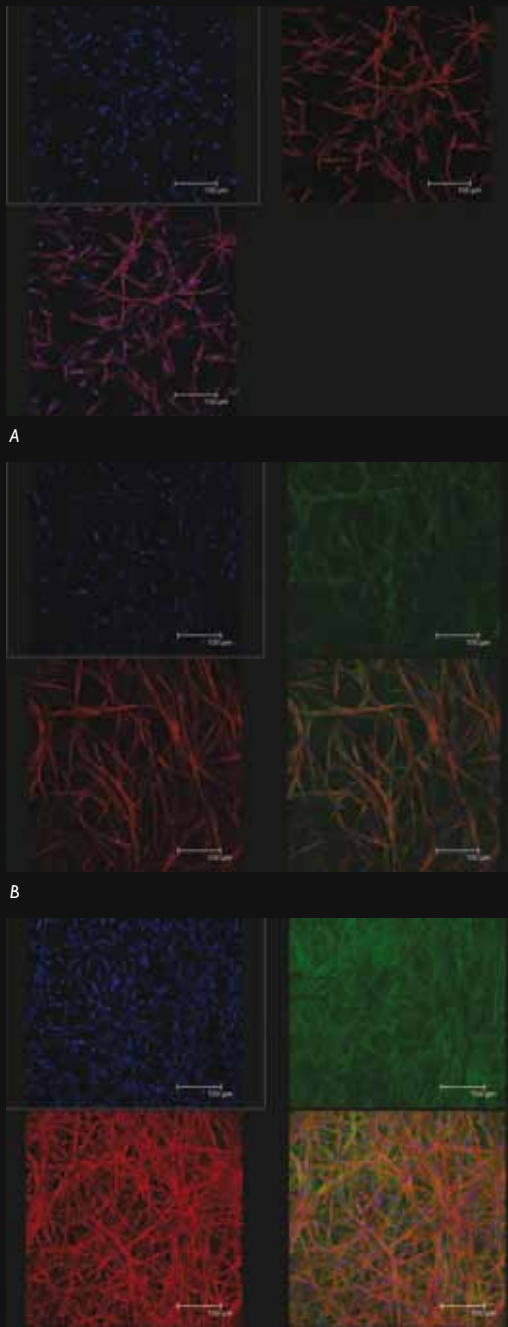
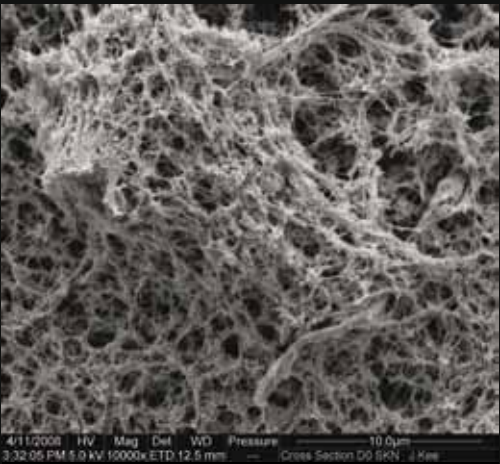


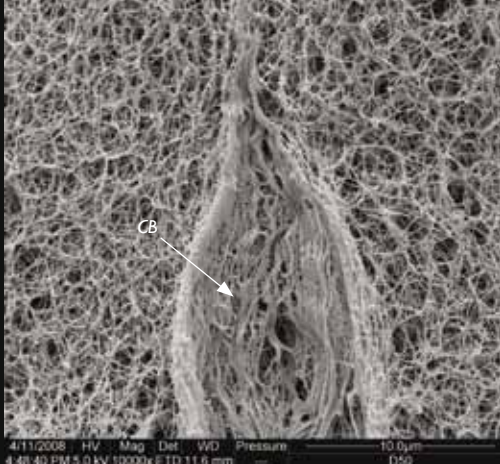
Fig 5. Stacked CLSM images acquired using sequential acquisition at intervals of 1 µm from top surface of constructs showing an increase in collagen type I and HDF cells over time. Quadrants show stacked images of individual components – collagen type I (green), actin filaments (red), cell nuclei (blue) and a compiled image of all components. A) 1 day construct with no collagen and few cells. B) 1 week construct with increasing collagen and cells. C) 7 week construct with abundance of collagen and cells.



B



A

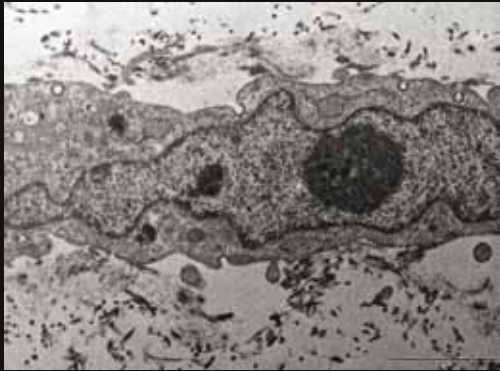


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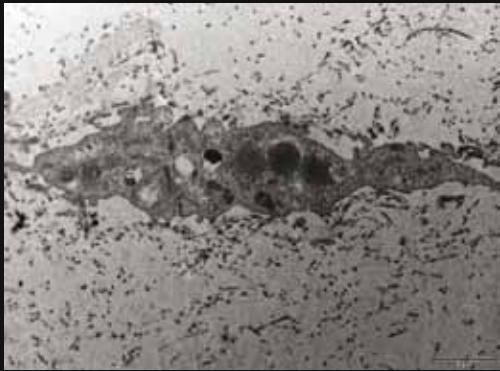
Fig 7. SEM cross-sections showing the change in matrix structure over time. A) 1 day construct with aggregates of fibrin fibres. B) 3 week construct showing HDF cell with collagen fibril bundles (CB) formed around cell membrane. C) 7 week construct with structured matrix of finer collagen fibrils forming fibril bundles.

Cell Growth and Viability

The total number of cells and cell viability in the ICX-SKN construct was quantified by releasing the cells from the construct using enzymatic digestion followed by counting using trypan blue. The total number of cells increased over 7 days before reaching a plateau and the viability began to decrease during the latter stages of the manufacturing process. The quantitative data was supported by the histology images which identified dividing cells in the first week of manufacturing (Figure 8). Also, the cells observed after 5 weeks of manufacturing by TEM identified less active cells with less convoluted cell membrane and cells with signs of apoptosis (programmed cell death) such as shrinkage of the cell membrane away from the surrounding matrix, fragmentation of nuclear components and increases in lysosomes and lipids (Figures 9A and 9B). After 7 weeks many of the cells showed characteristic signs of apoptosis (Figures 10A and 10B) but few cells showed signs of necrosis (premature cell death). These observations are consistent with the cell cycle during normal wound healing in the body where the cells undergo apoptosis as the wound heals.



A



B

Fig 9. TEM cross-sections of HDF cells after 5 weeks manufacturing. A) Live cell with less convoluted membrane and nucleus and fewer cell organelles compared to 1 day HDF cells. B) Apoptotic cell with increased numbers of lysosomes and lipids.

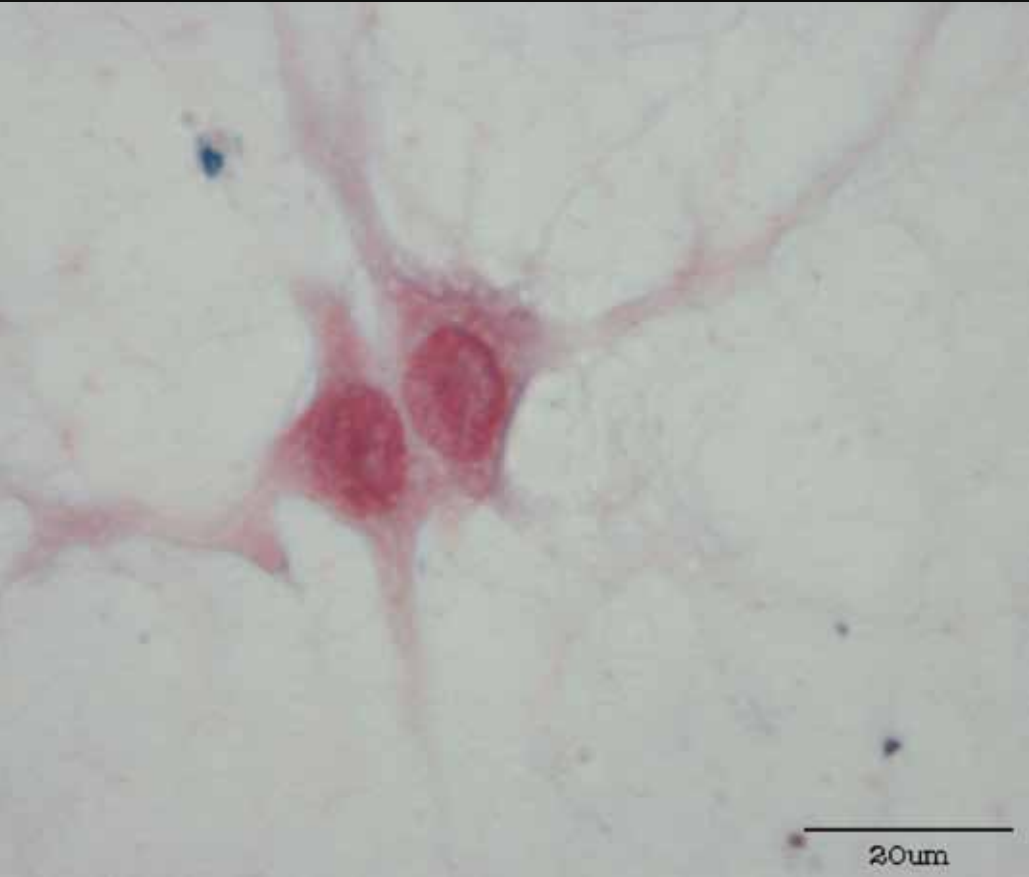
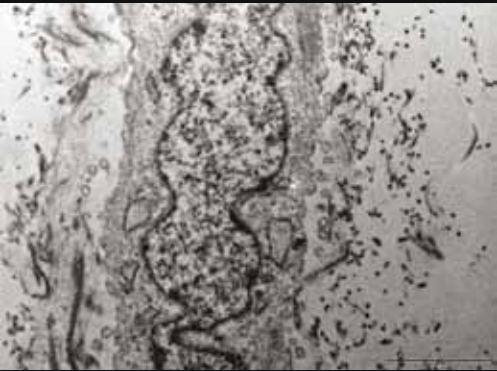
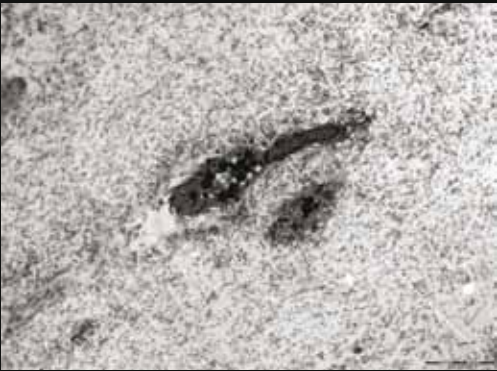


Fig 8. Haematoxylin and Eosin stained cross section of a dividing HDF cell in the first week of manufacturing.



A

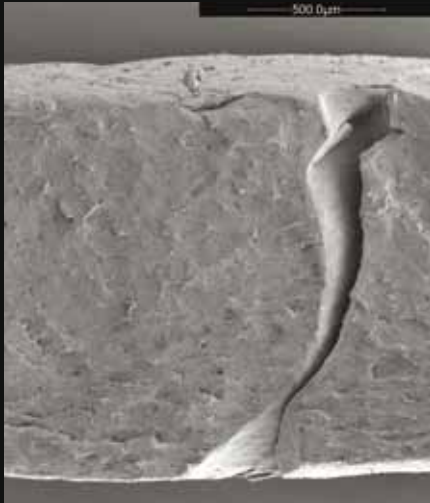


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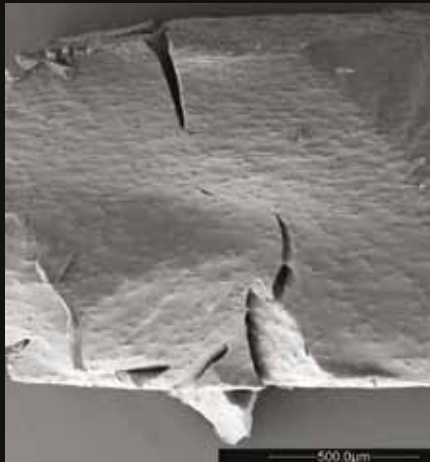
Fig 10. TEM cross-sections of apoptotic HDF cells after 7 weeks manufacturing. A) Cell showing fragmentation of nuclear components. Scale bar 2 μm. B) Cell with a build up of lipids and lysosomes and shrinking away from matrix. Scale bar 5000000 nm.

Cell Distribution

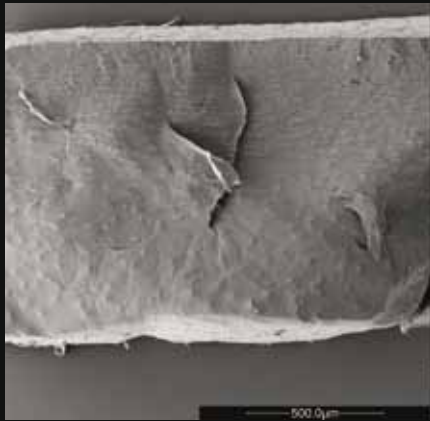
The CLSM and SEM images showed important observations that were not apparent from the quantitative cell data. Firstly, the SEM images showed that the cells formed a layer on the top surface of the construct over time (Figures 11A and 11B) but not on the bottom surface which was in contact with the base of the plastic culture dish (Figures 12A and 12B). This may be significant for the product as it may influence the orientation in which the construct is placed on the wound by the clinician. Secondly, the gallery CLSM images of individual 1 μ m sections of the construct viewed from the top (Figure 13A) and bottom surface (Figure 13B) respectively showed that the cell density was greater towards the top of the construct. The SEM cross-sections showed that this change in cell distribution occurred over time (Figure 14). In the first week of manufacturing the cells were evenly distributed through the construct. However, after 7 weeks there was a greater cell density toward the top of the construct. The reasons for this non-homogeneous cell distribution may be due the greater availability of nutrients and oxygen towards the top of the construct. Further investigation may identify areas for process and product improvement.



A

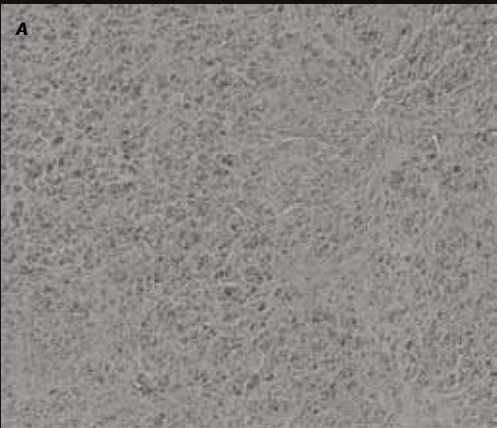


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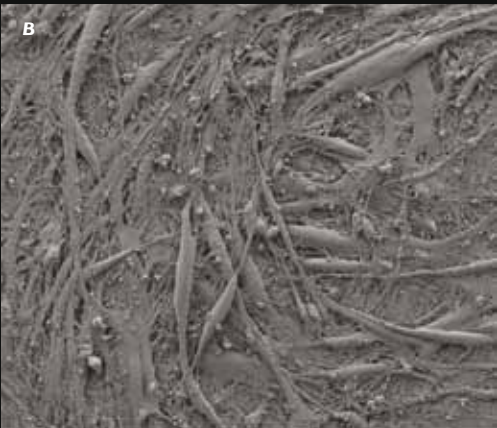


C

Fig 14. SEM cross-sections of the construct showing the changing distribution of cells over time. A) 1 day construct with evenly distributed cells. B) 3 week construct with increasing cell density in the upper region. C) 7 week construct with even greater cell density in the upper region.

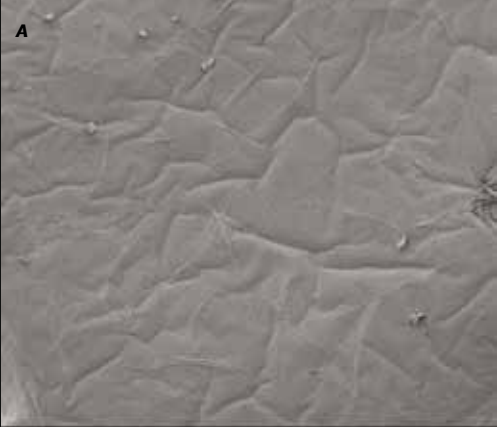


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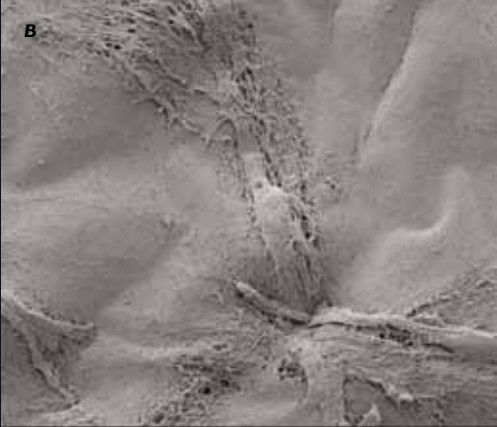


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Fig 11. SEM of the top surface of the construct. A) 1 day construct with no cells on the surface. B) 3 week construct with a layer of cells formed on the surface.

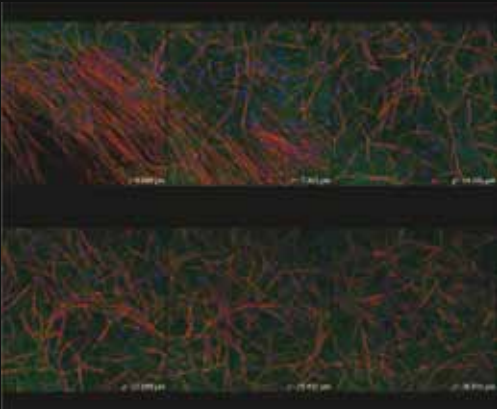


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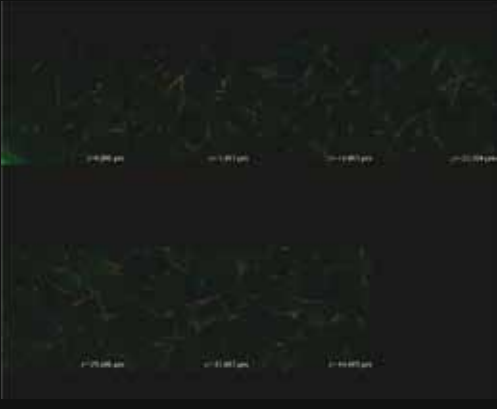


10/27/2008 HV Mag Det WD Pressure 20.0µm 2:51:41 PM 5.0 kV 2500x ETO 10.6 mm Control J. Kee

Fig 12. SEM of the bottom surface of the construct. A) 1 day construct with no cells on the surface. B) 3 week construct with isolated cells protruding through the matrix.



A



B

Fig 13. Gallery CLSM images labelled for collagen type I (green), cell nuclei (blue) and cell actin filaments (red). A) Higher density of HDF cells in the upper region of the construct. Individual images captured from the top surface $z=0.000\ \mu\text{m}$ to a depth of $z=44.409\ \mu\text{m}$. B) Fewer cells in the lower region of the construct. Individual images captured from bottom surface shown as $z=0.000\ \mu\text{m}$ to a depth of $z=44.409\ \mu\text{m}$.

Conclusion

The light and electron microscopy images in this study provided valuable information about the processes that occur during the manufacture of ICX-SKN. The basis of the ICX-SKN manufacturing process was to produce a naturally synthesised collagen matrix by mimicking the events of a normal wound healing process in the body. The light and electron microscopy images provided evidence of this with regards to the transition of the matrix from fibrin to collagen, the increasing ratio of collagen type I to collagen type III and the activity and life cycle of the cells. The images also provided information that was not apparent from the quantitative data. For example, the rate of degradation of the fibrin matrix, the ratio of apoptotic and necrotic cells, and the components responsible for the increase in viscoelastic properties. The use of CLSM allowed the construct to be studied in its native state, without dehydration and shrinkage. This was useful in its own right and as a tool to validate the results from other methods.

Regenerative medicine is an exciting industry with great potential to provide new treatments for millions of patients and provide alternatives to clinicians that have significant benefits over the current gold standards. The realisation of these products in everyday medical care requires much work to characterise and understand the impact of the interactions between the cells and matrix on the product properties in order to improve product efficacy and process efficiency and to meet regulatory requirements for commercialisation. Light and electron microscopy has been shown to provide a valuable technique for the development of regenerative medicine products.

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Jasmin graduated with a Masters in Mechanical Engineering from Loughborough University, UK, in 2003. After working as a Process Engineer in multi-national, fast moving consumer goods companies for several years, she decided to pursue an engineering career in the life science industry. She returned to Loughborough University to undertake a PhD in regenerative medicine, part of an ESRC funded Grand Challenge. Sponsored by healthcare company Intercytex, UK, the main focus of her research was to characterise and improve the ICX-SKN artificial skin graft manufacturing process and final product. Jasmin is now a Process Engineer at the leading tissue regeneration company Organogenesis Inc, USA, and is responsible for the development of a new automated facility for tissue engineered skin products and scale-up of cell culture processes.



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Susan graduated with a Masters in Ultrastructural Anatomy and Pathology from The Queen's University of Belfast and moved to the University of Nottingham in 1995. She established and led the Advanced Microscopy Unit, providing research support to academics and students from 15 University Schools and Departments in addition to Universities and industry from the East Midlands and beyond. Susan completed her PhD in orthopaedic biomaterials in 2001 and has a continuing active research interest in biomaterials and tissue engineering, and an ongoing interest in the application of microscopy to biomaterial and tissue engineered samples. Susan moved to the School of Graduate-Entry Medicine and Health in 2009 as Lecturer in Pathology. Susan has been a member of the RMS Materials Science Section Committee and in 2009, was invited to set up a new RMS section as Honorary Secretary for Education and Outreach.

