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CASE REPORT

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Nanotechnology, nanosurfaces and silicone gel breast implants: current aspects

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ABSTRACT

Nanotechnology is defined as the design of products that interact with biological systems on the nanoscopic scale. Creating a controlled nanotexture and understanding the ways in which surface properties impact inflammatory response is of the utmost significance in designing implants that can provide satisfactory outcomes.

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Introduction

In the field of plastic surgery, technical innovation tends to be a new technique which uses old devices or an existing procedure that uses new devices. The factors that determine the acceptance of new technology can be classified into two groups: features of the technology itself such as procedures, which are compatible with current practice and can be adequately sustained in available facilities, and contextual factors that advertise it. Plastic surgeons generally draw attention to a new technology if it can be easily and quickly learned and added to their existing practice with minimal disruption. If the improvement to their surgical practice is considerable, it is expected that surgeons will invest in training and tolerate interruption of their surgical routine to gain the competitive benefit of a new technology [1].

Progresses in nanotechnology yielded new biomaterials with individual properties that modulate cell functions, resulting in many therapeutic benefits [2]. The application of nanotechnology to medicine ('nanomedicine') impacts treatment of well-established diseases and diagnosis, as well as control of biological systems [2,3]. The scientific evidence in this field is represented not only by the volume of papers dedicated to this new field of research, but also in the number of new scientific journals dedicated to nanotechnology [2–16]. Areas of these new technologies that have already yielded advantages include drug delivery systems and materials engineering for surgical implants. Specific fields of research include wound healing, nerve regeneration, burns, and new implant devices with modified surfaces. These new technologies are related to drug delivery products, specific organ imaging, surgical tools, and gene therapies [2,3].

Definition of nanotechnology

Nanotechnology can be defined as the design, synthesis, and application of novel products that interact with biological, electrical and chemical systems on the nanoscopic scale. Nanomedicine is a sub-classification of nanotechnology that uses highly specific molecular interventions to both diagnose and treat different diseases. The concept was first introduced in the late 1950s by physicist Richard Feynman, who mentioned the possibility of manipulating materials on the scale of individual atoms and molecules and predicted the ability to control matter on the nanoscale [2]. The term nanotechnology was first used by Norio

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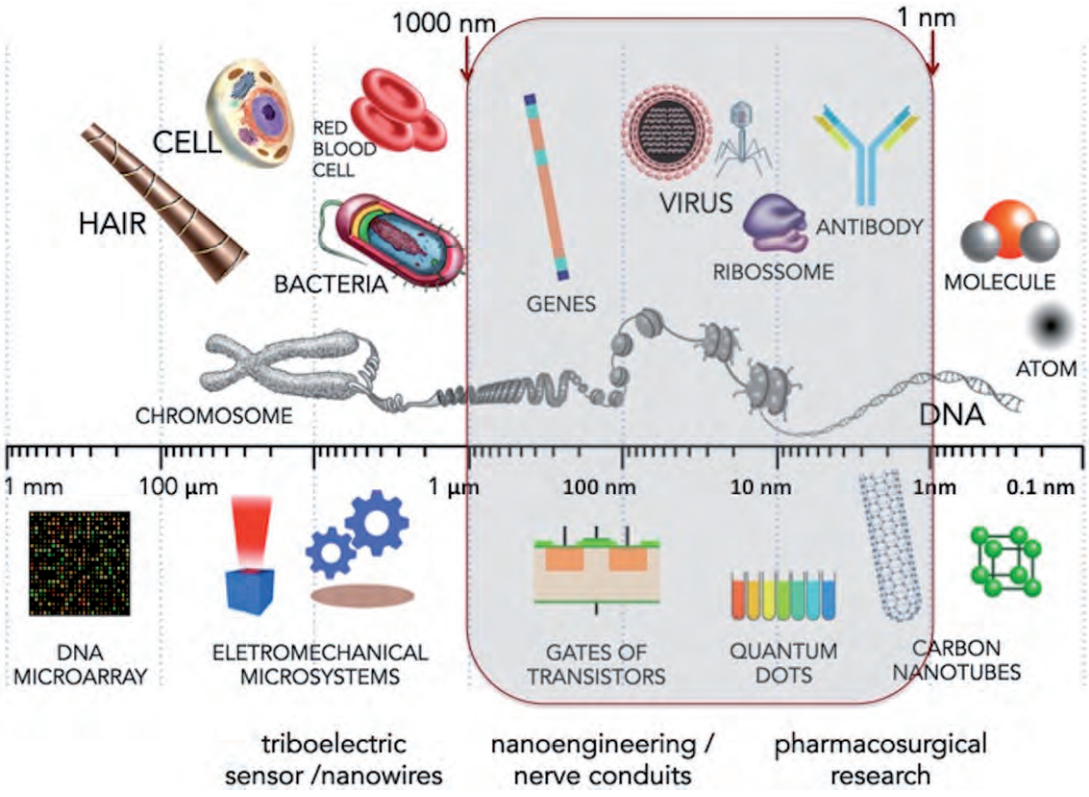

Figure 1. Scheme with nanoscale comparison. Nanotechnology are related to the study extremely small objects and can be used across all the other fields of science In pharmacosurgical research (polymer therapeutics), the nanoscale comprises 1–10 nm. In nerve regeneration using nanoengineering (self-assembled peptides) the nanoscale range is 200–600 nm. On a self-powered triboelectric sensor (pillars of nanowires), the nanoscale range is 700–1500 nm.

Taniguchi in 1974 in reference to the capacity to build materials precisely to the nanometre. The first attempt at miniaturisation came from the electronics industry, which was trying to develop tools for smaller electronic devices on silicon chips [2,3]. Meanwhile IBM was using a new technique to create nanostructures as small as 40 to 70 nm in the early 1970s [3]; for purposes of comparison, a red blood cell is approximately 7000 nm wide, atoms are smaller than 1 nm, and many proteins are 1 nm or larger (Figure 1) [2]. Consequently, nanotechnology is the manipulation of individual atoms, molecules, molecular clusters or surfaces into structures to create new materials and devices with different properties [2–5].

Nanotechnology can be built from the top down, which involves reducing the size of the smallest structures to the nanoscopic scale, or from the bottom up, which includes manipulating individual atoms and molecules into nanostructures. An important characteristic of nanoproducts is that they can present distinct physical, chemical, and biological behaviour from these aspects at the equivalent normal scale [3]. These singular aspects of nanotechnology surfaces result from the fact that nanoproducts have a large surface area-to-volume ratio, which causes them to be highly reactive [6,7].

Definition of nanosurfaces

Nanosurfaces are not well-defined concepts and there are some controversial points of view in terms of dimensional limits. Some authors have defined nanotechnology as engineering/technology conducted on the nanoscale (nm), in other words from 1 to 1000 nanometres, which correspond to 0.001 to 1 micrometer (µm), respectively [2,3]. This same point of view can be applied to defining microtechnology or even microsurfaces as engineering conducted on the microscale (µm), namely, ranging from 1 to 1000 micrometers (µm), which corresponds to 0.001 to 1 millimetres (mm), respectively. Microsurgery is commonly defined as surgery requiring an operating microscope to perform procedures on structure such as vessels or nerves in the range of 1mm. Julius H. Jacobson II described the first vascular anastomosis using an operating microscope in 1960, coupling vessels as small as 1.4 mm and coined the term *microsurgery* [8].

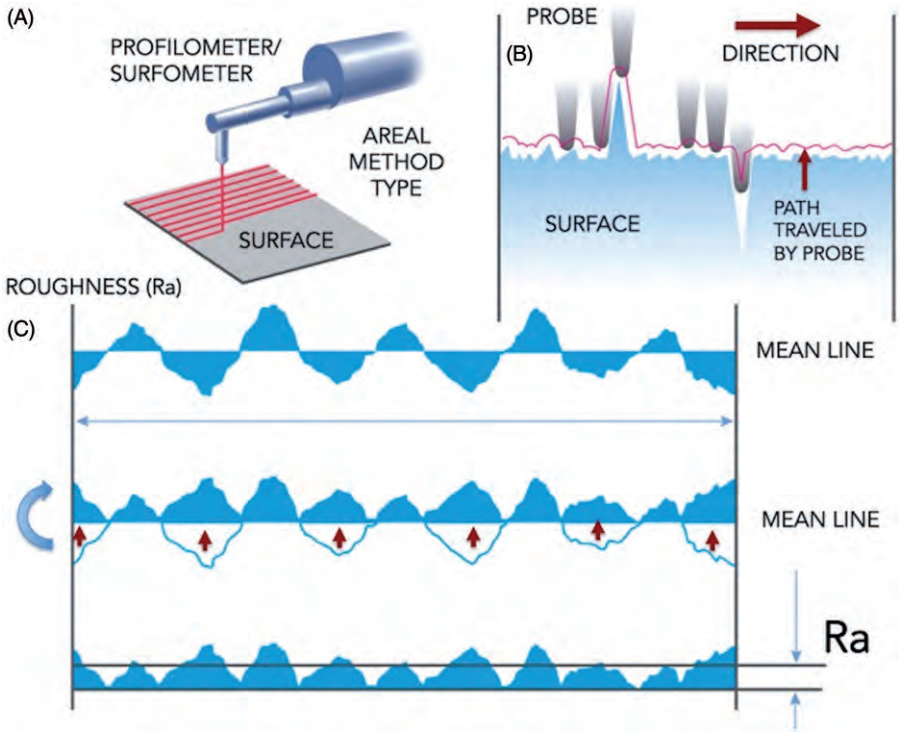

Figure 2. Scheme of surface texture and roughness. (A) Profilometer used for surface analysis, where a probe usually traces along a straight line on a flat surface. (B) Surface roughness refers to the variations in the height of the surface relative to a reference plane. (C) Roughness average (Ra) is the most commonly used parameter and is calculated as the average of a surface measured microscopic peaks and valleys and represent the arithmetic average of the absolute values of the roughness profile ordinates.

In pharmacosurgical research such as polymer therapeutics and drug delivery systems, the nanoscale comprises 1–10 nm [3,4,6]. However, in cases where research is related to nerve regeneration using nano-engineering with self-assembled peptides to build nerve conduits, the nanoscale range is 200–600 nm [6,9]. On this same scale, nano needles can be prepared from silicon and used to penetrate cell nuclei to deliver molecules [5,10]. On a slightly larger scale we can mention a self-powered triboelectric sensor with pillars of nanowires, where the nanoscale range is 700–1500 nm (Figure 1) [6,11]. For researchers who work with pharmacosurgery (1–10 nm), nerve conduits and triboelectric sensors are not considered nanoengineering or nanotechnology in terms of the size of the structures evaluated. In summary, microsurgery as well as nanotechnology is nothing more than a semantic issue and a question of view and perspective, since there is no consensus about the limits of the micro or nanoscale.

In surface engineering, surface texture is repetitive or random deviation from the nominal surface that forms the 3D topography of the surface. Alterations in the surface roughness of implants influence cell response by increasing the surface area of the implant adjacent to soft tissues, thereby improving cell attachment to the implant surface [12]. Surface texture includes roughness (nano- and micro-roughness), waviness (macro-roughness), lay, and flaws [13]. Surface roughness most frequently refers to the variations in the height of the surface relative to a reference plane. Roughness average (Ra) is the most commonly used parameter and is frequently adopted in engineering practice. However, Ra is not an adequate differentiator for surfaces as it is inefficient of differentiating between 'spiky' and 'scratched' surfaces having the same Ra. For this purpose, further parameters should be utilised, such as Rp (Maximum Peak Height), Rv (Maximum Valley Depth) and Ry (Maximum Peak-to-Valley Roughness Height). Usually, Ra measure microscopic peaks and valleys and represent the arithmetic average of the absolute values of the roughness profile ordinates. For this objective, a common method called profilometer is used for surface analysis, where a probe usually traces along a straight line on a flat surface (Figure 2). Usually, in a contact profilometer method, a diamond stylus is moved vertically in contact with a surface and then moved laterally for a determined distance and specified contact force. This method can evaluate small vertical aspects ranging in height from 10 nm to 1 mm. Most of the world's surface finish standards are written for contact

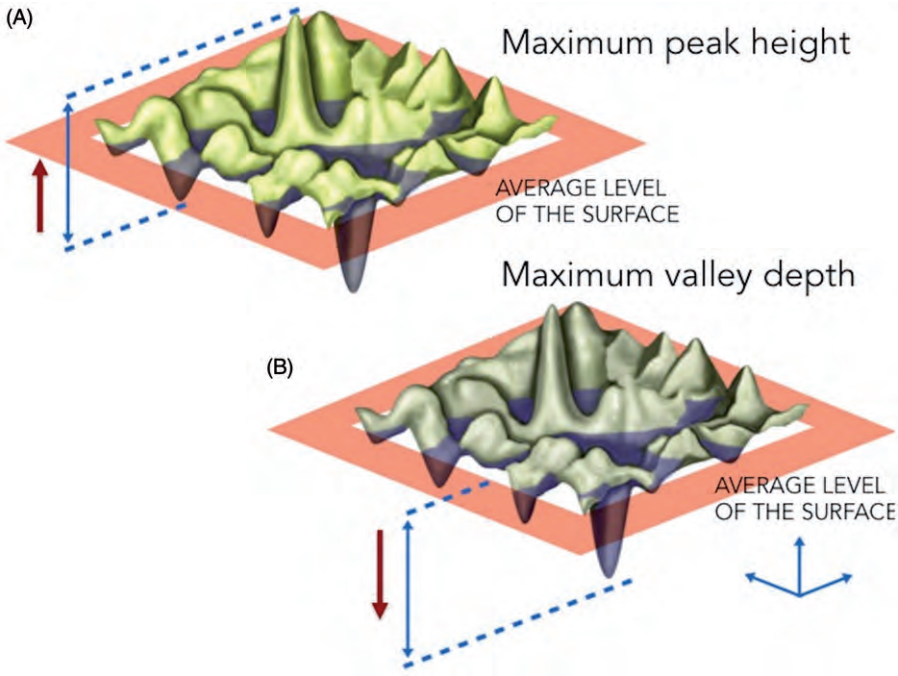

Figure 3. Scheme of fluctuations in the surface of short wavelengths, characterised by peaks/hills (*local maxima*) and valleys (*local minima*) of varying amplitudes. *Local maxima* are the peaks in a profile (two dimensions) and summits in a surface map (three dimensions).

profilometers. Another technology employed is the non-contact profilometers based on different systems of evaluation such as laser triangulation (triangulation sensor), confocal microscopy (used for profiling of very small objects), and digital holography [14].

Nano- and micro-roughness are formed by fluctuations in the surface of short wavelengths, characterised by hills (*local maxima*) and valleys (*local minima*) of varying amplitudes and spacings which are large in comparison with molecular dimensions. *Local maxima* are the peaks in a profile (two dimensions) and summits in a surface map (three dimensions). In other words, *local maxima* and *minima* measurements give the highest peak and lowest valley numbers, respectively (Figure 3) [12,13].

Soft tissue response to implants is broadly regulated by the nature and texture of the implant surface. Compared to smooth surfaces, textured implant surfaces exhibit more surface area, allowing ingrowth of the tissues or integration with the soft tissue. The role of surface topography has been an interesting area of investigation in implant research for several years, and different types of implant surface textures are currently available for clinical use. Alteration to the surface pattern has been shown to increase not only tissue-implant contact, but also the biomechanical synergy of the implant surface in early implantation periods [15]. In this field, different techniques have been studied in order to create rough surfaces and improve the integration of different implants. In fact, implant surface morphology influences cell behaviour, an aspect which can be observed in rougher surfaces where cell growth and attachment are usually seen. Cellular behaviour is also influenced by nanosurfaces, and the cell interactions signalling events occur on the nanoscale [16]. Consequently, research has focussed on the influence different nanosurfaces have on cell adhesion, proliferation, and synthesis, as well as the secretion of extracellular matrix molecules [16,17].

Breast implant technology and nanosurfaces

Most commercially available breast implants present some type of elastomer surface alteration to increase their surface roughness. This is partly a result of the large number of *in vitro* and clinical studies demonstrating positive results and satisfactory outcomes of texturising [18,19]. In fact over the last decades, known as "micro/macrotexturization", several surface modification to increase roughness have emerged [18], such as Siltex texturing, a patterned surface created as a negative contact imprint off of a texturing foam, and the Biocell surface, a more aggressive open-pore textured surface created with a lost salt technique in which the entire elastomer shell is placed on a bed of finely graded salt with light pressure (Figure 4) [20]. The size of the latter depressions are irregular, because created by salt with different particle sizes, ranging from 600

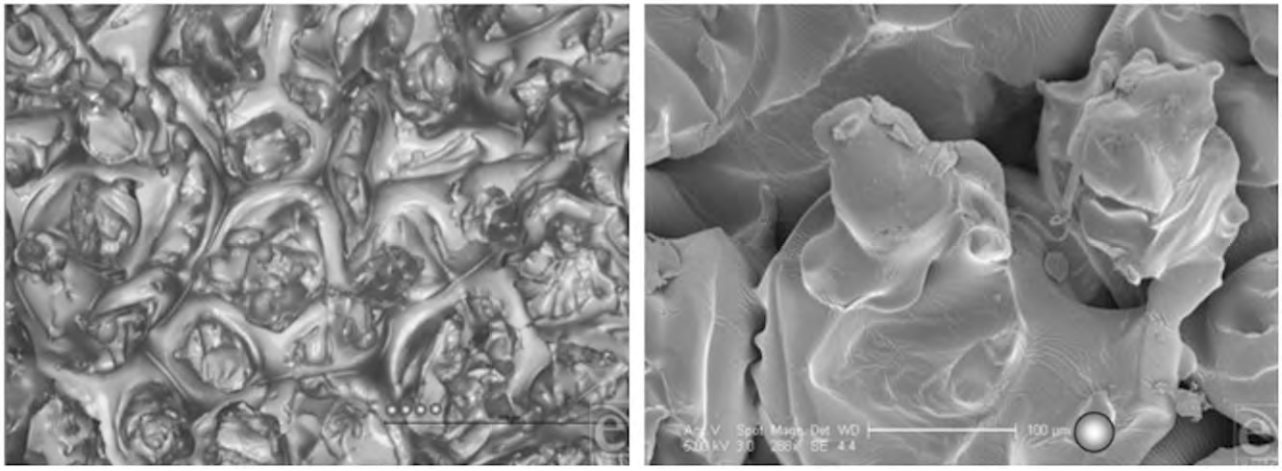

Figure 4. Left: Mentor Siltex (Santa Barbara, Calif) in light microscopy. 'Deep focus' composite at 100 × magnification with a 500-μm scale bar, showing the gross nodular texture of the surface at low magnification. Right: The same surface in scanning electron microscopy at 288 × magnification with a 100-μm scale bar and 25-μm representation of an average-sized human fibroblast. The large depth of field associated with this implant can be appreciated and the regularity of its gross texture, but the irregularity of its smaller topographies can be distinguished [22] (used by permission of Dr. Ardeshir Bayat PhD, MBBS, MRCS; Plastic & Reconstructive Surgery Research, Manchester Interdisciplinary Biocentre, The University of Manchester, Manchester, United Kingdom).

to 800 μm (0.6–0.8 mm) in diameter and from 150 to 200 μm (0.15–0.2 mm) in depth. An edge raised 70 to 90 μm around each of these depressions increases the total depth [20]. The distribution of these depressions is irregular on the surface, with an average of eight depressions per 1.5 mm^2 (Figures 5 and 9). The surface characteristics constructed by these different technologies vary widely, and although they are not frequently compared with each other, as a group they enhance the process of biointegration when compared to relatively smooth surfaces, as previously mentioned by Barnsley et al. [19].

The 'microtexturization', a more miniaturised type of roughness was later introduced into clinical practice. Microthane introduced by Polytech company is an implant shell cover of medical-grade micropolyurethane foam and has a mean surface roughness of 1500μm [21]. Barr et al. studied the currently available breast implant surfaces at high resolution and evaluate features within their surface using scanning electron and light microscopy [22]. The micropolyurethane surface has the deepest structure of all the textured surfaces, with a total depth of approximately 1500 μm and polyurethane foam outer of approximately 1000 μm in depth. The authors demonstrated that the polyurethane foam has a spider web–type pattern, with a mesh network that builds up in layers from its silicone base (Figure 6) [22].

The VelvetSurface® according to the Motiva company literature presents 1800–2200 contact points of 40–100 μm depth per cm^2 (40,000–100,000 nm) much narrow than in the macrosurface [23,24]. In terms of nanosurfaces the smallest surface available is the SilkSurface® recently introduced by the same company, with 49,000 contact points of 16 μm (16,000 nm) depth per cm^2 with smaller and shallower depressions compared to the previous 'micro' or 'macro' surface [24]. This last surface classified as a 'nanosurface' has proven a consistent surface with an average roughness of 3600 ± 400 nm, this low roughness implies low friction and therefore no lose particles (Figures 7 and 8).

In statistical field, Kurtosis it is also defined as the fourth moment in statistics and can classify how 'peaked' the graph is, or how high the graph is around the mean. In other words, Kurtosis is defined as the state or quality of flatness or peakedness of the curve describing a frequency distribution in the region about its mode. In SilkSurface® the Kurtosis value of profilometry testing is 4.0 ± 0.5, that suggest a measurements with a normal distribution because is within a value of (3 ± 2); the Skewness value is 0.6 ± 0.2, that indicates the presence of more peaks than valleys, this is when the Skewness value is a positive value (Sk >0), providing increased contact points with a density of peaks of approximately 49,000 peaks/cm^2, with an average contact angle of 131° ± 4°, this contact angle evidences how the topography increases hydrophobicity (hydrophobic surfaces have contact angles >90° and are known to show higher biocompatibility) when compared with a smooth PDMS surface contact angle of less than 110° ± 4°.

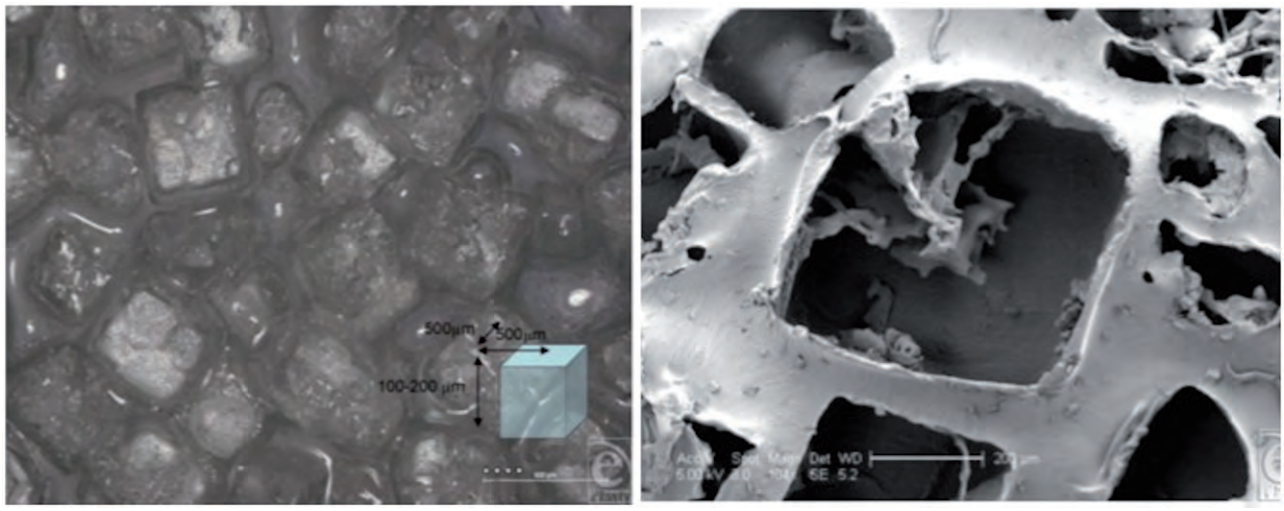

Figure 5. Left: Allergan Biocell (Santa Barbara, Calif) light microscopy 'deep focus' composite image at 50x magnification showing the granular surface secondary to the 'salt-loss' manufacturing process. Right: The same surface in scanning electron microscopy at 104 × magnification with a 200-µm scale bar and 25-µm representations of an average fibroblast [22] (used by permission of Dr. Ardeshir Bayat PhD, MBBS, MRCS; Plastic & Reconstructive Surgery Research, Manchester Interdisciplinary Biocentre, The University of Manchester, Manchester, United Kingdom).

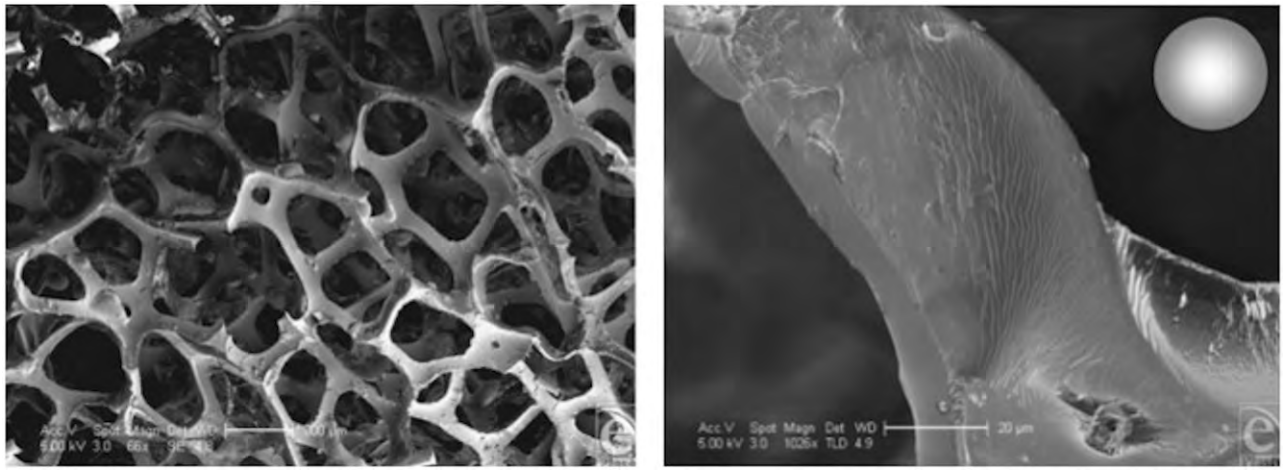

Figure 6. Left: Polytech MicroPolyurethane (Polytech Silimed Europe GmbH) surface in scanning electron microscopy at 66 × magnification with a 200-µm scale bar. This image shows the fibrillar nature of the polytech polyurethane surface at high magnification. Right: The same surface in scanning electron microscopy at 1026 × magnification with a 20-µm scale bar and a 25-µm representation of an average human fibroblast. This image shows one of the fibres that make up the surface of the polyurethane implant and its junction with another fiber [22] (used by permission of Dr. Ardeshir Bayat PhD, MBBS, MRCS; Plastic & Reconstructive Surgery Research, Manchester Interdisciplinary Biocentre, The University of Manchester, Manchester, United Kingdom).

In fact, the SilkSurface® was engineered to optimise biocompatibility by structuring uniform hierarchical micro/nano using a proprietary 3D nanotechnology imprinting on the polydimethylsiloxane (PDMS) material, in order to build the outer shell topography of the breast implants. The manufacturing process for SilkSurface® is particle-free and uses no foreign particle projection to create the surface, allowing also a uniform and controlled shell thickness. SilkSurface® has been physically characterised using the latest technologies such as SEM, 3D image topography, wettability, contact and non-contact profilometry. Thus, in theory this nanosurface has the propriety to improve compatibility between implant and tissues, minimising inflammation and possibly inflammation-related complications such as capsular contracture, double capsules, and late seromas.

These aspects, roughness, kurtosis and skewness are relevant because they are related to the foreign body response to the implanted device. Kyle et al. mentioned that micrometric and nanometric surface topographies influence cell attachment, proliferation,

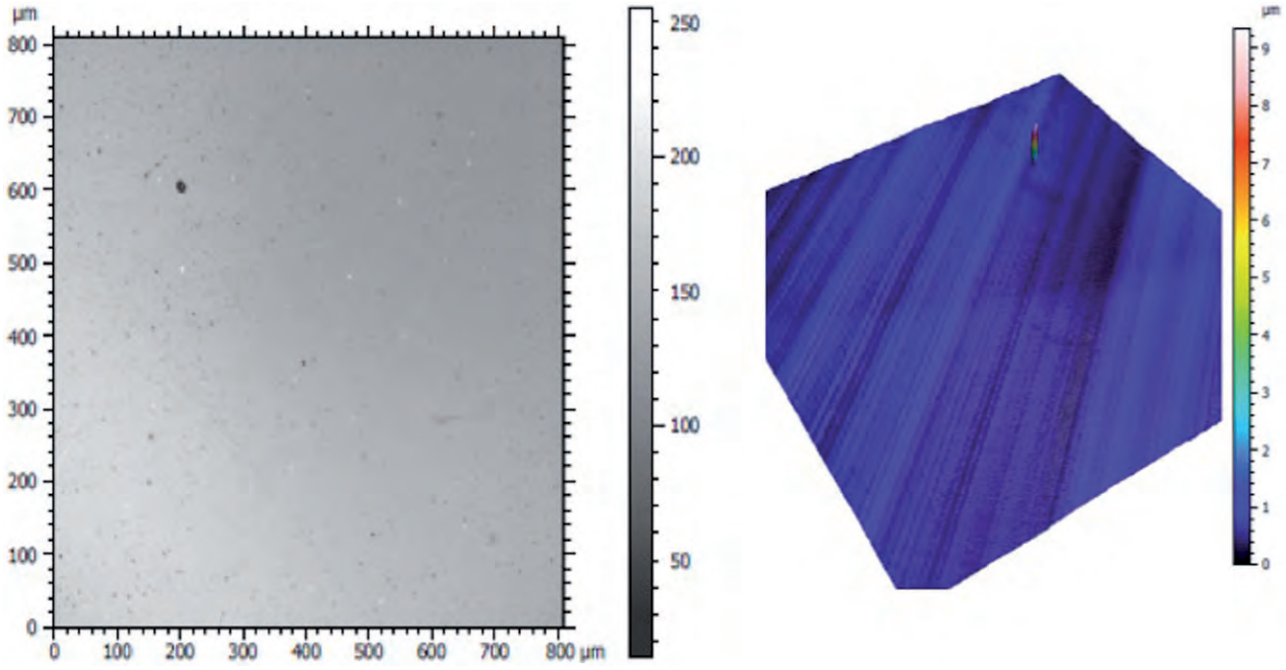

Figure 7. Images from a non-contact profilometry testing using the uSurf Mobile profilometer. Left: Microscopy image of smooth surface from Allergan SN 21123162 taken from apex section. Right: Topography image of smooth surface from Allergan SN 21123162 taken from apex section.

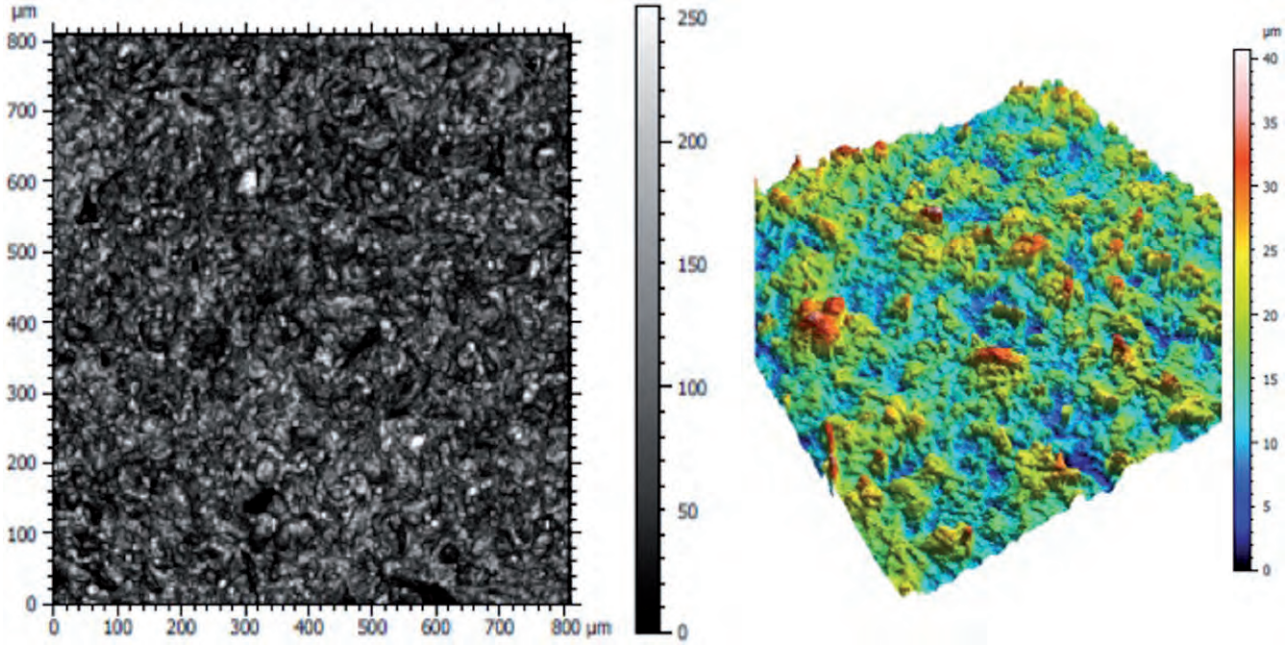

Figure 8. Images from a non-contact profilometry testing using the uSurf Mobile profilometer. Left, Microscopy image of SilkSurface® from Motiva Implants SN 151001021 taken from apex section. Right, Topography image of SilkSurface® from Motiva Implants SN 151001021 taken from apex section.

migration and differentiation in numerous cell types and on various substrates, both *in vitro* and *in vivo* testing [25]. Following with scientific research, it is proposed that initial implant cell attachment and cytokine release, may dictate the foreign body reaction and clinical outcome through cell transduction mechanisms, which mediate cytokine/chemokine release and extracellular matrix deposition. The fibroblasts form a confluent layer and produce collagen fibres evenly distributed and aligned together over smooth surfaces. But on rough surfaces, cells randomly arrange around features and cluster together.

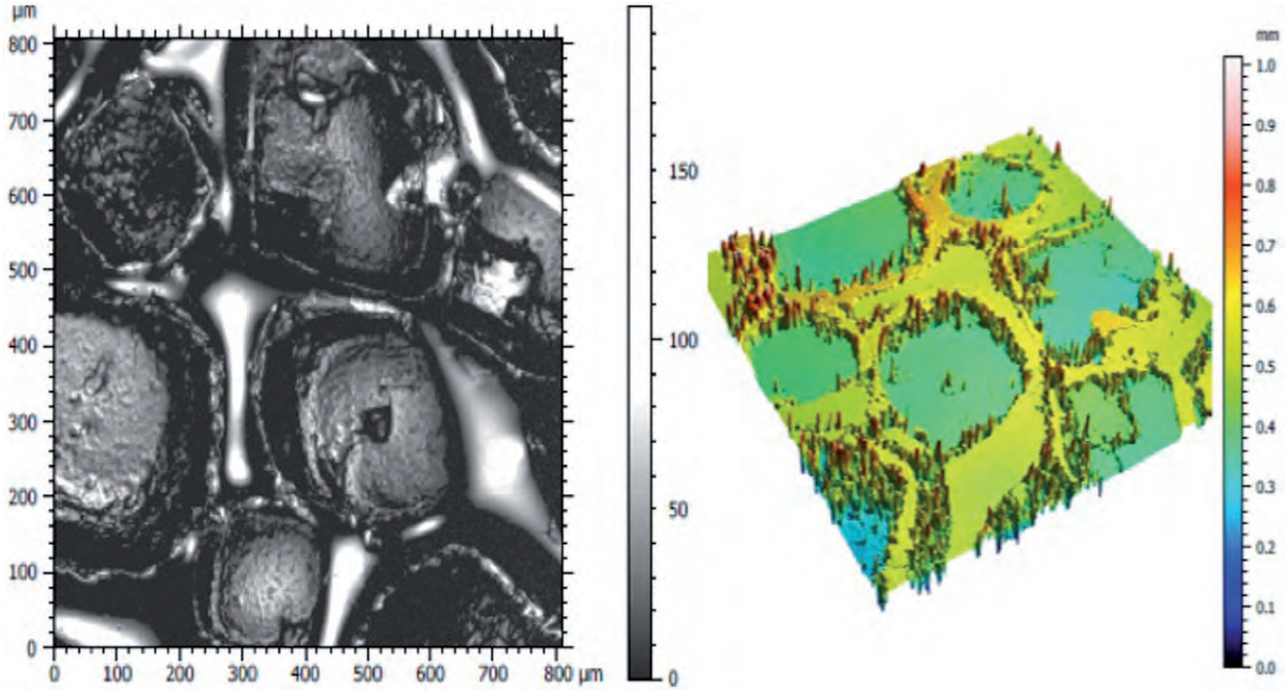

Figure 9. Images from a non-contact profilometry testing using the uSurf Mobile profilometer. Left: Microscopy image of macrosurface of BioCELL® SN 21848940 taken from apex section. Right: Topography image of macrosurface of BioCELL® SN 21848940 taken from apex section.

This random arrangement of cells on the rougher surface may lead to the production of a more randomly oriented collagen matrix, decreasing fibroblast growth as roughness is increased [25].

Another important aspect is related to fibroblast behaviour in relation to the environment. Fibroblasts filopodia are thin actin protrusions of the plasma membrane that function as an antenna for the cell to probe the environment. Therefore, filopodia are involved in cell migration and bound healing [26]. Cellular proliferation is augmented when fibroblasts can spread over the surface, and this is the case of textured surfaces, because there are more anchor points for the filopodia to attach [27]. This interaction is important for cell migration and wound healing, and encourages tissue to regenerate without capsular contracture generation [25]. On the other hand, the hydrophobicity affects the orientation and conformation of adsorbed proteins and thereby affects cell differentiation. Thus, controlling the hydrophobicity can change the protein adsorption to surface that promotes the subsequent cell adhesion and spreading, contributing to the capsular contracture formation [28]. In addition, surface hydrophobicity, chemistry and topography can have extensive effects on protein interactions including composition of the protein layer, orientation of adsorbed proteins and the degree of unfolding to reveal specific cell-binding sites. These findings support that for nanosurfaces their less roughness compared to other macro-surfaces, is contributing to the no promotion of biofilm and less long-term complications [25,28].

Clinical applications of nanosurfaces

Nanotechnology can be used to manipulate the surfaces of standard implants in order to maximise tissue ingrowth while minimising inflammation and unsatisfactory outcome. In the field of oral surgery, dental implantation is a widely accepted and reliable treatment that provides satisfactory outcomes with high success rates [29–32]. According to Gittens et al., on the macroscale the implant provides adequate and stable mechanical adhesion with bone [33]. On the nanoscale, cell membrane receptors such as integrins can identify proteins on the surface, which in turn are modulated by the nanostructures on the surface. Some studies have observed that a slightly roughened implant surface allows better osseointegration compared with a smooth implant surface [29,30], and nanostructured materials have shown increased cell attachment over microstructured or smooth surfaces [31]. Furthermore, studies have demonstrated that nanoporous topography tends to help the proliferation processes, which can accelerate the healing process around implants [32].

Bone grafting is the gold standard technique for reconstructing skeletal defects, but this technique is

not free of negative aspects such as resorption and morbidity [31–36]. Nanotechnology to promote bone regeneration has been investigated in recent years and incorporating nanosurfaces into scaffolds may enhance biocompatibility and fewer complications [31–36]. Tsukimura et al. compared outcomes from sandblasted titanium alloy implants to those of sandblasted and nanomodified implants in an experimental model [36]. Biomechanical evaluation found that push-in forces for sandblasted, alkali, and heat-treated implants were significantly higher when compared to implants which were only sandblasted. These results were also confirmed by histomorphometrical analysis which showed greater bone-to-implant contact after implantation on the surface of the extracted nanomodified implants.

Breast implants' complications and the role of nanotechnology

In the field of aesthetic and reconstructive breast surgery, use of breast implant often leads to different complications such as capsular contracture, double capsule and late seromas. Different breast implant surfaces have been developed and proposed with the aim of decreasing those complications. The formation of capsular contracture is nowadays addressed with different breast implant surfaces together with a sterile, atraumatic technique, meticulous haemostasis and local antimicrobial agents. A general consensus has not been yet reached, but in literature the idea that textured surfaces decrease the incidence of capsular contracture prevails [37–39] .Concerning seroma, factors mostly incriminated are surgical site dead space, patient BMI (Body Mass Index), micro and macro repetitive trauma and the use of acellular dermal matrix and adjuvant radiotherapy in reconstructive patients [40]. In a literature review, by Park et al., they found that, in 49 patients out of 60 cases (82%) late seroma occurred with Biocell® textured implants, suggesting that its formation is strongly associated with the mechanical features of certain implants surfaces [41]. According to works by Giot et al. [42] and Efanov et al. [43] double capsule is also associated to macrotexturing implant surface. The histological examination of double capsules removed from patients with Biocell® textured implants, revealed a delamination process that leads to the creation of the intercapsular space (ICS), therefore, promoting the formation of a double capsule. The inner capsular layer demonstrated highly organised collagen in sheets with delamination of fibres. At the prosthesis interface (PI) scanning electron microscopy (SEM) revealed a thin layer that mirrored the three-dimensional characteristics of the implant texture. On the contrary, the external surface of the inner capsular layer was flat. SEM examination of the inner capsule layer revealed both a large bacterial presence as well as biofilm deposition at the PI but a significantly lower quantity of bacteria and biofilm were found at the ICS interface. These findings suggest that double capsule is of mechanical origin [42,43].

The three, above-mentioned complications are directly or indirectly related to a newly discovered pathology associated with breast implants, which is Anaplastic Large Cell Lymphoma (ALCL), being the late seroma the most common (79.5%). Recently the WHO has redefined the classification of ALCL including three types, ALK−, ALK + and the Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL) [44].

Beginning from 1976, various authors have postulated that, beside a genetic predisposition, different mechanisms as an excessive chronic inflammatory reaction due to the presence of the implant itself, or possibly enhanced by chronic subclinical infection or tribology due to texturization characteristics, should be considered as important etiologic factors in the development of breast implant complications, attempting to associate the increased incidence with the recent introduction of textured surface implants [42–53]. Consequently implant surface may play a key role into development of complications as well as their control.

The chronic inflammatory reaction refers to the foreign body effect when silicone released from implants by direct rupture, bleeding through the exterior shell and particulation from the peaks of the macrotextured surface. Particulate coming from peaks of textured implants creates extra foreign bodies, giving a chronic immunologic inflammatory reaction with tissue growth, the periprosthetic capsule. Although implant producers have coped with rupture and bleeding by implant core structure modification (cohesive gel, triple shell, etc.), particulation is not addressed at all with the macrotextured surfaces still routinely used. Silicone particles when captured by macrophages ignite a complex mechanism that leads to chronic inflammation and activation of T-lymphocytes [53,54].

Based on a study showing the presence of high concentrations of *Ralstonia Spp.* in biofilm around implants with BIA-ALCL, some authors formulated the second theory, the subclinical infection hypothesis. Although a tempting theory, one should also note that: biofilm is associated with all medical devices used in humans, and more specifically *Ralstonia Spp.* is found also in the biofilm of non-ALCL-related implants;

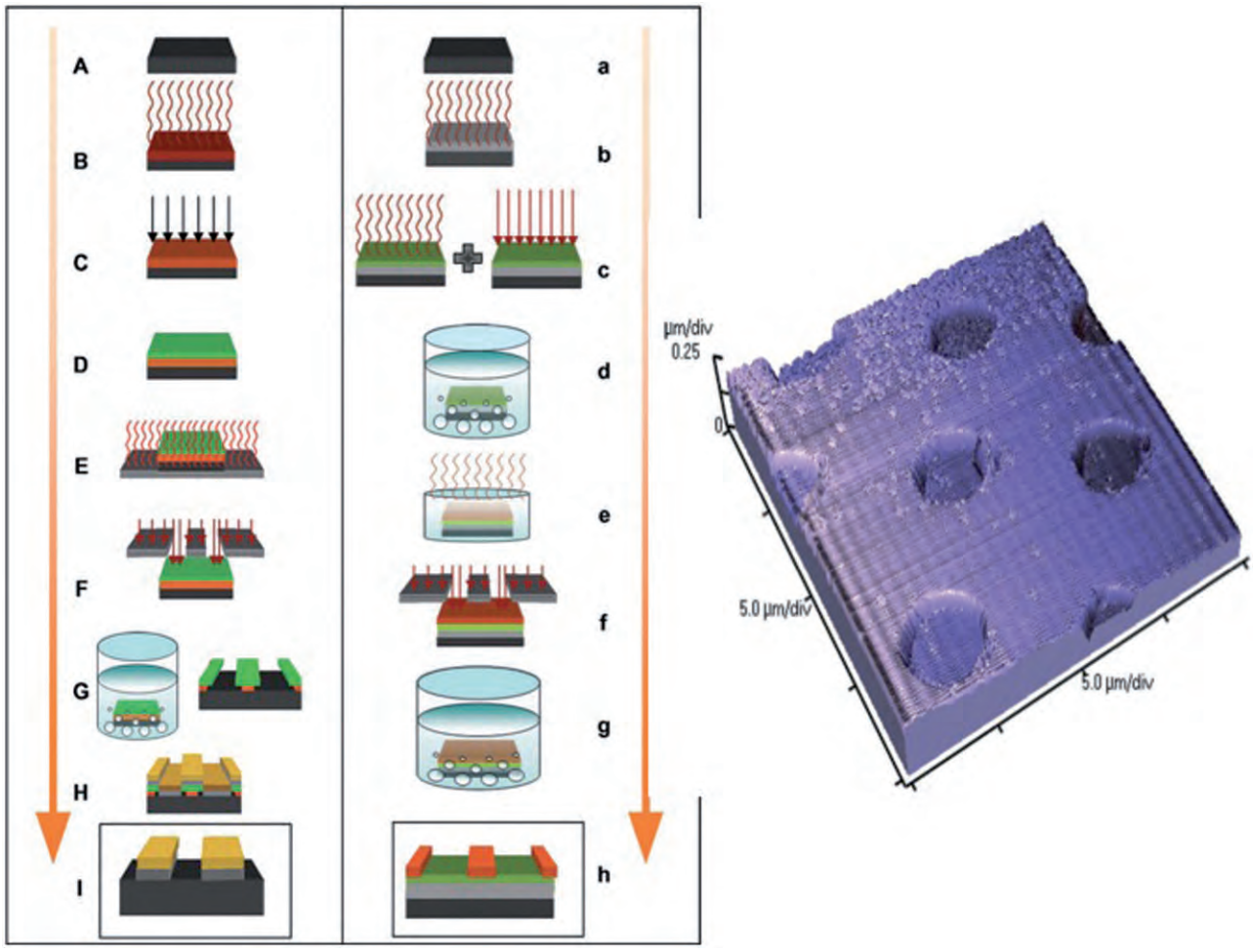

Figure 10. Left: Flow diagram of the processes used to produce S1805 and the SU-8 surfaces. S1805 resist protocol: (A) Clean 22 mm ×25 mm silicon wafer (black); (B) 1 mm3 of HMDS applied to the wafer and spun at 3000 rpm for 45 s; (C) 1 mm3 of PMGI applied to the wafer, spun at 3000 rpm for 45 s and ultraviolet, and exposed for 10 s; (D) 1 mm3 of S1805 applied to the wafer and spun at 4000 rpm for 30 s; (E) baked surface of the fibronectin-coated PDMS at a concentration of 1 × 105 cells per millilitre of media, which was achieved by using a C-Chip disposable haemocytometer (Labtech, Ringmer, East Sussex). (F–I) It is the final sequence of the nanosurface building process. Right: Atomic force microscope image of 4-µm-wide and 5-µm-spaced pits in silicone that illustrates how well the features were transferred to silicone [44] (used by permission of Dr. Ardeshir Bayat PhD, MBBS, MRCS; Plastic & Reconstructive Surgery Research, Manchester Interdisciplinary Biocentre, The University of Manchester, Manchester, United Kingdom).

it has always being 'around', yet only now, and mainly only patients with textured implants are affected by BIA-ALCL; it is correlated to capsular contracture but not to 'sterile' seroma, the main symptom of BIA-ALCL [55,56]. There is also confusion regarding the type of bacteria involved, as the main author generically refers to *Ralstonia spp*, yet some commentators incriminate specifically the *Ralstonia Pickettii* without any scientific report [57].

The third etiopathogenetic mechanism refers to the 'tribology hypothesis'. The delamination process in textured implants described above, due to the mechanical shear stress, not only is responsible for the double capsule formation but it also bolsters the inflammation process that through DNA injury and genetic instability can activate maladaptive homeostatic responses and dormant transcription factors. This theory is reinforced by the fact that silicone devices have been routinely used in medical practice, yet, only, and in particular textured breast implants, are associated with ALCL [58–60].

Barr et al. recently investigated the biocompatibility of silicone via cell-surface interaction [61]. These authors created well-defined topographies containing numerous micron-sized pillars, pores, grooves, and ridges in medical-grade silicone and evaluated how fibroblasts derived from breast tissue reacted and aligned to these surfaces (Figure 10). High-magnification images of vinculin, vimentin, and the actin cytoskeleton highlighted differences in fibroblast adhesion between the fabricated silicone surfaces. According to these authors, the results indicated that fibroblast

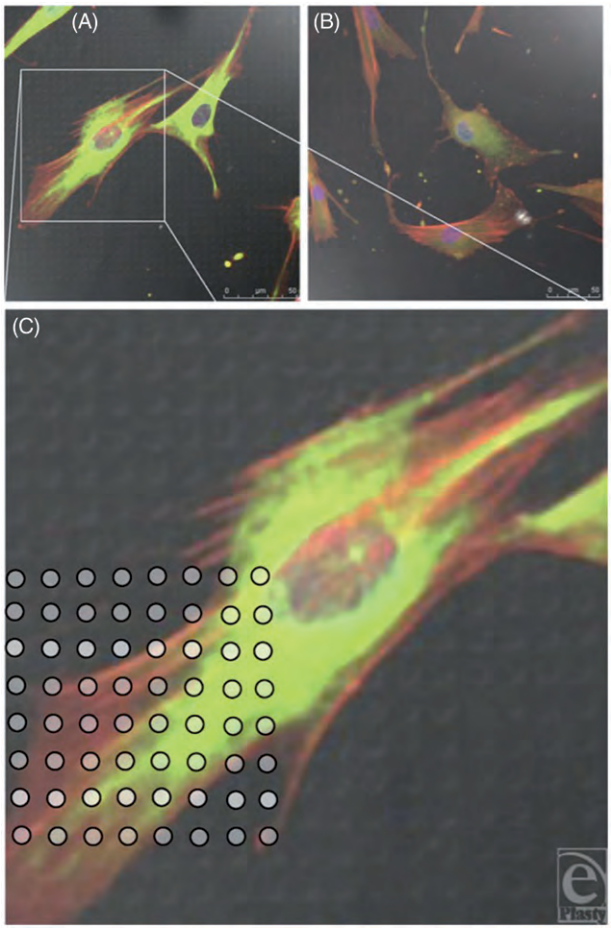

Figure 11. S1805-derived surfaces. (A and B) Cells randomly spread upon this surface. (C) White dots (indicating surface features beneath the fibroblast) highlight the lack of increased staining of fibroblast cytoskeleton in relation to surface features. Actin fibres (red) and vimentin (green) [44] (used by permission of Dr. Ardeshir Bayat PhD, MBBS, MRCS; Plastic & Reconstructive Surgery Research, Manchester Interdisciplinary Biocentre, The University of Manchester, Manchester, United Kingdom).

adhesion and the reactions these cells have to silicone can be manipulated to enhance biointegration between the implant and the breast tissue. A modification of the fibroblast phenotype was also observed, exhibiting the propensity of these surfaces to induce categorical remodelling of the fibroblasts (Figure 11). This study introduced a novel process of nanomaterials and provides an additional example of nanotechnology use to enhance the performance of standard breast implant surfaces. In addition, these preliminary observations stimulate further research to develop more biocompatible constructs capable of eliminating capsular contracture by subverting the foreign body response.

Valencia-Lazcano et al. reemphasized the importance of breast implant surfaces for optimal enhancement of cell adhesion [62]. To evaluate the behaviour of fibroblasts with silicone implant surfaces, these authors used a confocal laser scanning microscope, a microtest 5 kN tensile testing device, and a contact angle goniometer. In this study the textured surfaces were rough and nodular, while smooth implant surfaces were less rough, more regular. Significant numbers of fibroblasts were attached to the textured surfaces compared to the smooth surfaces, which had higher levels of cell adhesion with surface roughness. The authors concluded that surfaces with arithmetical mean deviation of greater roughness and reduced hydrophilicity with high water contact angles enhanced cell adhesion. These findings have immediate implications for designing improved surfaces, which may help prevent breast capsular contraction double capsule, seroma formation or BIA-ALCL for aesthetic and reconstructive applications [62].

In a recent article, Kyle et al. discussed the manufacturing techniques and properties of breast implant surfaces based on nanotechnology by reproducing extracellular matrix topographical cues such as those present within the acellular dermal matrix (ADM) in synthetic implant surfaces [25]. According to these authors, this technique could lead to enhanced implant integration and performance while reducing complications. In this study, the micro- and nanoscale features of ADM were replicated in polydimethylsiloxane (PDMS) using an innovative maskless 3D greyscale fabrication process. Fibroblasts derived from human breast tissue were cultured on PDMS surfaces and compared to commercially available smooth and textured silicone implant surfaces. The authors found that the PDMS with replicated ADM surfaces promoted cell adhesion, proliferation and survival, as well as increased focal contact formation and spread fibroblast morphology compared to commercially available implant surfaces. In addition, vinculin and collagen 1 were up-regulated in fibroblasts on biomimetic surfaces, while IL8, TNFa, TGFb1, and HSP60 were down-regulated. Similarly, Anderson et al. studied the impact of nanotopography on cell morphology and cytokine production [63]. For this purpose, the authors seeded uroepithelial cells on three different substrate types: two with defined nanometre topographies and one flat control, all with identical surface chemistry. The nanostructured substrates contained hemispherical pillars or step edges in the form of parallel grooves and ridges. Qualitative and quantitative analysis of cell morphology and cytokine production were evaluated. The cell morphology and production of IL-6 and IL-8 were studied when uroepithelial cells were cultured on grooved, hemispherically structured and flat TiO2 surfaces. The cells appeared partially aligned to the

grooves and had a cytokine release similar to that found from cells on flat surfaces. Cells on hemispherical pillars had a smaller area, were less round, and had more outgoing membrane projections compared to cells on flat surfaces, i.e. they were more stellate. These morphological changes correlated with a diminished release of IL-6 and IL-8. Based on this experimental model, the organisation and form of nanoscale topographic structures can influence both the morphology and function of adherent cells, which is relevant to the study of cell interaction with biomaterials *in vivo*. In addition, increased knowledge of the interactions between cells and organised nanoscale structures may lead to new functional materials. These studies emphasised the relevance of a novel approach to the development of functionalised biomimetic breast implant surfaces, which were demonstrated to significantly attenuate the acute foreign body reaction to silicone *in vitro*.

Future prospects for nanotechnology in breast surgery

Nanotechnology has the potential to bring enormous changes to the fields of breast surgery. Breast implants with nanofiber coatings to deliver specific anti-cancer drugs are currently under study [64]. Additionally, a breast implant surface modification with antifibrotic drugs could reduce capsular contracture. Zeplin et al., in a comparative experimental study in rats, observed that submuscular embedded silicone implants coated with halofuginone (a type I collagen synthesis inhibitor that interferes with the TGF-beta signalling pathway) presented a significant decrease of CD68 histiocytes, TGF-beta, fibroblasts, collagen types I and III, and capsular thickness [65]. These authors concluded that there were fewer foreign body responses to surface-modified silicone implants, noting their potential for reducing capsular fibrosis via a local antifibrotic effect, suggesting yet another application of nanotechnology in breast surgery. Chun and Webster showed that nanostructured polytetrafluoroethylene (PTFE) is less immunogenic *in vivo* as a result of low-macrophage adhesion and low-protein absorption [66].

Nanomaterials have also been shown to reduce the ability of microorganisms to create biofilms [67–69]. Bacterial adhesion to surfaces is the starting point for chronic biofilm-associated infection and antibiotic resistance [67]. Consequently, nanotechnology will provide important tools for designing and fabricating a new generation of substrates with antimicrobial properties and modifying standard surfaces in order to avoid bacterial adhesion [68]. The main factors related to bacterial adhesion are physical and chemical aspects of the implant and environmental characteristics [68,69]. Despite their theoretical advantages, surface alterations have negative aspects such as potential toxicity and the possible occurrence of local immunogenicity [67]. As a result, recent investigations have focussed on surface topography, and nanotechnology presents methods for designing surfaces with controlled nanotextures; for example, implants with immunologically inert nanosurfaces could resist infection and reduce the immunologic response [5,67]. Studies investigating the clinical applications of silver polymeric nanosurfaces seem to be rather consistent due to their broad-spectrum antimicrobial characteristics as well as their morphologies, chemical composition, and biocompatibility compared with their synthetic counterparts [67]. Despite the promise offered by nanotechnology with antibacterial surfaces, at present the data is limited and there is no clear conclusion concerning the interactions between bacterial adhesion and surface features. Furthermore, the type of antibacterial substrate or surface that should be designed using nanostructure remains unclear and requires further investigation. Future efforts should be directed toward new methods, physical and chemical characterisation of surfaces, and biochemical and molecular investigations of bacteria–surface interactions [67].

The notion that such small-scale alterations can be so effective is intriguing, and the concept of nanosurfaces can be applied extensively in the field of breast implant integration and manipulation of inflammatory response. However, these preliminary results also indicate that many questions remain in the search to assimilate nanotechnology into clinical practice. The positive results of *in vivo* experiments can be considered a satisfactory first step in bringing these implant surface alterations closer to plastic surgeons, but conclusions related to the impact these new surface aspects have on implant performance for breast surgery applications will not be completely understood until long-term clinical studies are performed.

Conclusions

In conclusion, nanotechnology has a vast array of applications in aesthetic and reconstructive breast surgery. Specifically, advances in nanotechnology have influenced implant design, tissue engineering, and drug delivery systems. As our understanding of physiology on the nanoscale advances, the use of these new technologies will increase exponentially. Creating a controlled nanotexture on implant surfaces via

additive surface modification techniques has shown positive results in terms of bacterial growth and guided tissue integration, aiming at moving from a 'foreign body reaction' to 'known body bidirectional interaction'. These aspects make nanotechnology a strong resource when applied to all aspects of breast surgery. Understanding the ways in which surface properties impact inflammatory cell response is of the utmost significance in designing implants that can provide satisfactory solutions by minimising clinical complications in the long term.

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