
Supplementary information

The surface topography of silicone breast implants mediates the foreign body response in mice, rabbits and humans

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Supplemental Materials

The surface topography of silicone breast implants mediates foreign body response in mice, rabbits and humans

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Supplementary Table 1: International Organization for Standardization (ISO) classification (ISO 14607:2018 “Non-active” surgical implants - Mammary implants-Particular requirements) based upon topography determined by scanning electron microscopy (SEM) and roughness (Ra) as determined by optical, contact or non-contact profilometry and last renewed in May 2018. According to the ISO classification and based on Ra measurements breast implants are stratified into smooth (Ra<10 µm), microtextured (Ra, 10 µm to 50 µm), and macrotextured (Ra > 50 µm)^{58,60}.

Implant	Average Peak Projection (mean roughness, µm)	Texture Designation (based on ISO criteria)
Control	0.716	Smooth
SmoothSilk®	3.424	Smooth
VelvetSurface®	14.62	Microtextured
Siltex®	32.38	Microtextured
Microcell®	53.04	Macrotextured
BIOCELL®	82.74	Macrotextured

Supplementary Table 2: a) Reported capsule contracture rates for different human-scale implants, with follow-up periods post-implantation as notated. In general, capsular contracture was the largest reason for either removal or re-operation across macrotextured implants. b) Incidence of rippling/tensions lines in the skin and implant capsules observed in this rabbit study (retrieval photos in Supplemental Figures 2 and 4 as examples), over 3 weeks, 6 months, and (in half of the cases) 1 year, respectively.

a)

Implant (manufacturer)	Reported contracture rates (over time in years-yr, as noted; following primary augmentation)
Control smooth	Inamed study: ~18.4% (10-yr for ~260 cc implants; other manufacturers) ⁶⁰
SmoothSilk® (Motiva)	0% (3-yr) ⁶¹ 0% (6-yr) ⁶²
VelvetSurface® (Motiva)	0% (3-yr) ⁶¹
Siltex® (Mentor)	8.1% (3-yr) ⁶³ 10.9% (8-yr) ⁶³
Microcell® (Allergan)	Not available due to lack of comprehensive study
BIOCELL® (Allergan)	13.2% (4-yr) ⁶³ 19.1% (10-yr) ⁶³

b)

Implant Group	Tension lines/Rippling observed (from n = 5/group), 3 weeks	Tension lines/Rippling observed (from n = 5/group), 6 months	Tension lines/Rippling observed (from n = 5/group), 1 year
Control	3/5	4/5	4/5
SmoothSilk®	0/5	1/5	1/5
VelvetSurface®	1/5	2/5	N/A
Siltex®	4/5	5/5	N/A
Microcell®	1/5	3/5	N/A
BIOCELL®	3/5	4/5	5/5

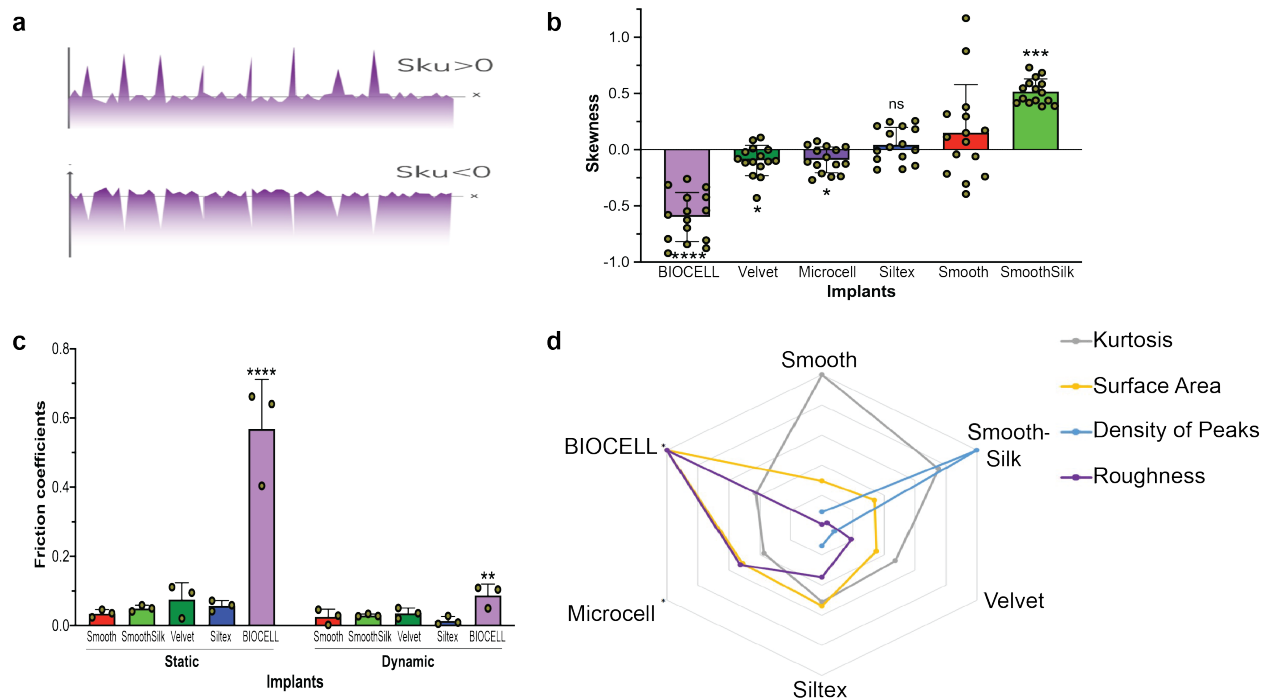
Supplementary Table 3: Quantification of rabbit histology, following H&E and Masson's Trichrome staining for capsule tissue samples at 3 weeks and 6 months following implantation. Capsule thickness was determined by sampling 4 areas total (2 for both above and below) of all retrieved breast implants for n = 5 rabbits/group/time point. In addition, a minimum of 5-10 individual capsule thickness measurements were taken along the implant periphery in each of the 20 implant samples per group for each time point. Data is displayed as mean +/- SE, μm . These numbers are in graphical form in Figs. 2e-h.

Implant	Capsule Thickness (mean +/- SE, μm)	Capsule Thickness (mean +/- SE, μm)
	3 weeks post-implant	6 months post-implant
Control	Top: 730 ± 66.3	Top: 630 ± 28.8
	Bottom: 330 ± 53.9	Bottom: 377 ± 62.5
SmoothSilk®	Top: 230 ± 25.5	Top: 285 ± 26
	Bottom: 140 ± 17	Bottom: 195 ± 15.7
VelvetSurface®	Top: 475 ± 19.2	Top: 489 ± 24
	Bottom: 354 ± 93	Bottom: 344 ± 42.9
Siltex®	Top: 1560 ± 151	Top: 846 ± 54.4
	Bottom: 1077 ± 97.3	Bottom: 538 ± 34.4
Microcell®	Top: 1270 ± 59.3	Top: 646 ± 30.8
	Bottom: 1200 ± 118	Bottom: 892 ± 55.6
BIOCELL®	Top: 1500 ± 165	Top: 1231 ± 42.1
	Bottom: 923 ± 97.3	Bottom: 195 ± 15.7

Supplementary Table 4: Human breast implant patient information. Table showing implant type, years of implantation, as well as healthy vs. active disease status.

Patient #	Manufacturer	Implant Type	Incubation time	Disease Status
1	Motiva	SilkSurface®	7 months	Healthy
2	Motiva	SilkSurface®	1 year	Healthy
3	Motiva	SilkSurface®	4 years	Healthy
4	Motiva	SilkSurface®	5 years	Healthy
5	Motiva	SilkSurface®	8 years	Healthy
6	Allergan	Smooth	4 years	Healthy
7	Allergan	Smooth	4 years	Healthy
8	Allergan	Smooth	5 years	Healthy
9	Allergan	Smooth	2 years	Healthy
10	Allergan	Smooth	2 years	Healthy
11	Allergan	BIOCELL®	6 years	Healthy
12	Allergan	BIOCELL®	4 years	Healthy
13	Allergan	BIOCELL®	4 years	Healthy
14	Allergan	BIOCELL®	4 years	Healthy
15	Allergan	BIOCELL®	4 years	Healthy
16	Allergan	BIOCELL®	6 years	ALCL, one breast only
17	Allergan	BIOCELL®	11 years	ALCL, one breast only
18	Allergan	BIOCELL®	6 years	ALCL, one breast only
19	Allergan	BIOCELL®	7 years	ALCL
20	Allergan	BIOCELL®	7 years	ALCL
21	Allergan	BIOCELL®	5 years	ALCL

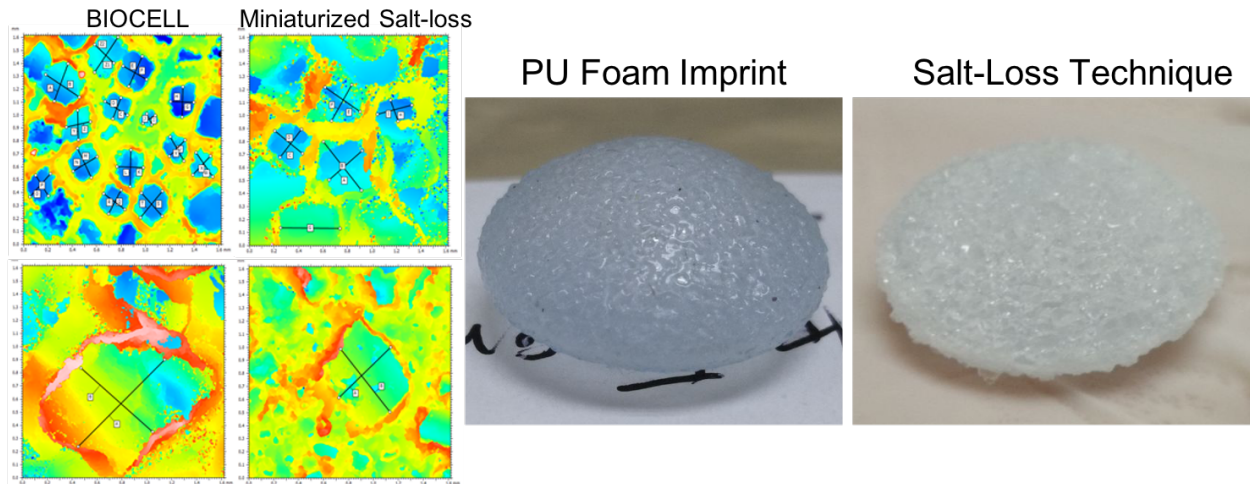
2. Supplementary Figures –



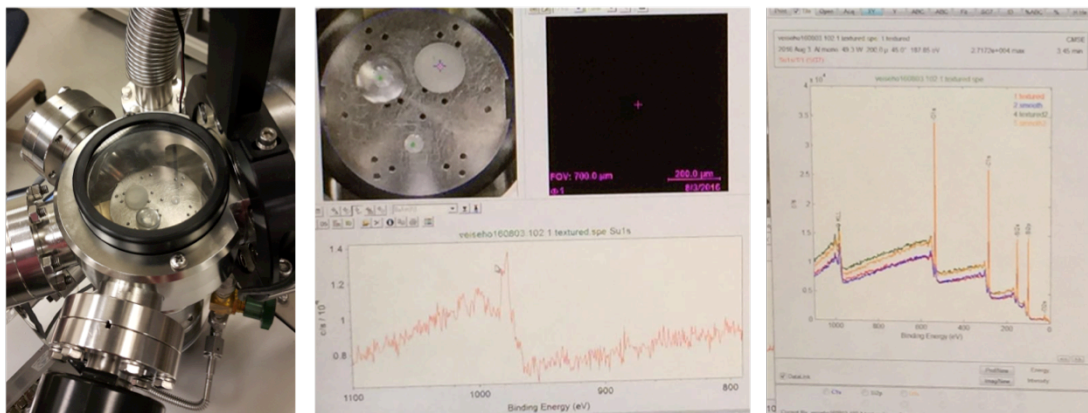
Supplemental Figure 1. Surface characterization of commercial human-scale breast implants. Non-contact profilometry (μ Surf Mobile) technique was used to determine breast implant surface topographical features (i.e., variations in the height of the surface relative to a reference plane) and roughness for human-sized, commercial control Smooth (Mentor), SmoothSilk®/SilkSurface® (Motiva), microtextured VelvetSurface® (Motiva) and Siltex® (Mentor), as well as macrotextured Microcell® and BIOCELL®. Schematic (**a**) and quantification (**b**) for implant surface skewness, a measure for prominence of surface peaks vs. valleys; positive skewness means more peaks than valleys, relative to a reference plane where most of the implant surface (x) resides. Negative skewness means more valleys than peaks. (**c**) Quantification of static as well as dynamic friction coefficients, as measures of shear force application needed to start or maintain active implant movement at a constant velocity against the tissue. (**d**) To help understand how different surface features collectively map across implant types, we created a spiderweb plot where implant surface area, kurtosis (measure of sharpness or lack thereof of peak size distribution or dispersity), density of peaks, and roughness were all simultaneously considered. Peak density unfortunately doesn't apply as it is not determinable for Microcell® and BIOCELL® implants due to the nature of the surface topography which has cavities left by salt crystals that are used for texturization. Of note, ISO14607:2018 states that "certain features are not applicable for all texture types". All bar graph data: mean $\pm$ SD. Statistical analysis: one-way ANOVA plus Bonferroni

multiple comparison correction; $p < 0.05$, 0.01, 0.001, 0.0001 for comparisons to all implants vs. Smooth control for Skewness and BIOCELL® for Friction coefficient (*, **, ***, ****). All subpanels reflect representative data from *in vitro* experiments repeated 2 times. Subpanel a is reproduced from⁶¹ (Fig. 3), and d is a newly graphed representation of data originally reported in⁶¹.

a) Examples of miniaturized, higher roughness mouse implants:

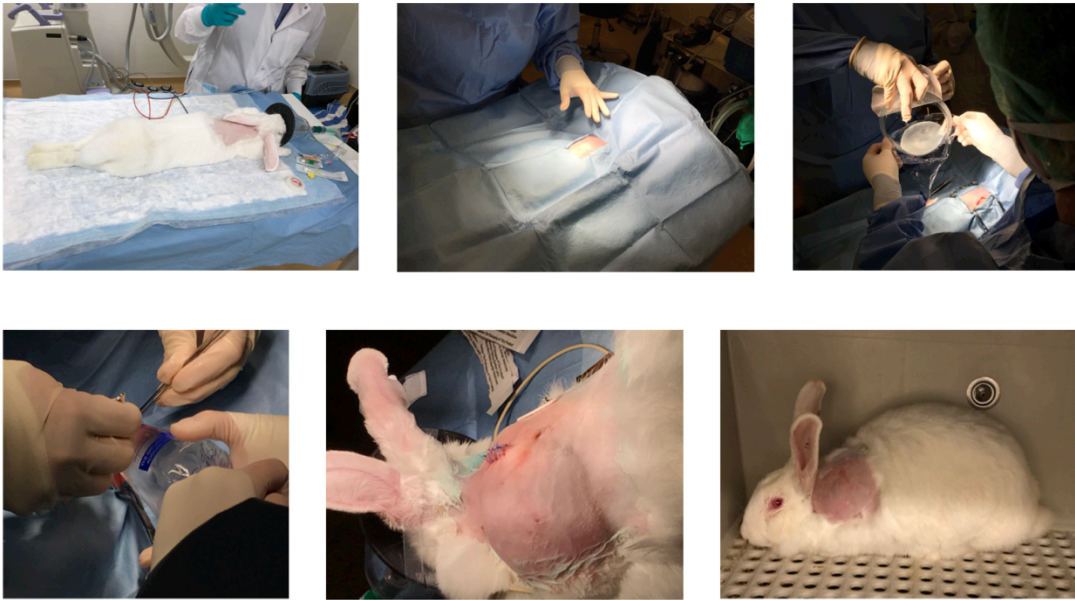


b) Examples of implant surface chemistry analysis by XPS:



Supplemental Figure 2. Additional information on production and characterization of miniaturized implant mimics for use in mice – a) Examples of surface topography imaging of human-scale (BIOCELL®) vs. salt-loss (SL) produced miniaturized implants, *left*; photos of polyurethane foam imprint (PU) and salt-loss (SL) produced miniaturized implants, *right*. **b)** Representative photos of XPS surface chemistry analysis performed on mini implants (smooth and SmoothSilk®-like implant mimics, left and top center, with elemental analysis, middle bottom and right).

a)

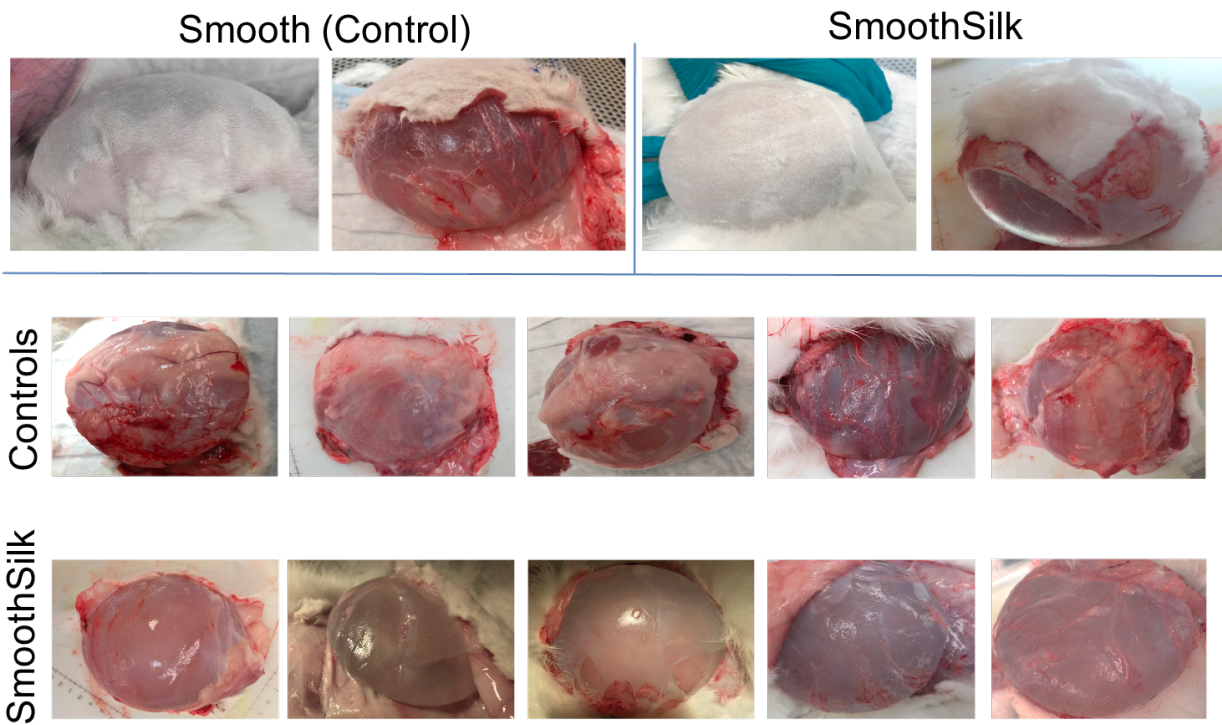


b)

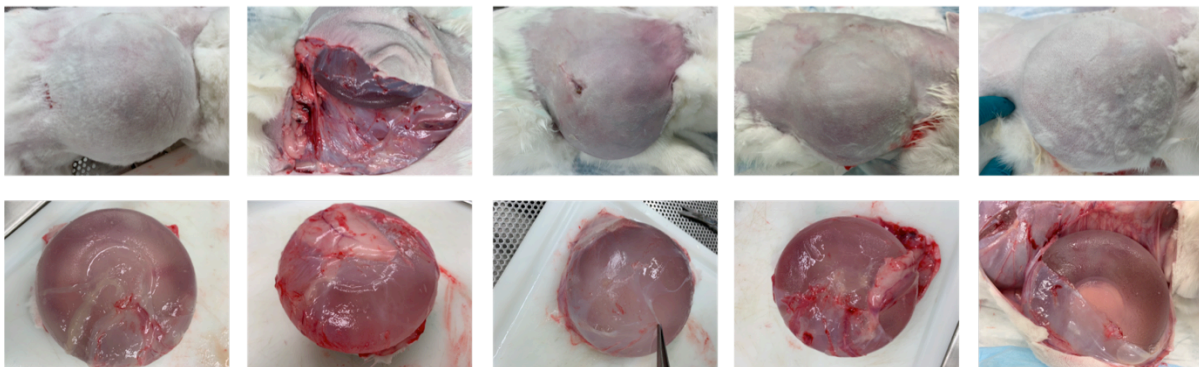


Supplemental Figure 3. Flow of rabbit implantation procedure – a) Photos (left to right, top and then bottom row) obtained on the day of implantation, preparation of rabbits under anesthesia, shaving and sterilization of the surgical field, insertion of sterile implants straight out of their package into sterile sleeves, their insertion and then suturing to close the minimal incision (~2-3 cm), and recovery of rabbits for incubating implants for either 3 weeks or 6 months. **b)** Photo of sterile packaged human-scale implants, along with Motiva Imagine insertion sleeves used for easy placement with minimal incision lines. N = 5 rabbit/group per time point. Photos are representative of all procedures carried out for all implants.

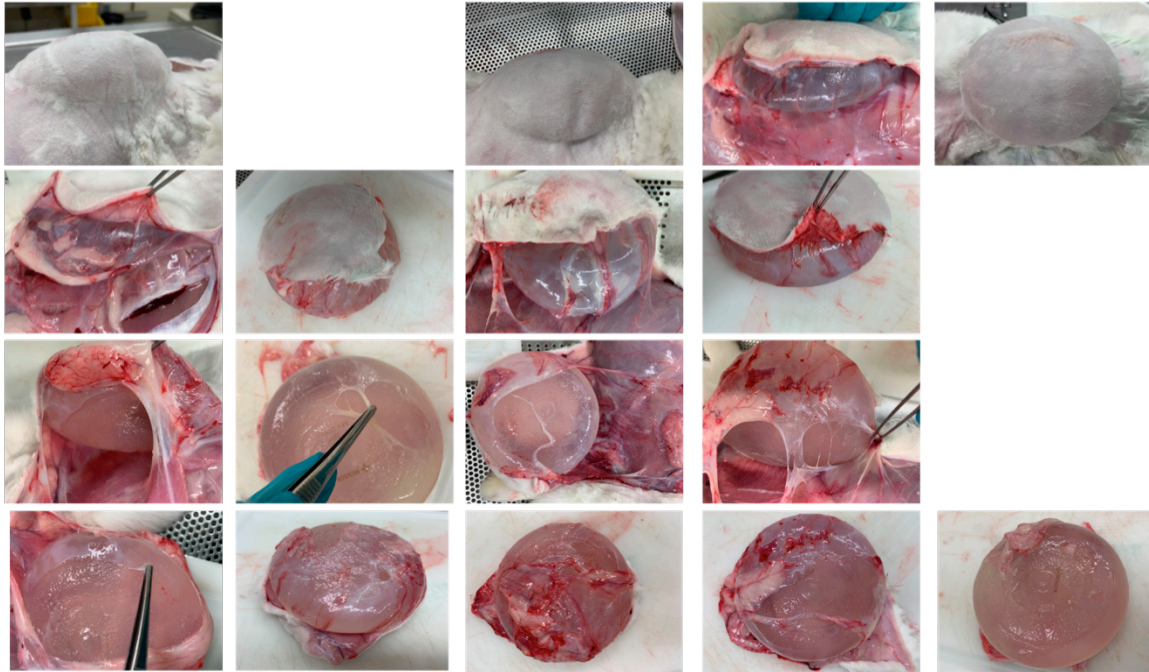
a) Smooth (Control) vs. SmoothSilk/SilkSurface



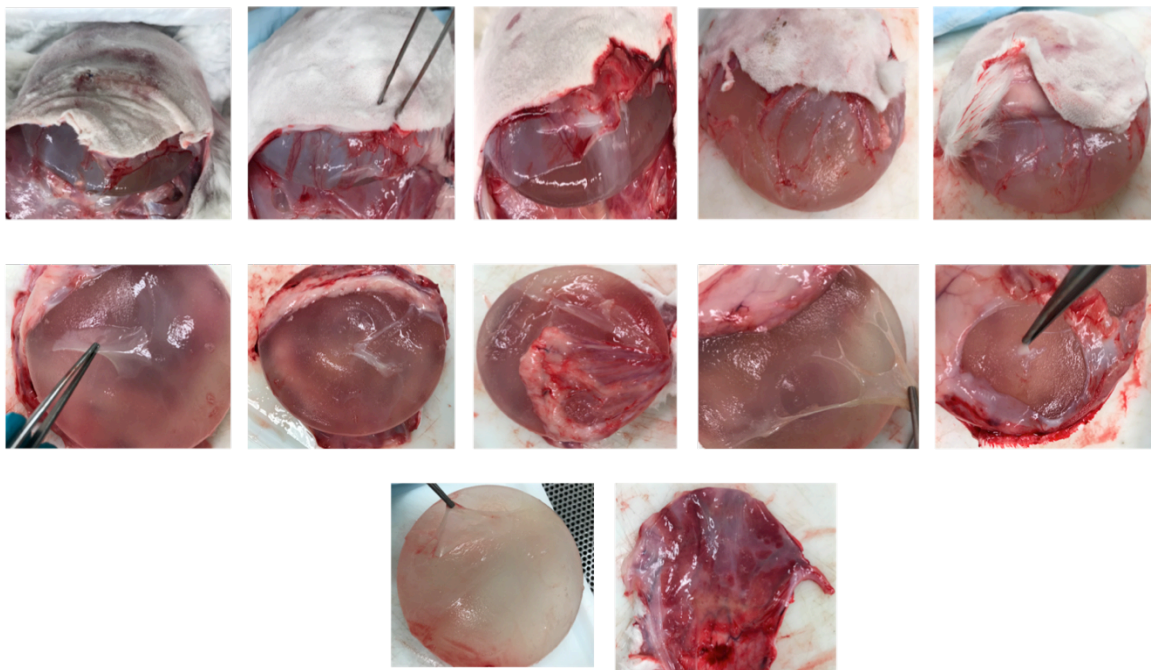
b) VelvetSurface



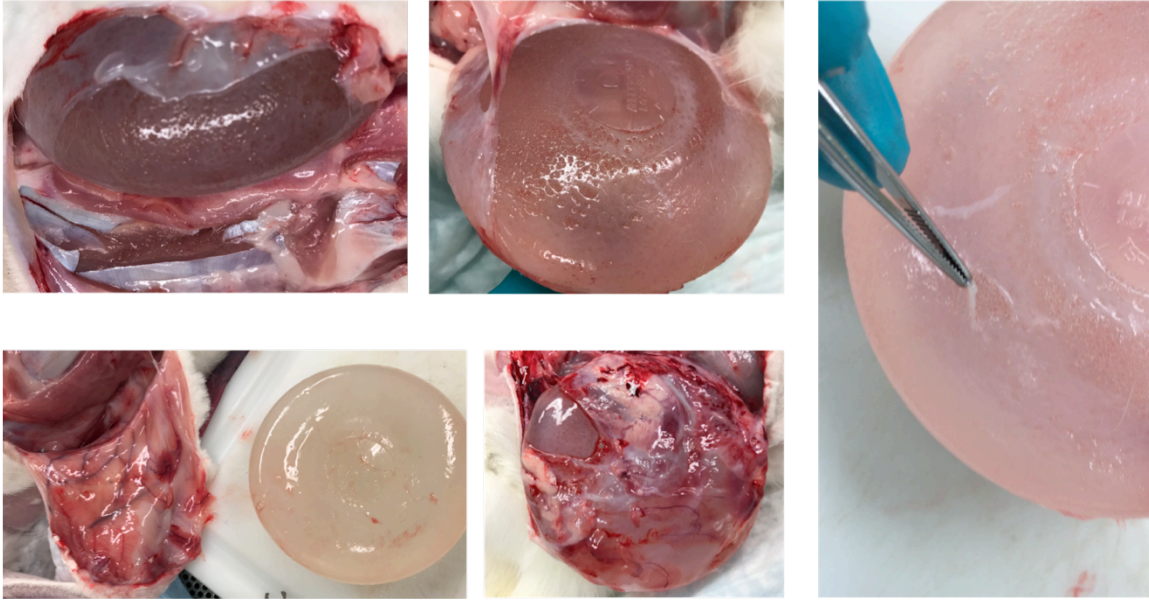
c) Siltex



d) Microcell

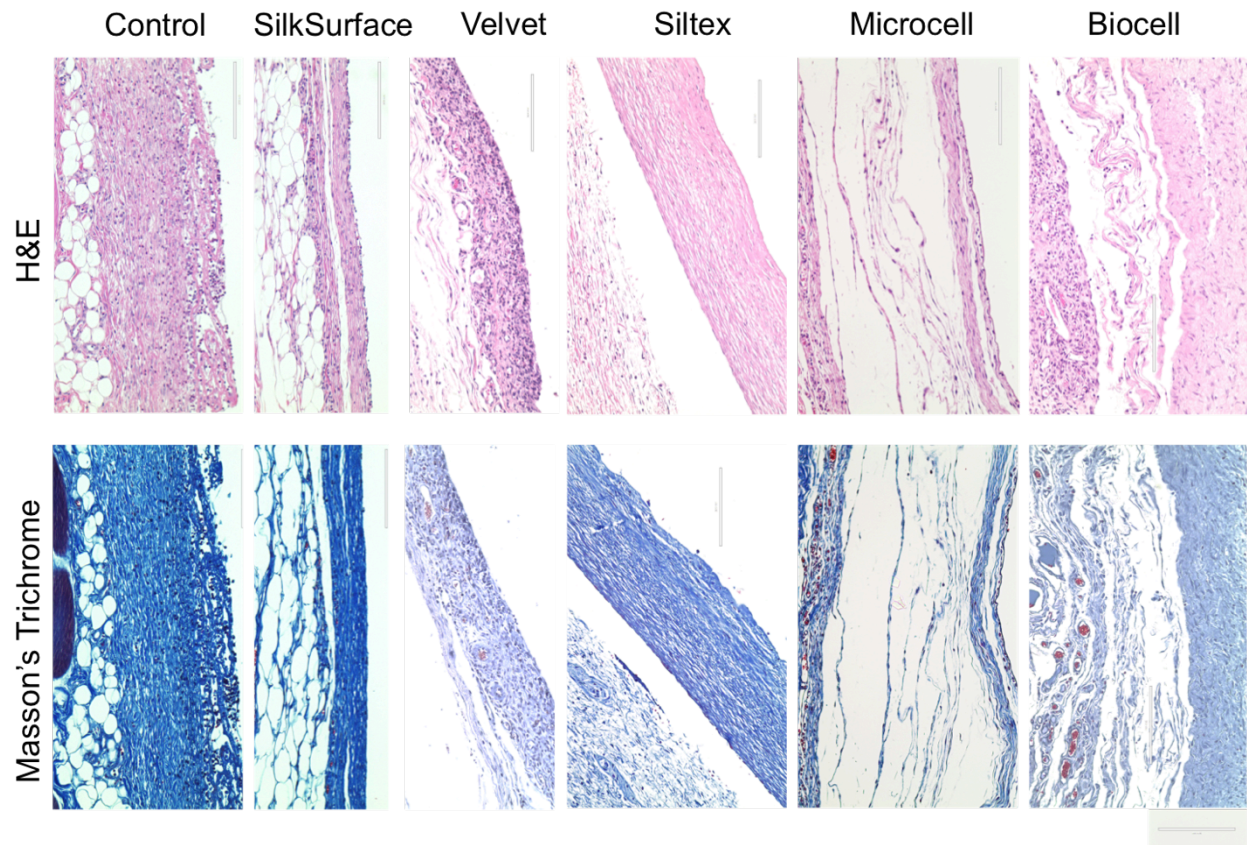


e) BIOCELL

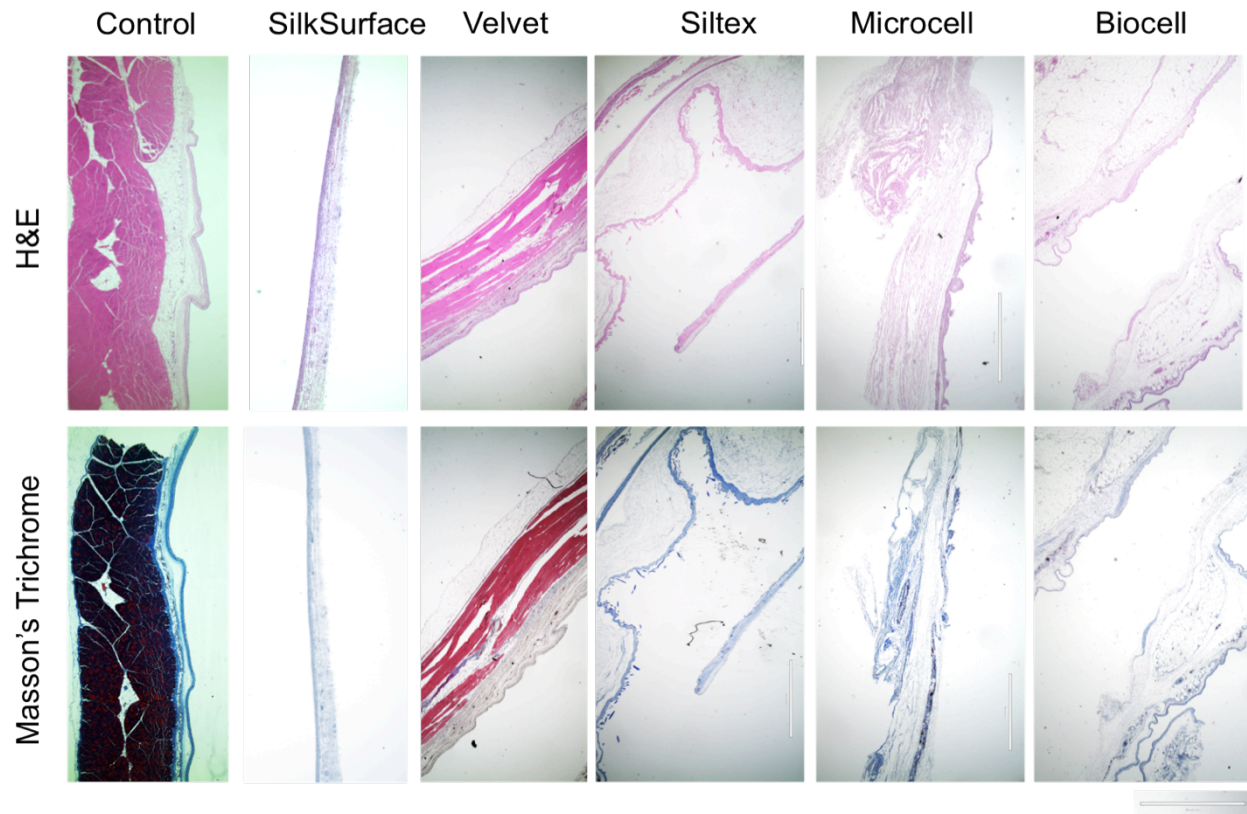


Supplemental Figure 4. Short-term implant retrievals – Photos of human-scale implants after 3-week subcutaneous incubations in female New Zealand White rabbits before explantation (while still under the skin), with the skin resected (opened), with the full implant removed leaving the full capsule intact, and in later cases (Siltex®, Microcell®, and BIOCELL®) for the higher roughness implants, after cutting through the implant capsule to show both the hard inner as well as softer outer layers of prominent double capsules. **a)** Comparing smooth controls, with observed contracture lines even by 3 weeks, and SmoothSilk® implants, over which skin looked normal and pliable. **b)** Images for VelvetSurface® implants. **c)** Images for Siltex®. **d)** Images for Microcell®. **e)** Images for BIOCELL®. All three highest roughness implants had higher levels of capsular fluid, beginnings of harder and more solid white inner double capsules which were Velcroed to Microcell® and BIOCELL® implants (with Siltex® inner capsules filling in more like spider web bands especially in areas where implants rippled). Retrieval photos correspond to those also shown in Fig. 2a. N = 5 rabbits/group.

a)

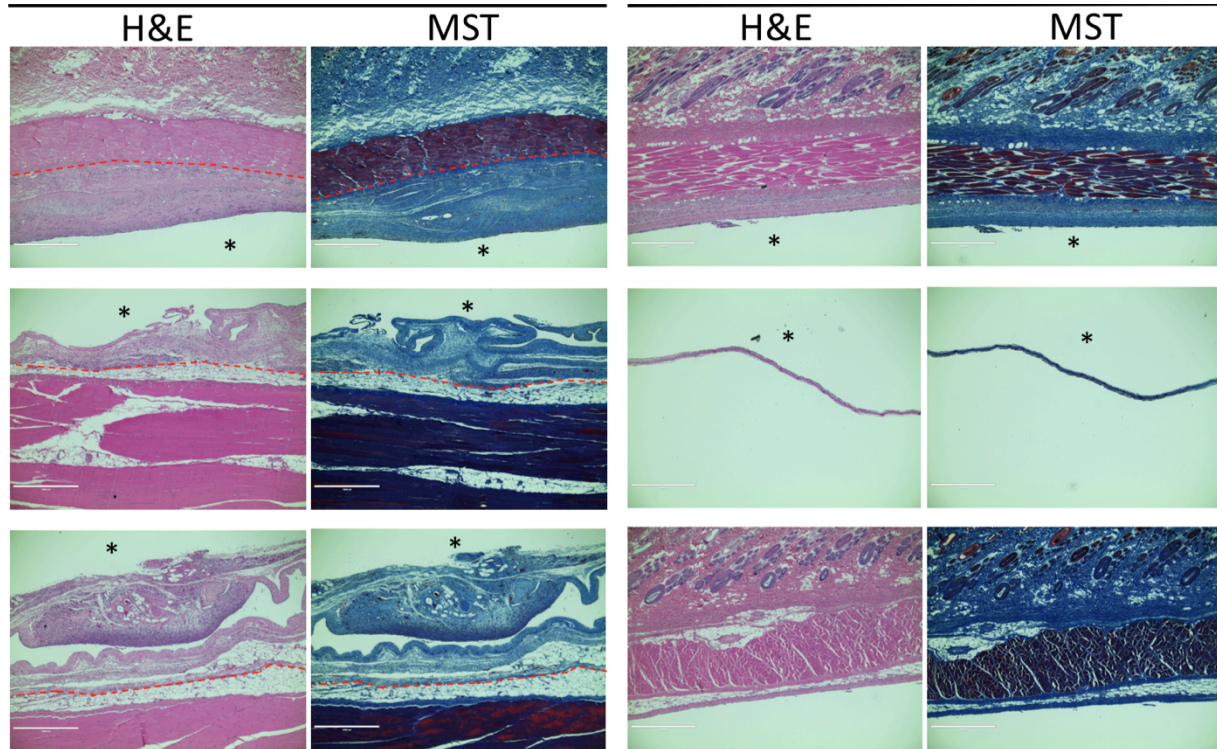


b)



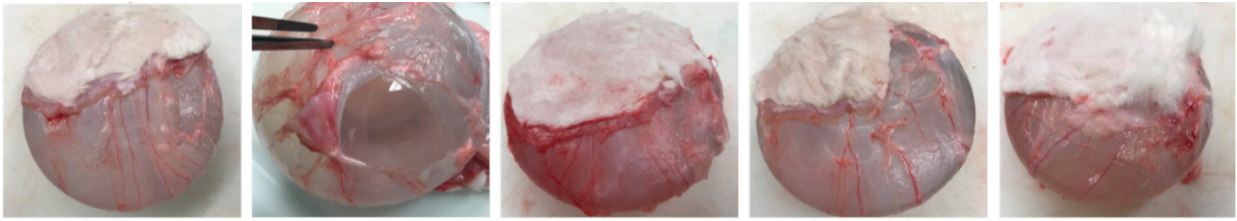
c) Control - 20x

d) SmoothSilk - 20x

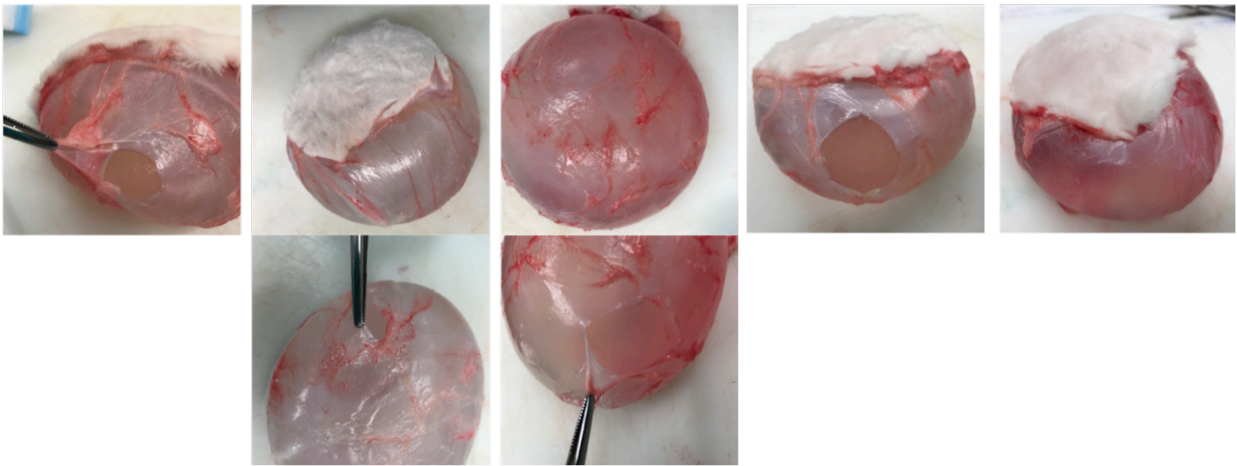


Supplemental Figure 5. Histology of short-term (3-week) implantations – Micrographs of H&E and Masson’s Trichrome-stained histological sections of excised implant capsules at 3 weeks post-implant showing reduced fibrosis with SmoothSilk® and VelvetSurface® groups, as compared to smooth (control) and more micro/macrot textured implants. **a)** Histology summary with higher magnification (20X) micrographs for H&E and Masson’s Trichrome for the upper pole of implants (shown at lower magnification in main Fig. 2c). **b)** Histology summary with micrographs (top: H&E; bottom: Masson’s Trichrome), taken at a lower 2X magnification, for the bottom pole (underside) of human-scale, commercial implants retrieved from New Zealand White rabbits (see histology panel in Fig. 2c for similar corresponding images taken along the upper topside of the same implants). Contoured “mirror image” capsules are observed for higher roughness implant groups. Higher magnification images comparing rippling and thicker capsules for control implants (**c**) vs. lack of rippling and much thinner capsules for SmoothSilk® (**d**). Histology also corresponds to implants shown in retrieval photos in Fig. 2a as well as completely unperturbed in packaging in Supplementary Fig. 3. (Scale bar = 200 μ m (20X) or 2000 μ m (2X), respectively). Images are representative across N = 5 rabbits/group.

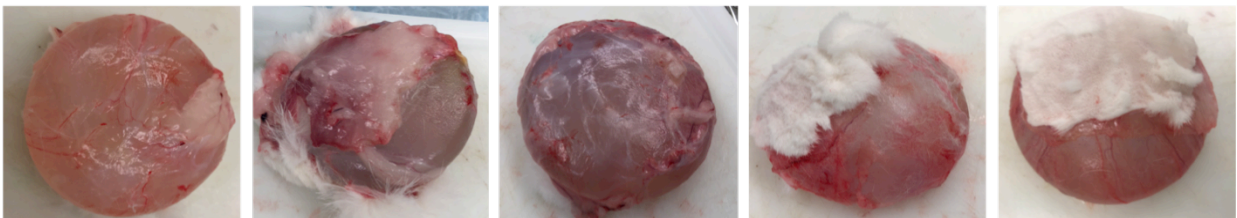
a) Control (smooth)



b) SmoothSilk



c) VelvetSurface

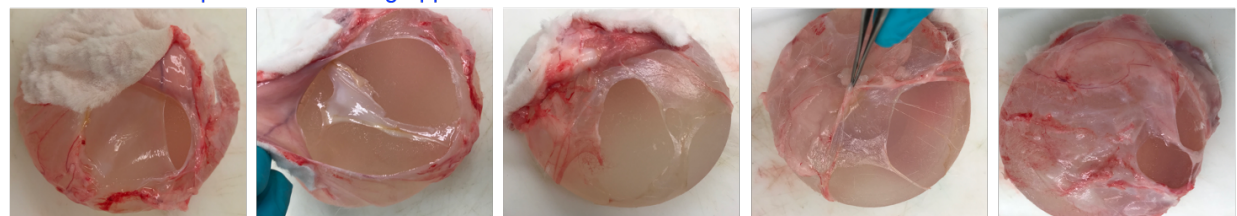


d) Siltex

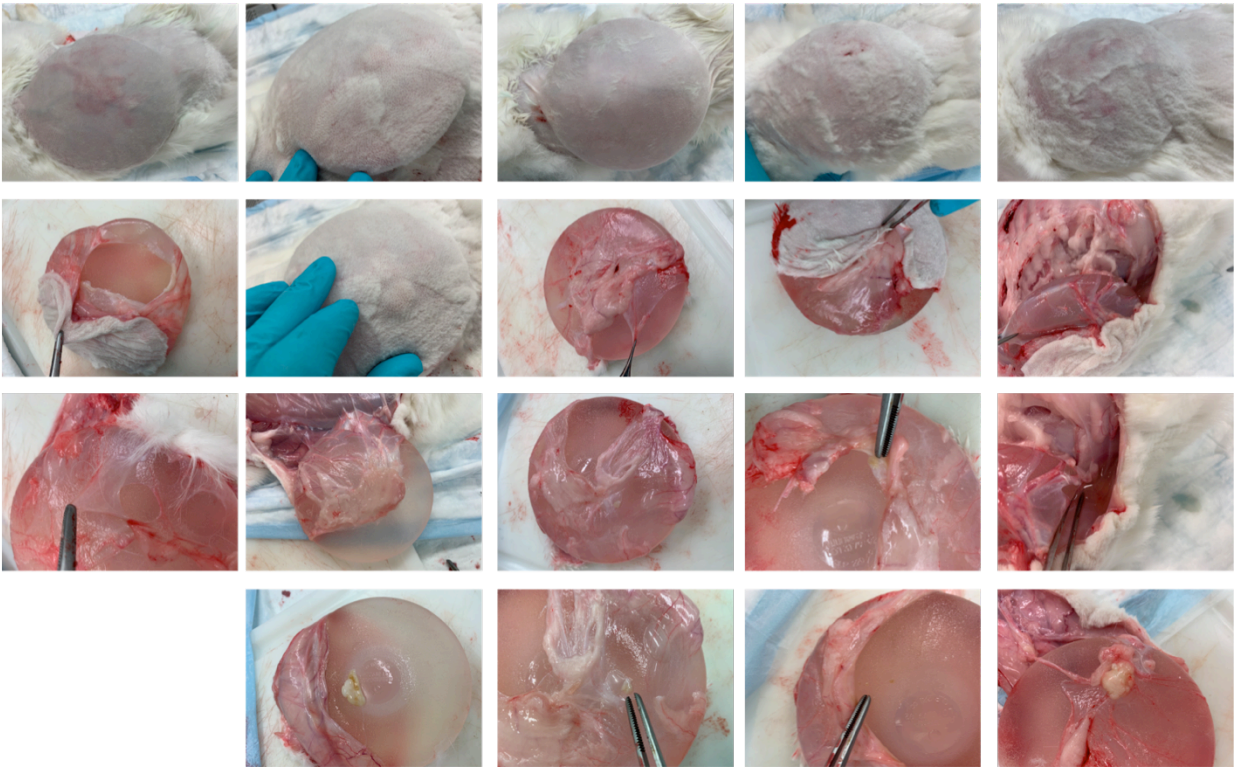
Siltex (less formed double capsules also observed):



Thicker inner capsule bands along ripples of BLs.



e) Microcell



f) BIOCELL



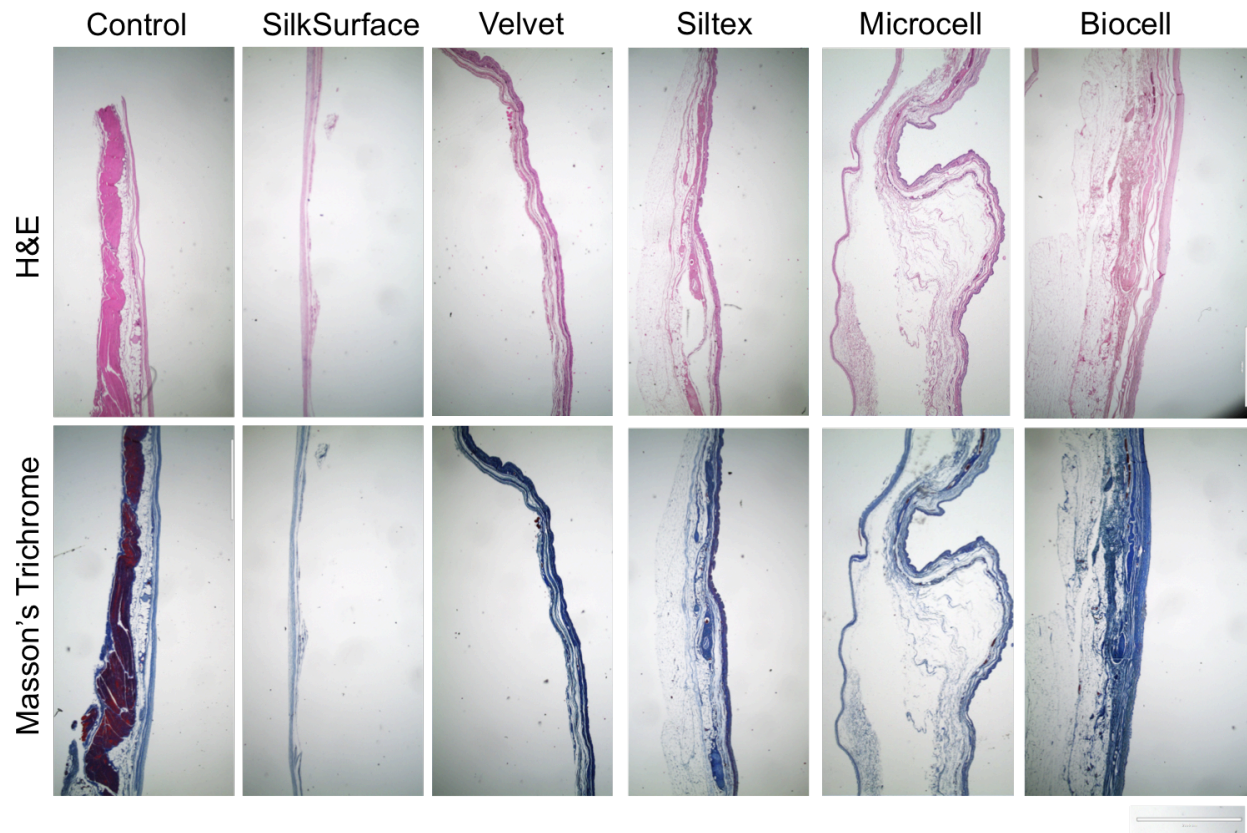
Double capsule on all 5 Biocell implants:



Thicker inner capsule bands along ripples of BIs.

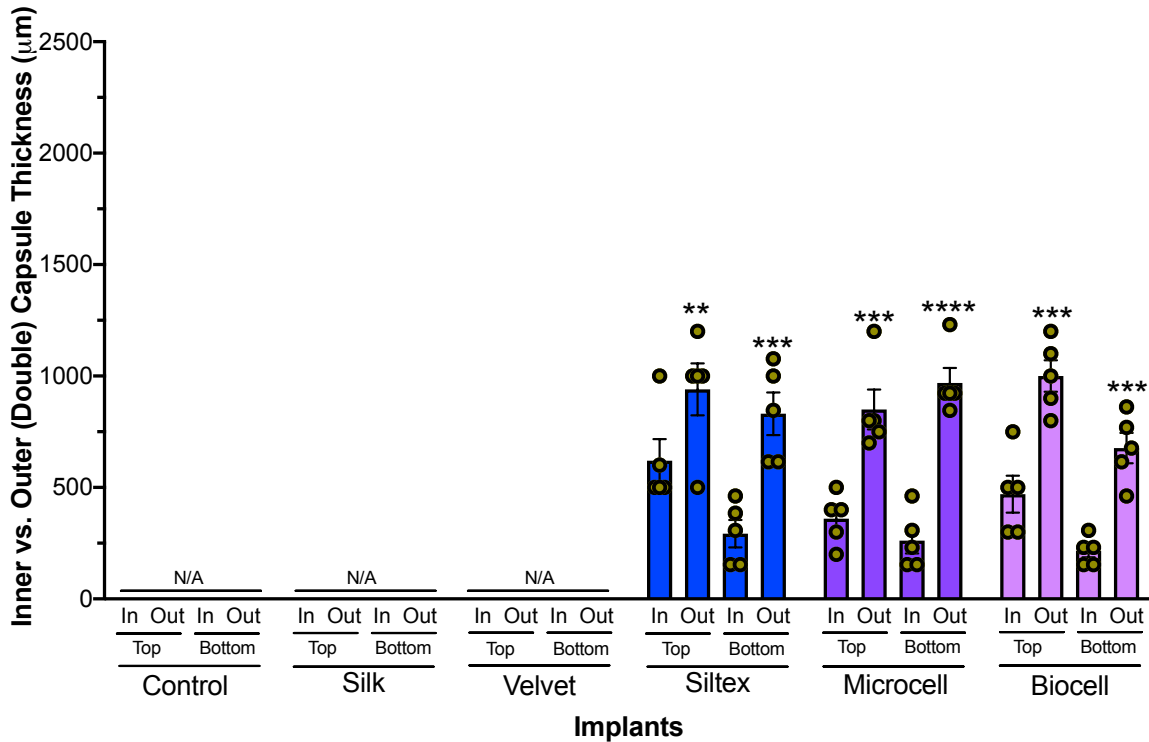
Supplemental Figure 6. Retrievals of long-term (6-month) implantations – Photos of human-scale implants after 6-month subcutaneous incubations in female New Zealand White rabbits with the skin resected as well as with the full implant removed while leaving the full capsule intact. In some cases images are shown also before explantation (while still under the skin). In later cases for the higher roughness implants (Siltex®, Microcell®, and BIOCELL®), images are also shown

after cutting through the implant capsule to show both the hard inner (dense white) as well as softer outer layers of prominent double capsules. **a)** smooth controls, showing vascularized ripple lines in the capsule, **b)** SmoothSilk® implants, over which skin looked normal and pliable, **c)** Images for VelvetSurface® implants. **d)** Images for Siltex®. **e)** Images for Microcell®. **f)** Images for Biocell®. All three highest roughness implants had harder and more solid white inner double capsules, with Velcro effect apparent in all cases, with increasing intensity corresponding to increases in surface roughness. Although, for Siltex® implants, inner tissue capsule deposition (of the “double-capsule”) appeared more like a spider web and less like a complete sheet, with dense bands of deposition in areas where implants rippled. Retrieval photos correspond to those also shown in Fig. 2b. N = 5 rabbit/group.

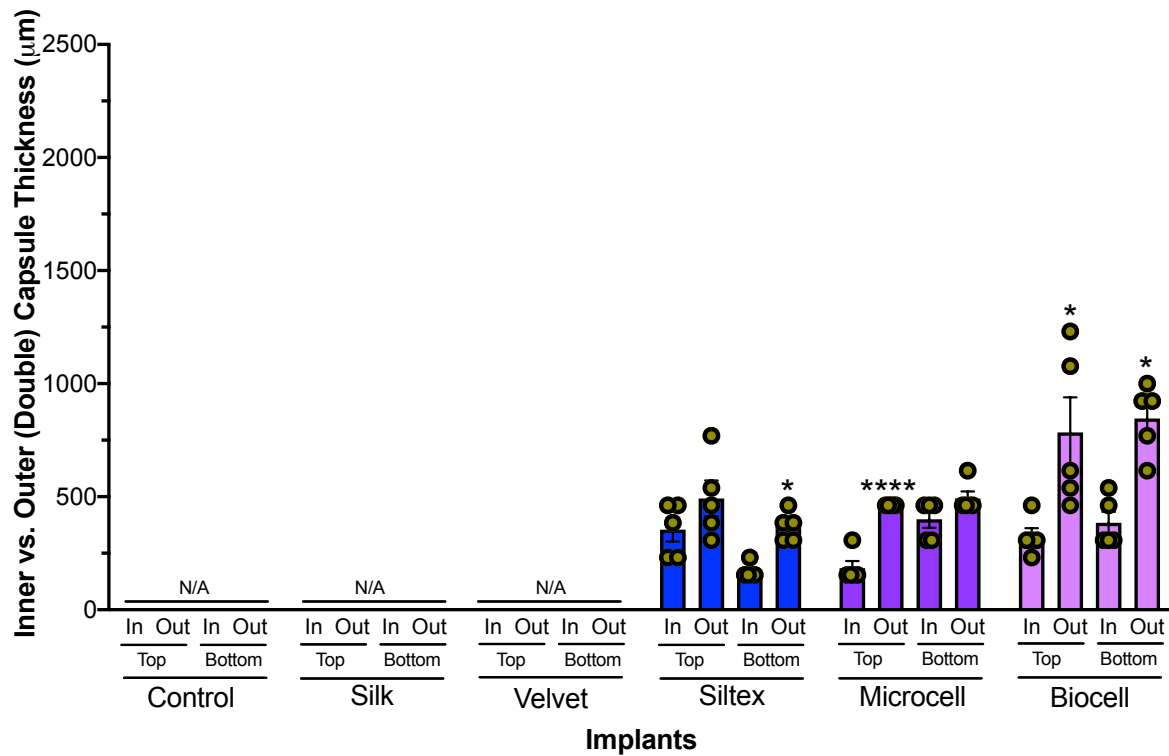


Supplemental Figure 7. Histology of long-term (6-month) implantations – H&E (top) and Masson's Trichrome (bottom) stained histological sections from the bottom underside of excised implants at 6 months post-implantation showing reduced fibrosis with SmoothSilk® and VelvetSurface® groups, as compared to smooth (control) and more micro/macrot textured implants. Histology summary of images taken at a lower 2X magnification, for human-scale, commercial implants retrieved from New Zealand White rabbits (see histology panel in Fig. 2d for similar corresponding images taken along the upper topside of these same implants). Histology also corresponds to implants shown in retrieval photos in Fig. 2b and Supplementary Fig. 6. Scale bar = 2000 μ m. Images are representative across N = 5 rabbits/group.

a) Double (Inner vs. Outer) Capsule Thickness – 3 weeks



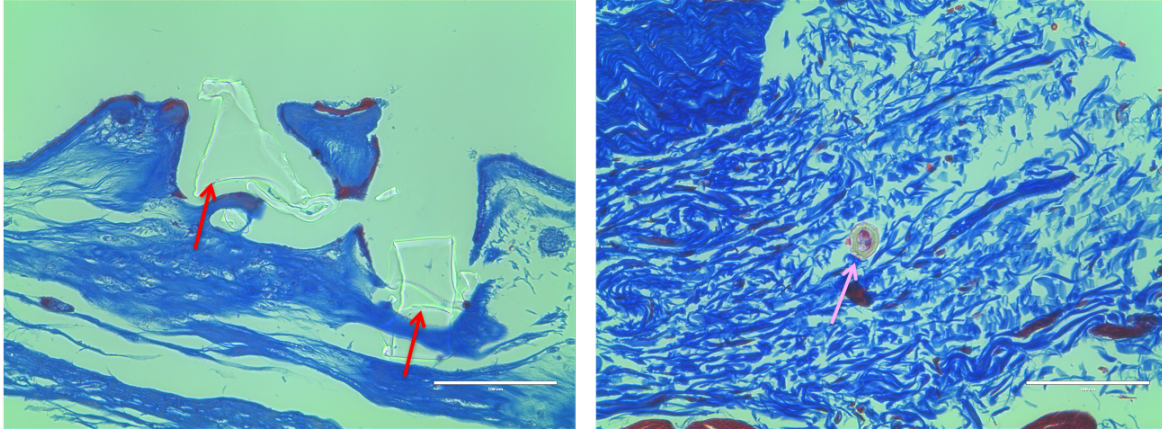
b) Double (Inner vs. Outer) Capsule Thickness – 6 months



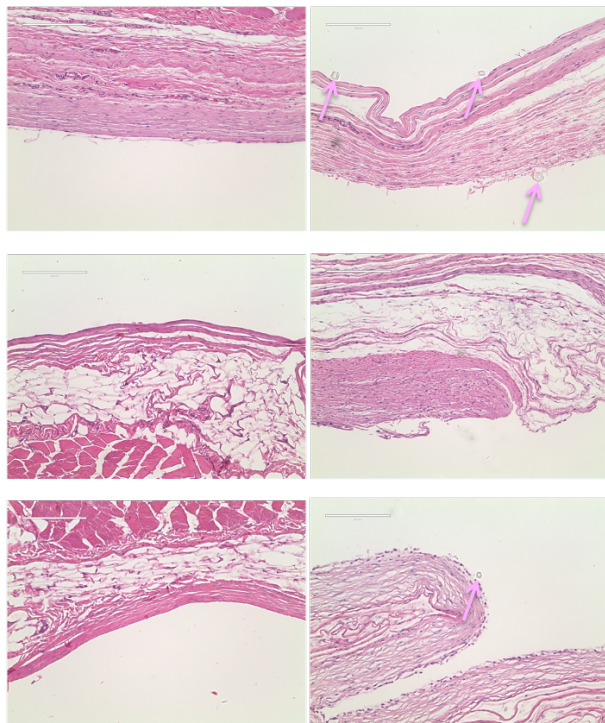
Supplementary Figure 8. Topography affects whether double capsules form. Quantitation of fibrotic capsular thickness surrounding 3-week (a) or 6-month implants (b) on their subcutaneous (top) side or lower (bottom) side. Double-capsule phenomena were observed as early as 3 weeks

for Siltex®, Microcell® and BIOCELL®, with strong Velcro effects upon dissection and separation of implant and tissue capsule for histology processing. 5 measurements of capsule thickness were taken per 5 different fields of view from 2 different regions of tissue, with numbers then compiled across N = 5 rabbits/group. All bar graph data: mean $\pm$ SEM (biologic replicates). Statistical analysis: one-way ANOVA plus Bonferroni multiple comparison correction; $p < 0.05$, 0.01, 0.001, and 0.0001 for comparisons of inner vs. outer layers within each capsule (*, **, ***, ****). Data is broken down from total capsule thickness as reflected in Fig. 2e-h.

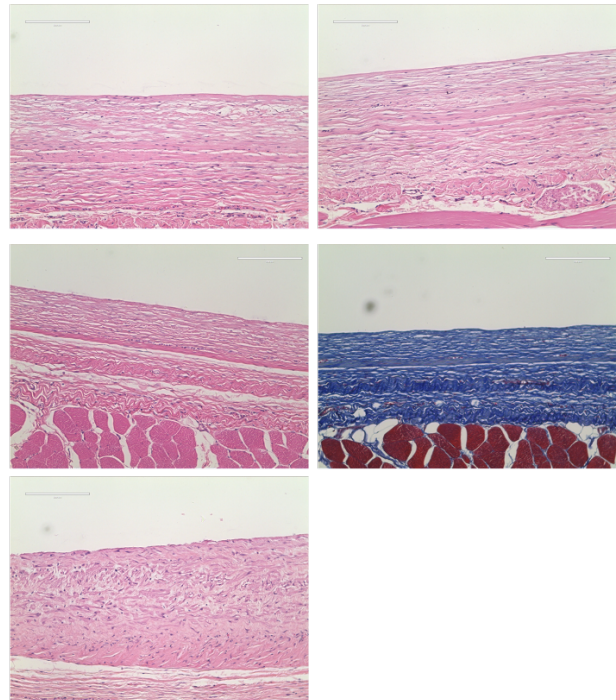
**a) Examples of implant wear debris (red arrows) and immune cell presence (blue arrows):
(BIOCELL implant)**



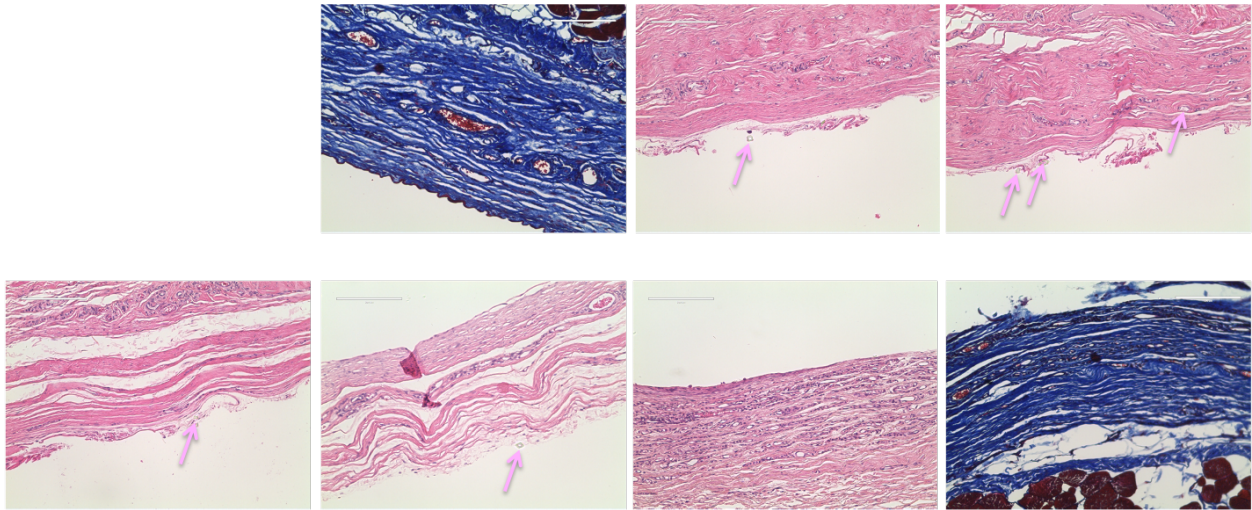
b) Control



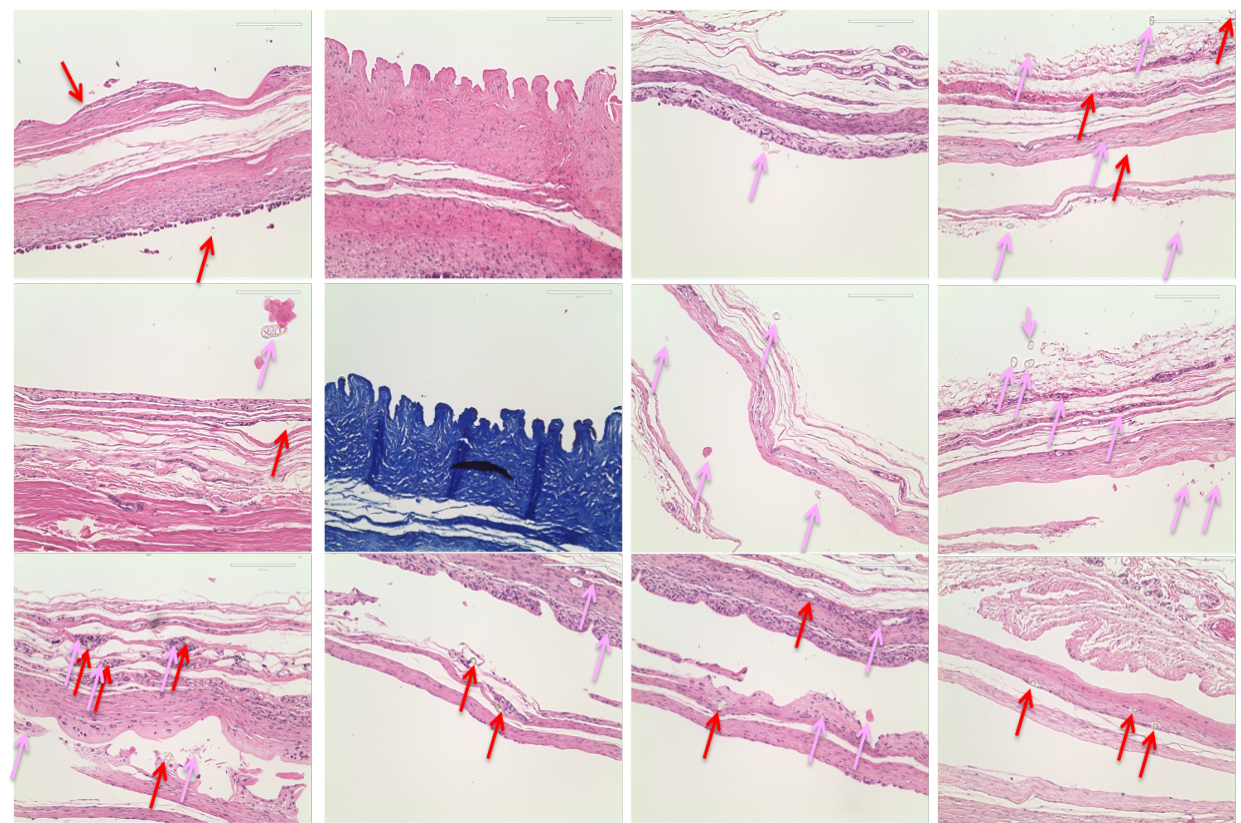
c) SilkSurface



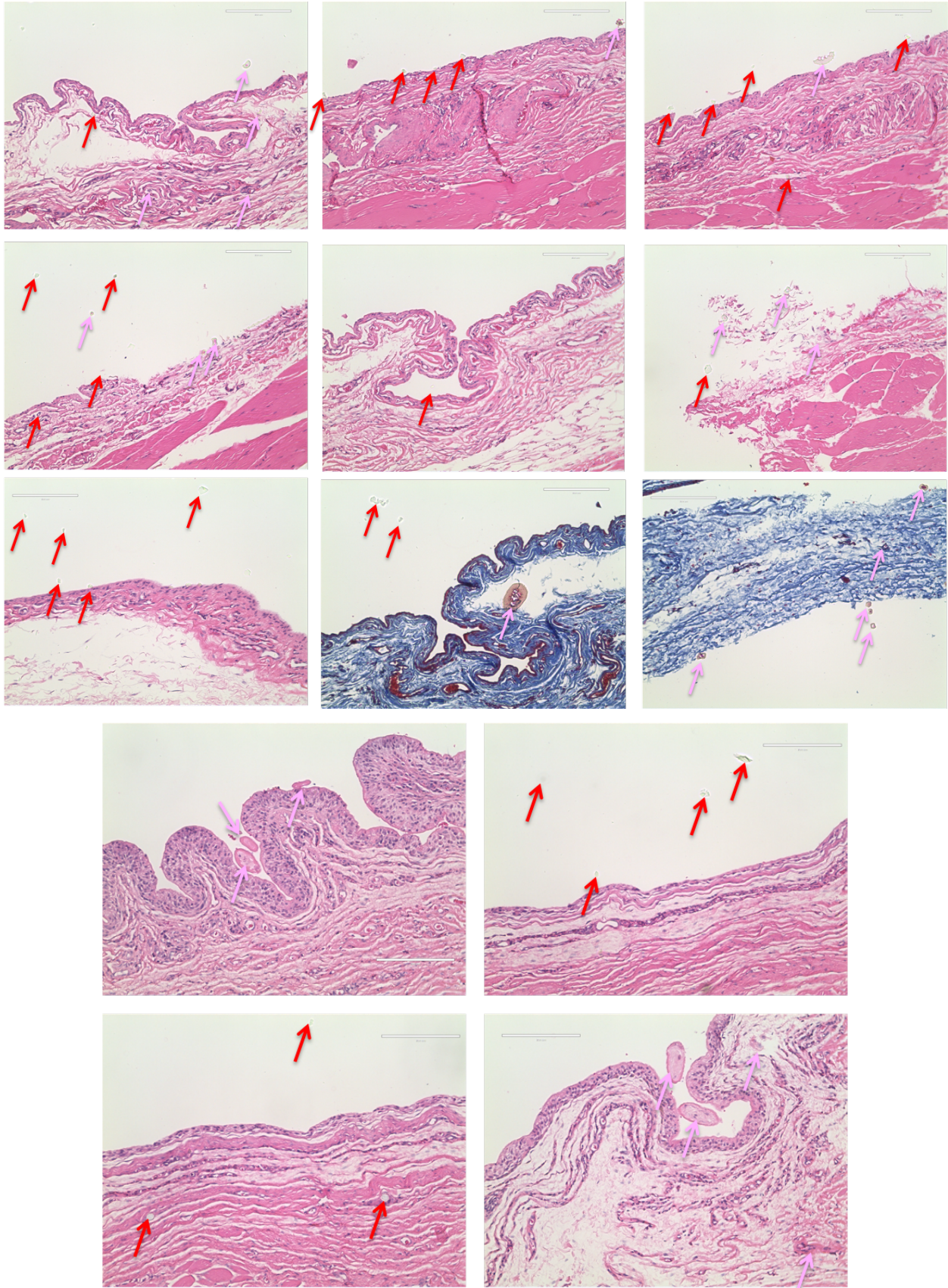
d) Velvet



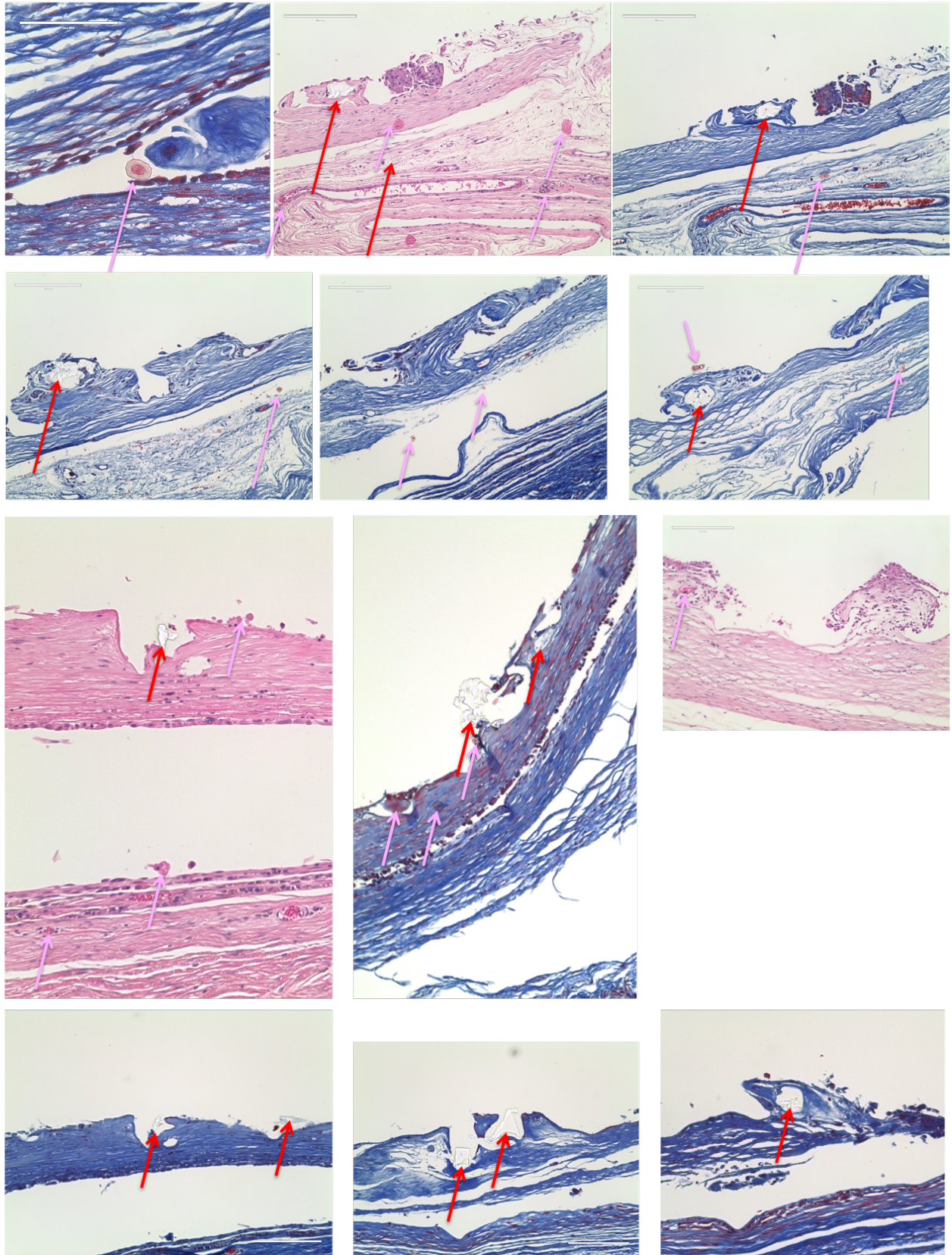
e) Siltex



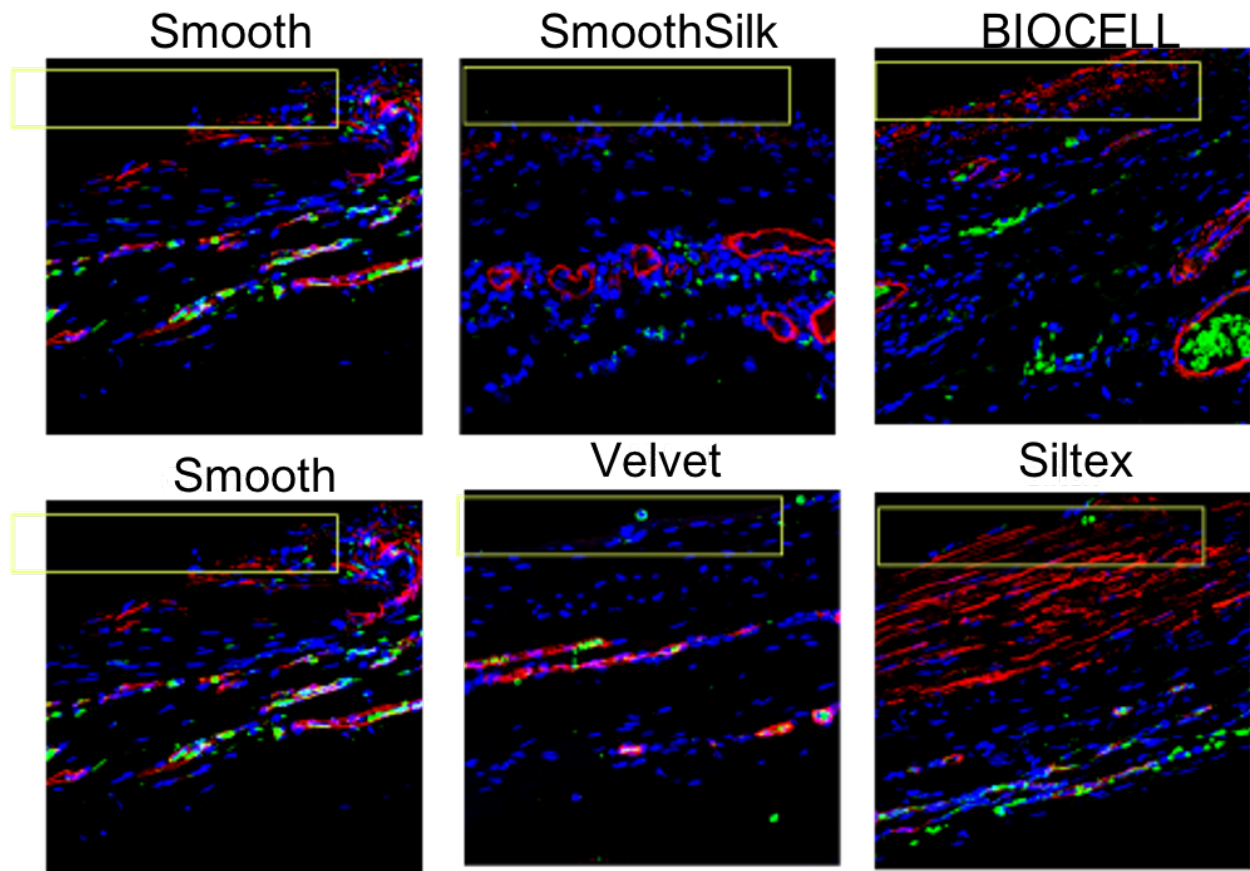
f) Microcell



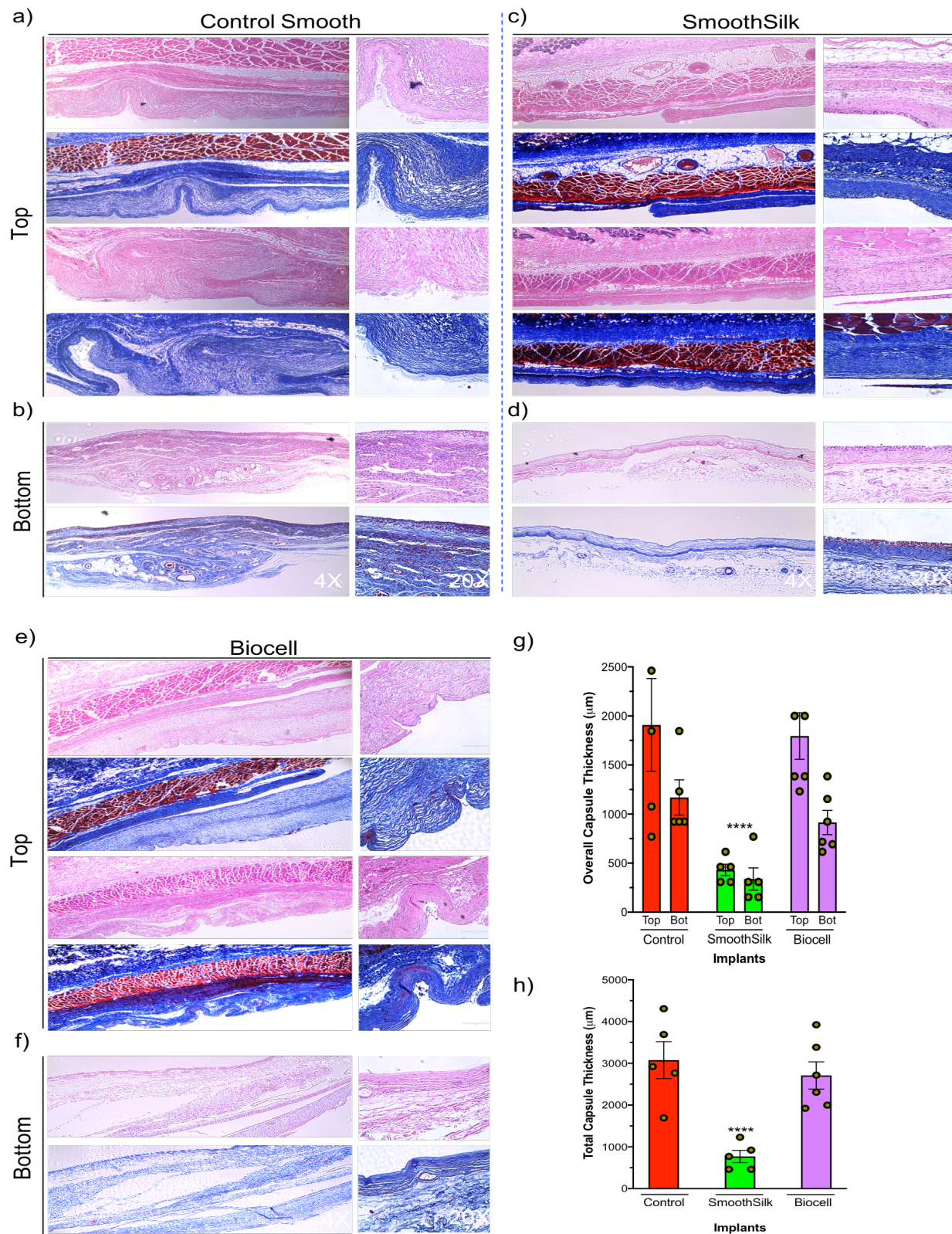
g) BIOCELL



Supplemental Figure 9. Histology of long-term (6-month) implantations reflecting presence or lack of implant surface wear debris or fused foreign body giant cell infiltration – Micrographs of H&E and Masson’s Trichrome stained histology sections for implant capsules at 6 months post-implantation showing example debris and giant immune cell presence for BIOCELL® (**a**). Furthermore, no debris was observed for **b**) smooth controls, **c**) SmoothSilk® and **d**) VelvetSurface® groups, as compared to more micro/macrot textured implants (Siltex® (**e**), Microcell® (**f**), and BIOCELL® (**g**)). In addition, higher levels of observed large giants cells were also observed as a function of surface roughness. These findings are summarized in Supplemental Table 1. Histology images taken at a 20X magnification, for human-scale implants retrieved from New Zealand White rabbits. Red arrows indicate implant debris or immune cell presence, and is much higher incidence for 3 implants with highest roughness. Semi-quantitatively assessed levels are reflected in Supplementary Table 1. Scale bar = 200 µm. Images are representative across N = 5 rabbits/group.

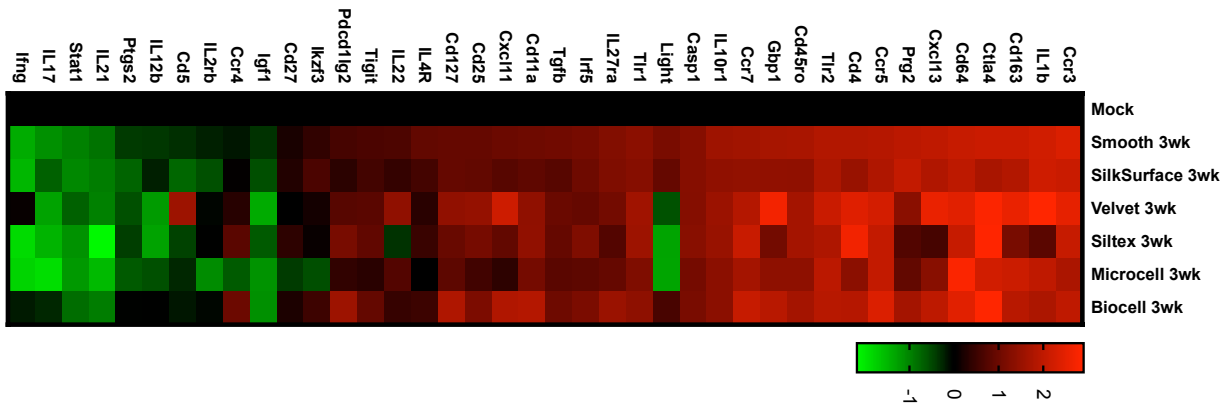


Supplemental Figure 10. Confocal of (6-month) implantations reflecting presence or lack of fibrosis and immune cell responses – Confocal microscopy images showing reduced or no fibrotic overgrowth with more nano/micro-roughness ranged SmoothSilk® and VelvetSurface® implant surfaces retrieved from New Zealand White Rabbits. (Blue, DAPI nuclear stain; Green: Macrophage CD68; and Red: Fibrosis marker α -smooth muscle actin). All subpanels reflect data from N = 5 animals/group.

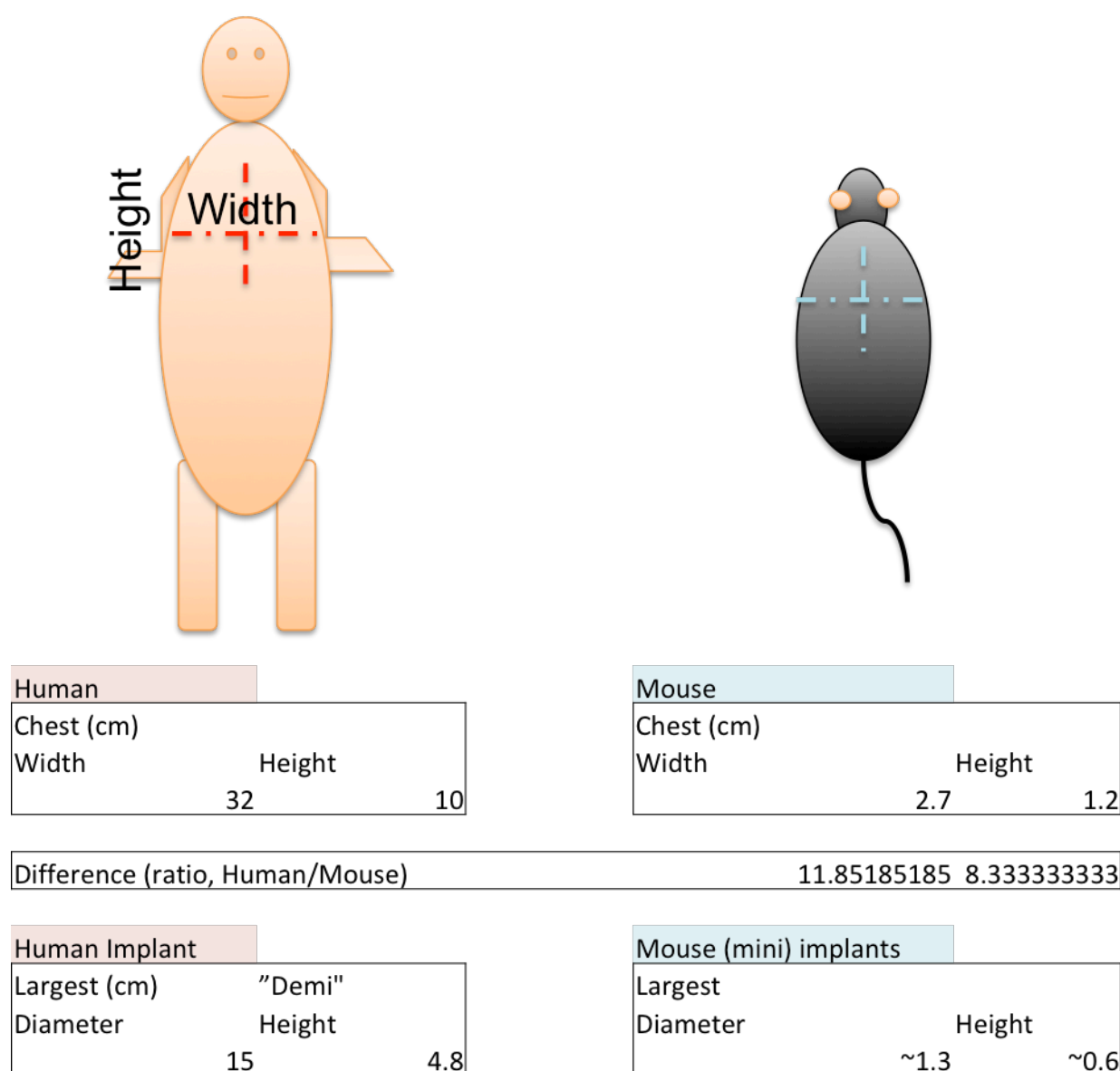


Supplemental Figure 11. Histology of long-term 1-yr rabbit implant capsules – H&E (top) and Masson's Trichrome (bottom) stained histological sections from the capsule (upper vs. lower bottom pole) of excised implant capsules at 1 year post-implantation. Significantly thicker

encapsulation and fibrosis was observed with Smooth controls (**a & b**, *top vs. bottom side*) vs. reduced capsule thickness with SmoothSilk® implants (**c & d**, *top vs. bottom side*) as well as equally thick (vs. control) encapsulation with macrotextured BIOCELL® implants (**e & f**, *top vs. bottom side*). Histology micrographs taken at a lower 2X magnification, for human-scale implants retrieved from New Zealand White rabbits. Scale bar = 2000 µm. Images are representative across N = 5 rabbits/group. Capsule thickness was quantified on both top and bottom sides of implants (**g**) as well as in total (**h**). Statistical analysis: one-way ANOVA plus Bonferroni multiple comparison correction; ****, $p < 0.0001$ for comparisons of inner vs. outer layers within each capsule.

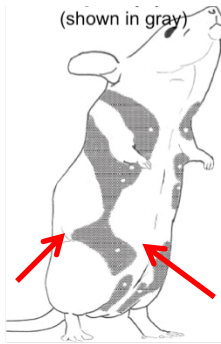


Supplemental Figure 12. NanoString analysis of capsule tissue explanted from human-scale implants placed subcutaneously in New Zealand White rabbits for 3 weeks. This was done to assess cell and cytokine marker responses, as compared to mock (saline-injected) controls. This gene set represents the remaining factors that showed no significant difference in expression levels between breast capsule tissue retrieved for Smooth control and SmoothSilk® breast implants. Otherwise, patterns of down- vs. up-regulation in the SmoothSilk® group are represented in main Fig. 2i-j. Samples were collected from multiple rounds of rabbit implantation procedures.

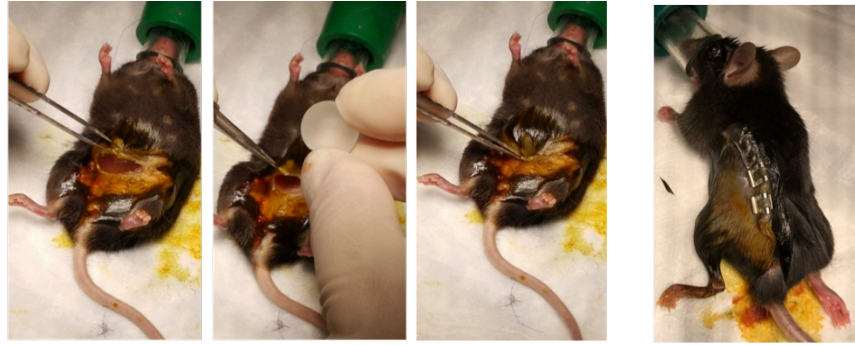


Supplemental Figure 13. Conversion of human-scale implant size down to miniaturized mimic dimensions based on chest size (human vs. mouse). Diagrams of chest width and implant area height measurements from either clinical practice (left) vs. as measured on C57BL/6 mice (right). Human and mouse chest area measurements—width and height (cm), were used to convert human, full-scale implants into their miniaturized mouse-intended counterparts. First, differences in scales were determined, and then implant dimensions (diameter and height/projection) for a moderate volume (“demi”) human implant was used to convert down based on the scaling difference between a human and mouse chest.

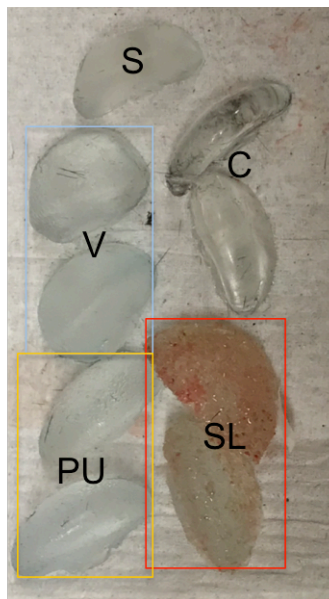
a) Implant procedure



b) Modified



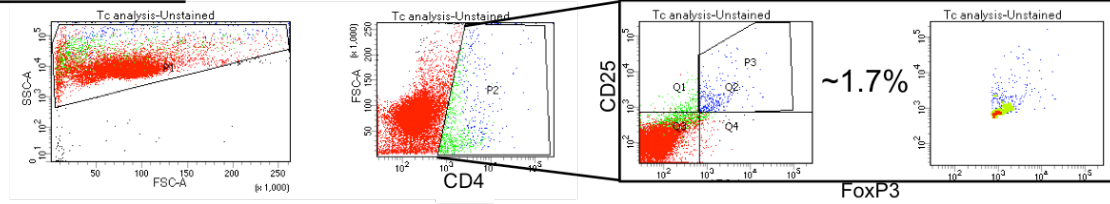
c) Retrieved miniaturized, titered roughness mouse implants (after capsule removal):



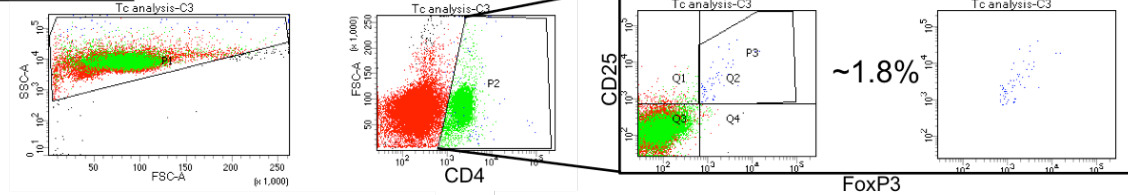
Supplemental Figure 14. Additional characterization of miniaturized implant mimics retrieved after incubation in mice – a) Photos of placement of miniaturized control smooth (0 μm) vs. 4 μm implants. Mammary fat pads wrap around hip and back of female mice (left), which allowed us to move incisions and implant placement away from the lower mammary fat and less clean cage bedding to the side flank of the animals where there is additional loose skin (red arrows) (b). This allowed us to address additional issues of skin tension, which would pull wound clips open exposing implants as the dissected fascia repaired itself following surgery. c) Photos of retrieved miniaturized mouse implant mimics with titered surface roughness after capsule removal (dissociated for immune cell analysis).

Example FACS plots and gating strategy for regulatory T (Treg) suppressor response:

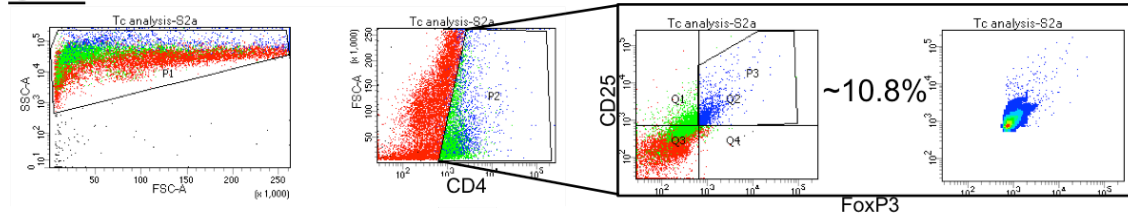
Unstained:



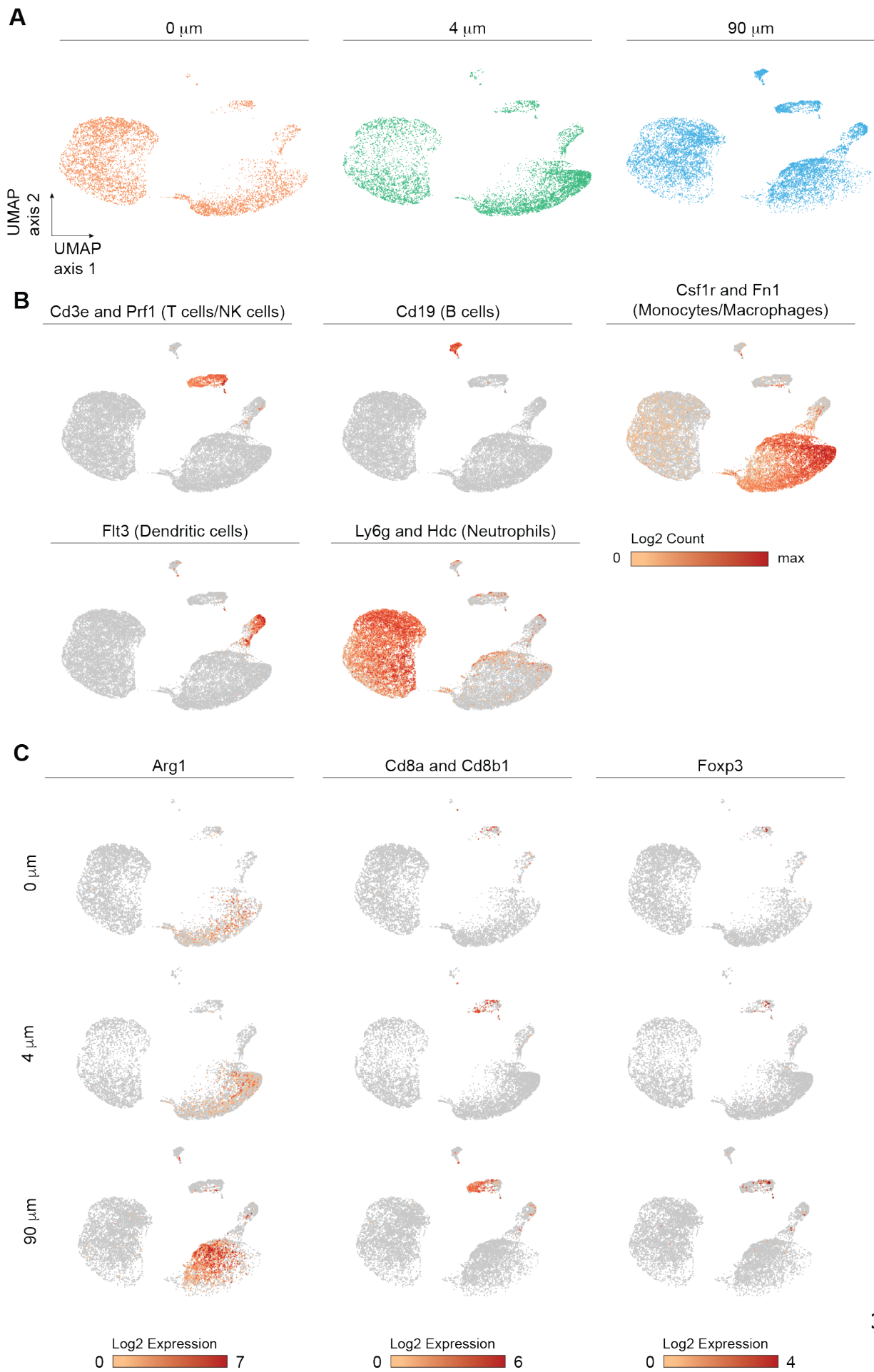
Control:



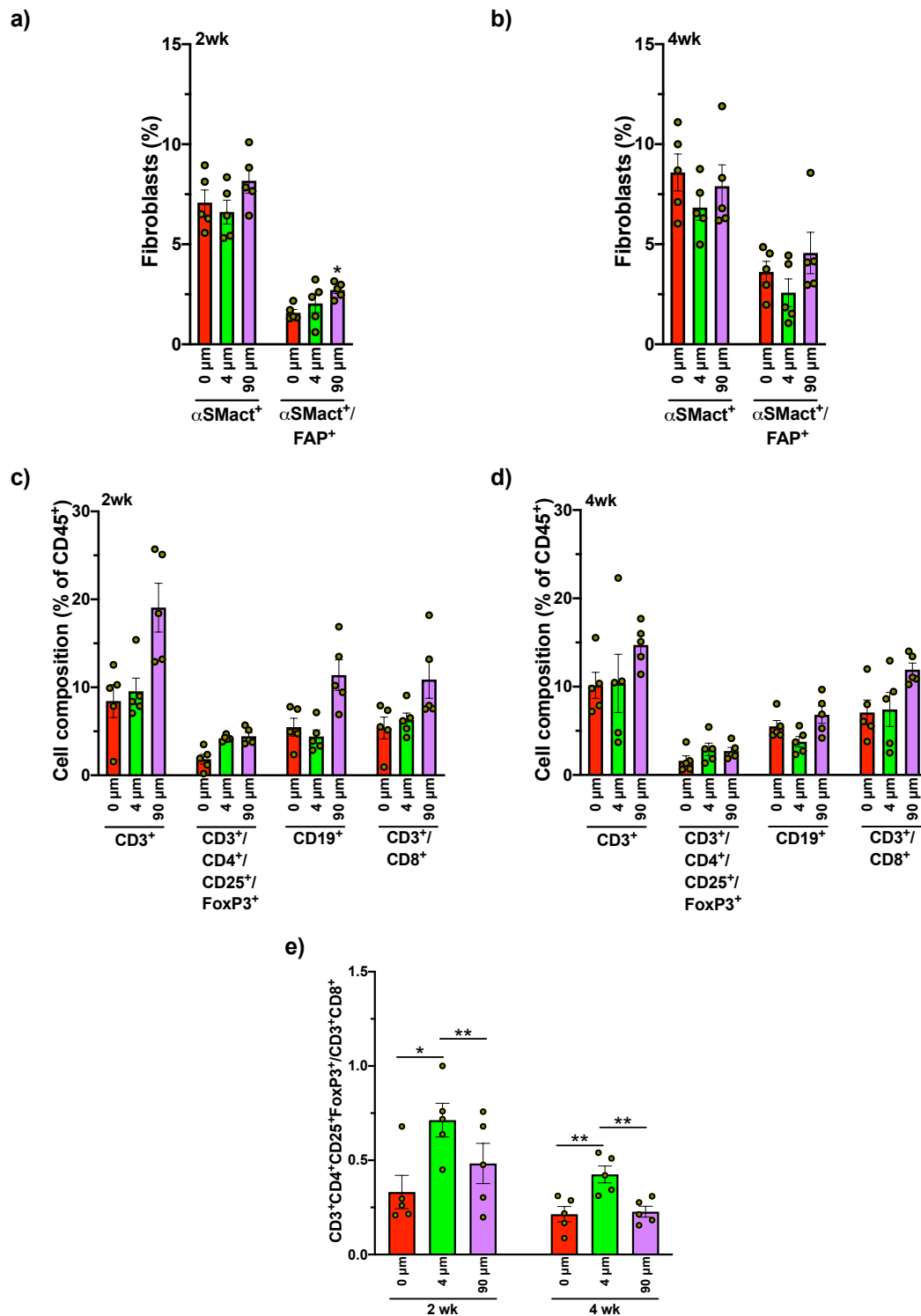
Silk:



Supplemental Figure 15. Quantitative FACS analysis performed on cells dissociated from explanted miniaturized implant capsules – Capsules were retrieved at 3 and 6 weeks for control smooth (0 μm) vs. 4 μm mini implant mimics from T cell deficient (B6-nude) or over a longer period of time (up to 6 months) in wildtype female C57BL/6 mice (complete cell number-adjusted wildtype and B6-nude data in main Fig. 5). All subpanels reflect data from experiments repeated 2 times (N = 5 animals/group).



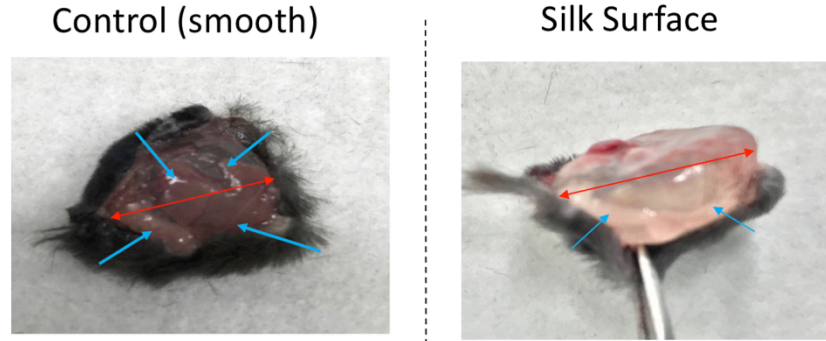
Supplemental Figure 16. Classification of cell types in single-cell RNA-seq data sets. **a)** UMAP embedding of individual cells separated by implant topology (0, 4, and 90 μm). **b)** Expression of cell-type-specific markers used to identify distinct immune cell populations across all 3 sample groups. Resulting clusters are classified by immune cell type based on expression profile with the following markers: T cells/NK cells (Cd3e and Prfl), B cells (Cd19), monocytes/macrophages (Csf1r and Fn1), dendritic cells (Flt3), or neutrophils (Ly6g and Hdc). **c)** Expression of genes indicative of immune cell subsets: Arg1 (M2 macrophages), Cd8a and Cd8b1 (effector T cells), and Foxp3 (Tregs). All subpanels reflect representative data from *in vivo* experiments performed once; scRNA sequencing was run on one sample pool/treatment group (from n=5 animals).



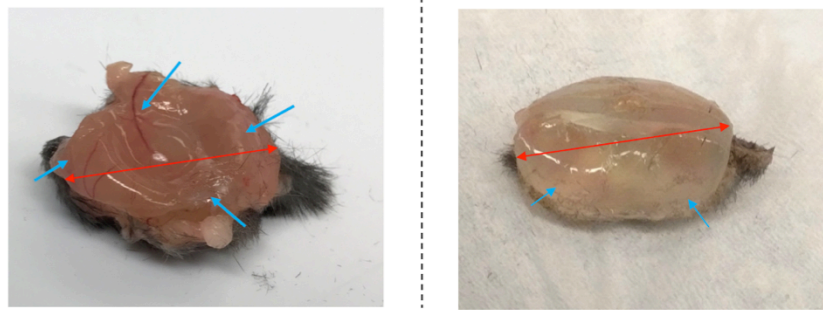
Supplementary Figure 17. Single cell fibroblast cell population dynamics at 2 & 4 weeks post-implantation. To look at the potential for shifts in fibroblast cell response, we used flow cytometry on retrieved capsule tissues that were dissociated into single cell suspensions, and measured myofibroblast markers αSMA and fibroblast activation protein (FAP) at both 2 (a) and 4 weeks (b) post-implant. Overall, we only observed a significant compositional shift between 0 and 90

μm sample groups at 2 weeks post-implantation. *, $p < 0.05$ vs. 0 μm (For aSMact⁺FACP⁺). In addition, we also examined adaptive immune regulatory CD3⁺CD4⁺CD25⁺FoxP3⁺ T, CD19⁺ B, and effector CD3⁺CD8⁺ T cell populations at 2 (c) and 4 weeks (d). e) A significant increase in the ratio of FoxP3⁺ Tregs over CD8⁺ effector T cells was observed for the 4 μm group at both 2 and 4 weeks. *, **: $p < 0.05$ or 0.01 (for comparisons as indicated). All immune subsets were also gated as CD45⁺. All subpanels reflect data from one experiment (N = 5 animals/group).

a) 3 weeks

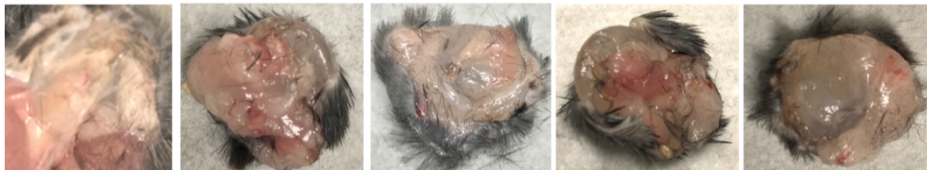


b) 12 weeks

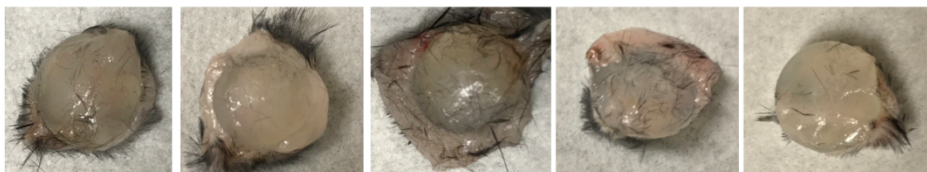


c) 6 months

Controls:

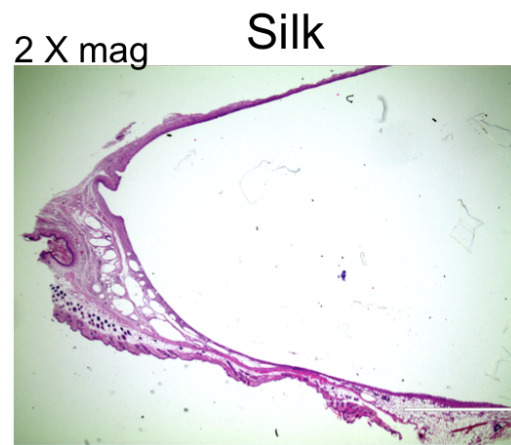
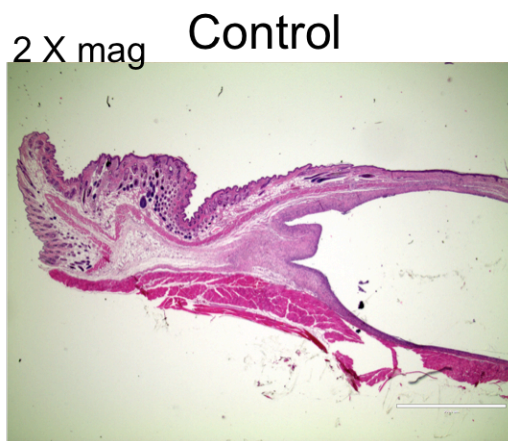


Silk:

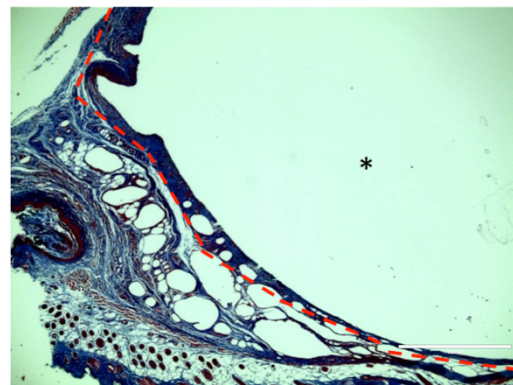
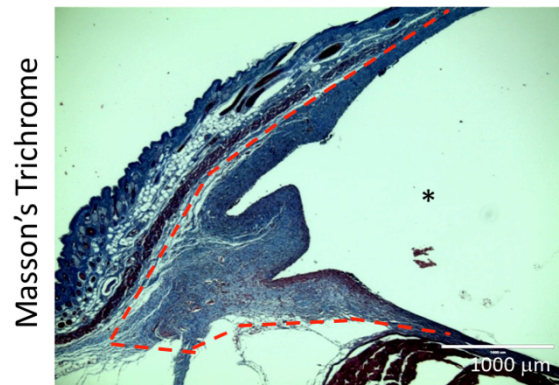
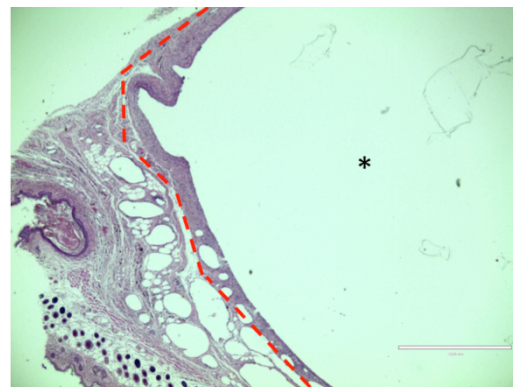
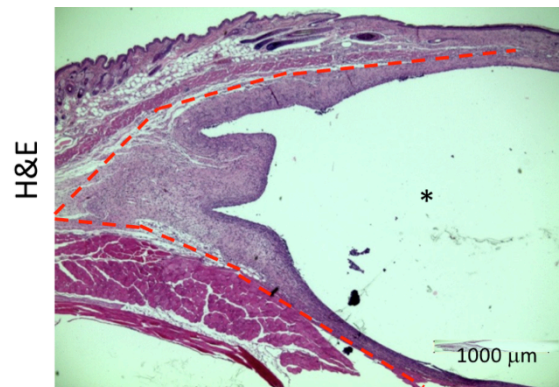


Supplemental Figure 19. Rodent retrievals of short and long-term implantations in mice – Retrieval photos for control 0 μm vs. 4 μm miniaturized implant mimics after 3-week (**a**), 12-week (**b**), and 6-month (**c**) subcutaneous incubations in female C57BL/6 mice, with the skin resected and the full implant removed while leaving the capsule intact. Blue arrows, fibrotic capsule; red arrows, implant diameter. Retrieval photos correspond to sample set data shown in Fig. 5. N = 5 mice/group per time point. Experiments repeated at least twice.

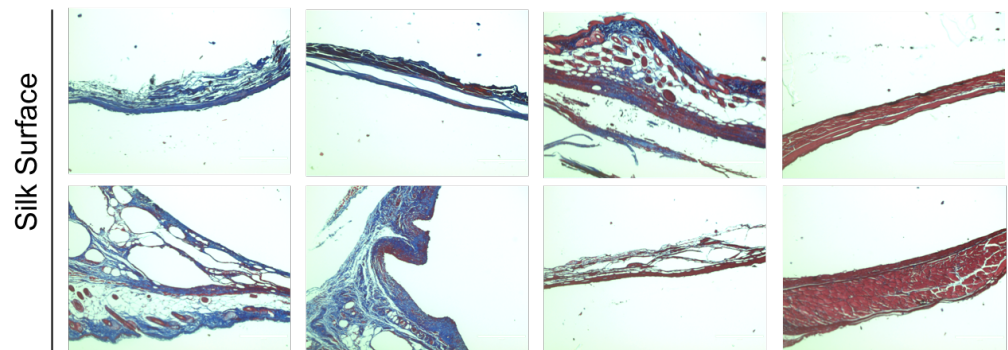
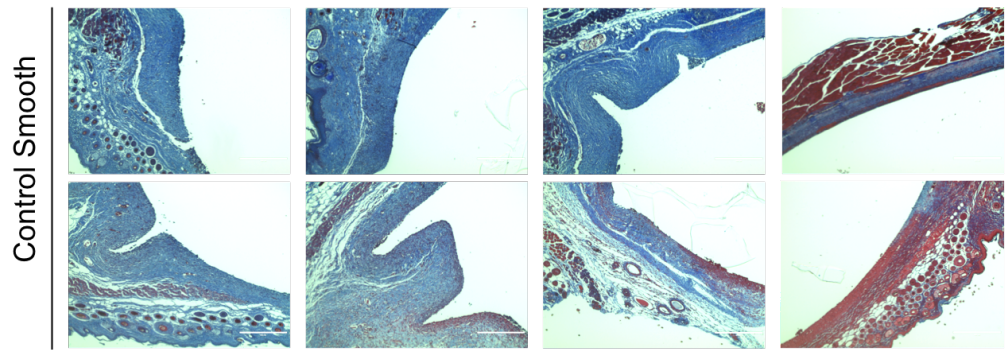
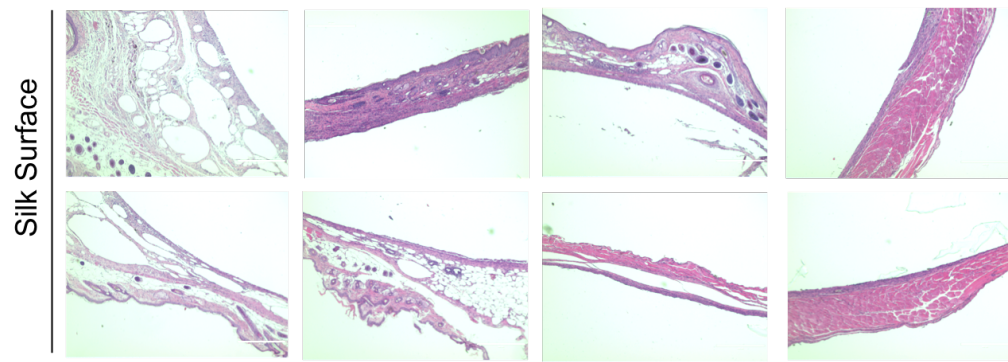
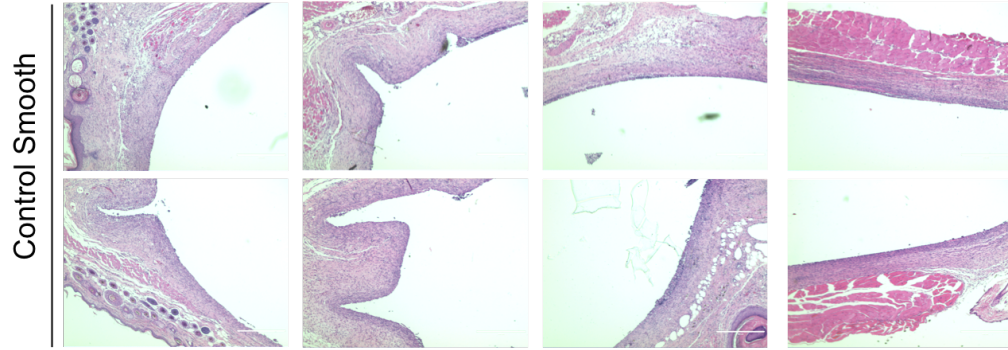
a) 3wk:



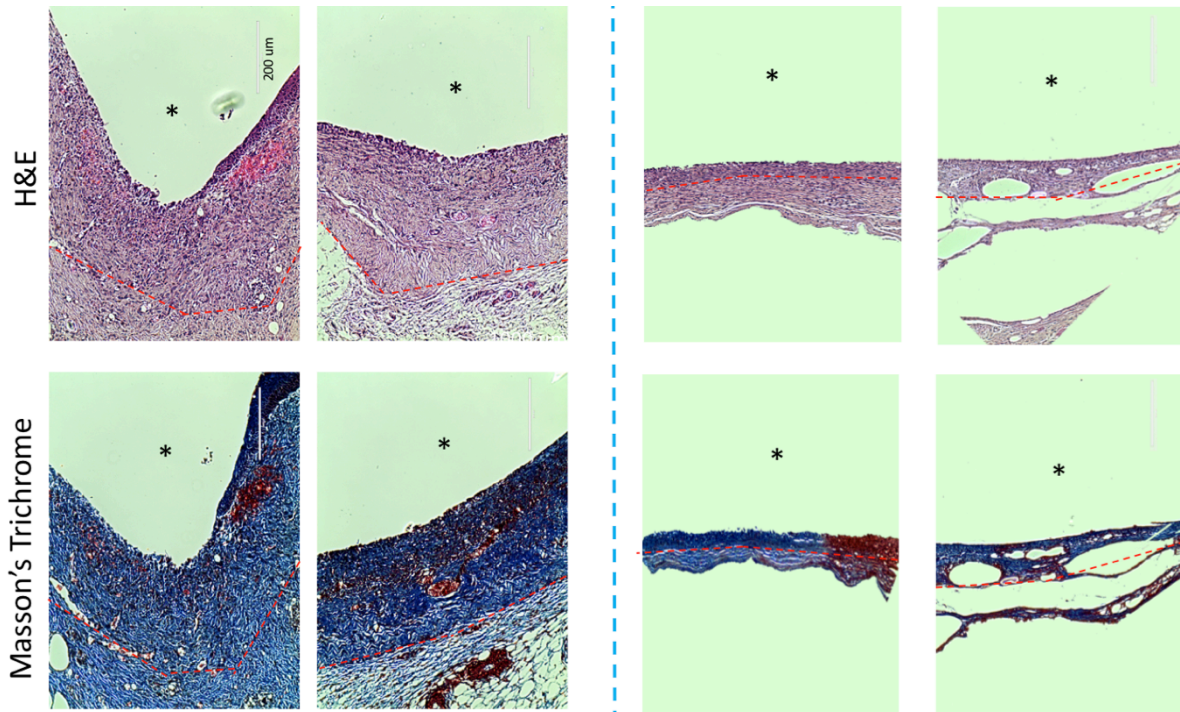
4x:



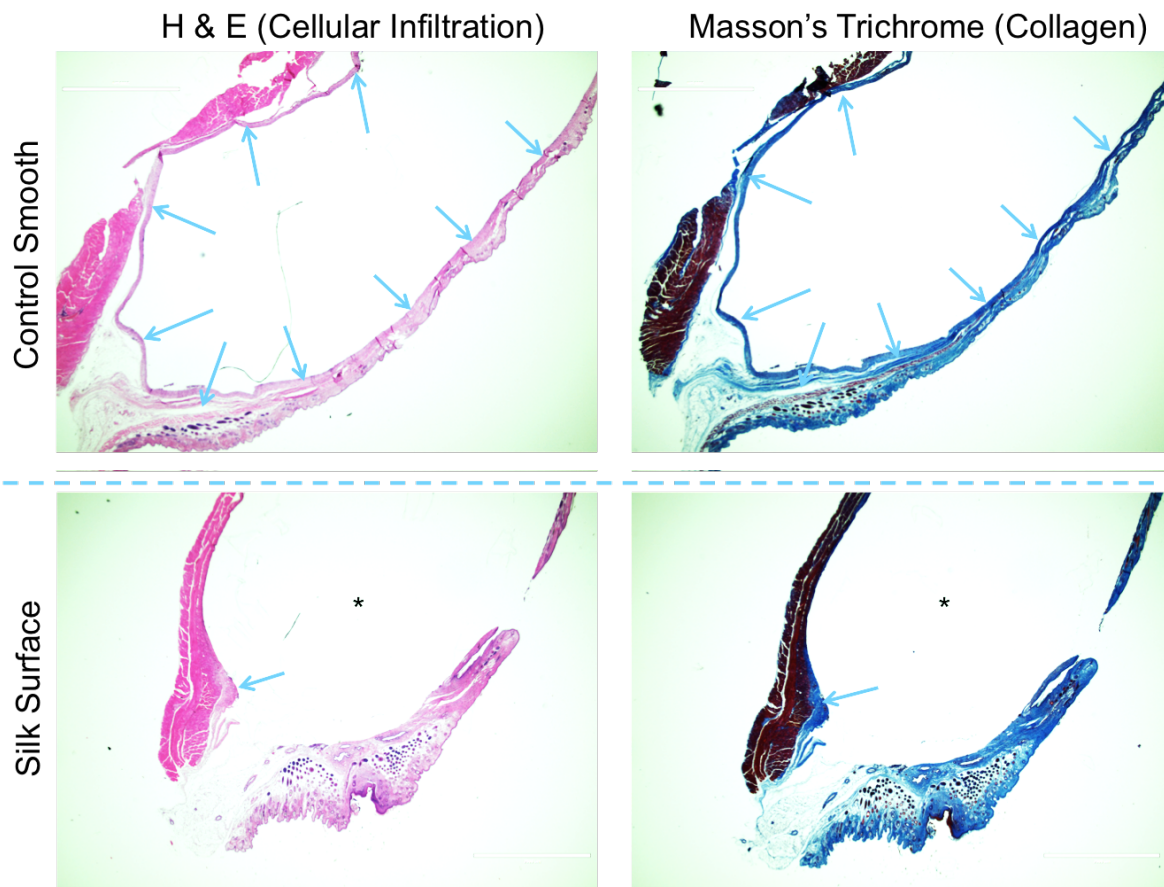
10x:



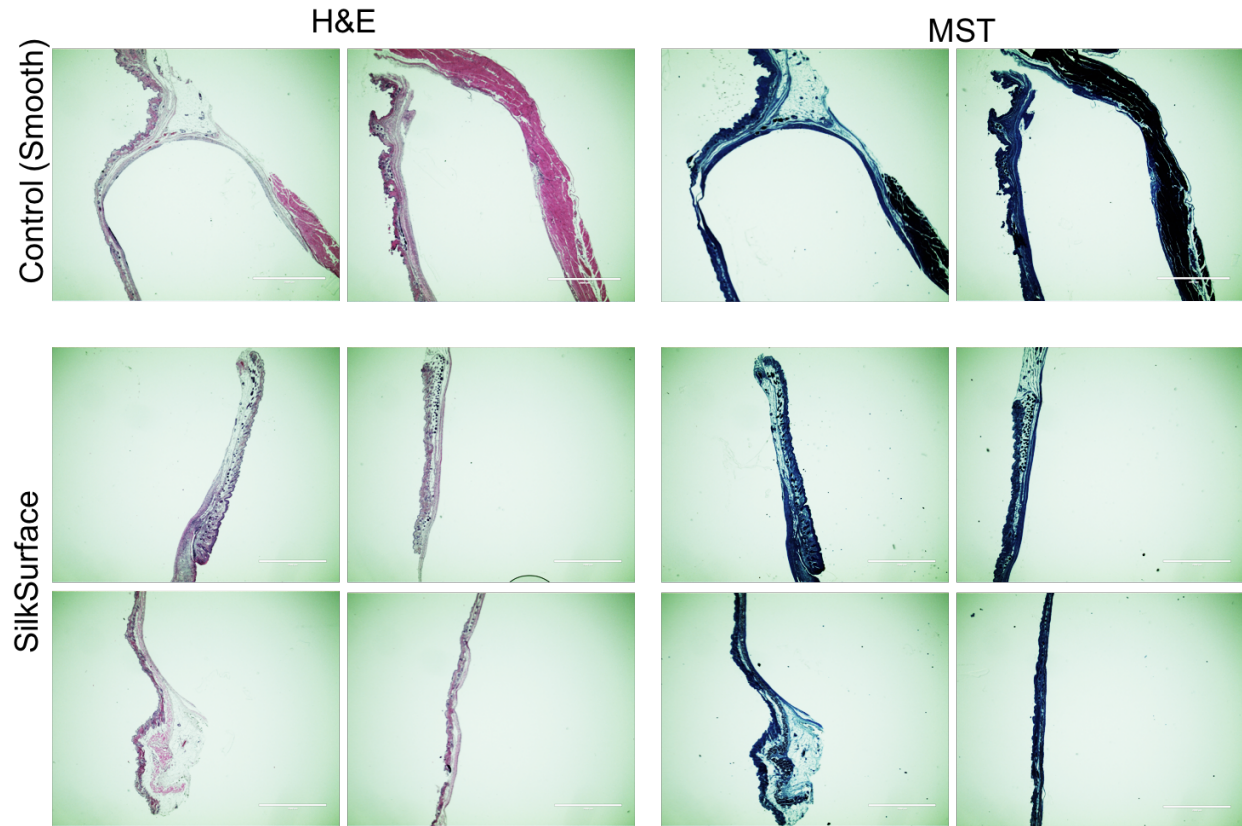
20x:



b) 6wk (2x):



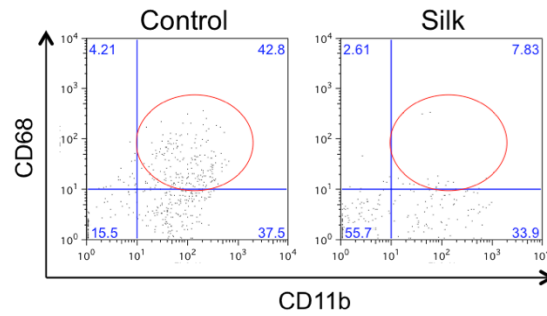
c) 12 wk (2x):



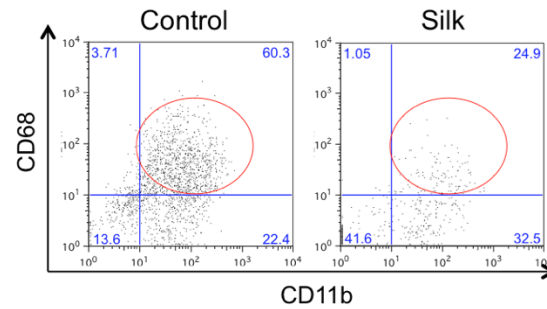
Supplemental Figure 20. Histology of long-term implant capsules retrieved from C57BL/6 mice – Micrographs of H&E and Masson’s Trichrome-stained histology sections prepared from excised capsules from control 0 μm and 4 μm roughness-range miniaturized implant mimics, incubated in wildtype C57BL/6 female mice for 3 weeks (**a**), 6 weeks (**b**), and 12 weeks (**c**). Histology summary showing images taken at specified magnifications, also representing quantified fibrotic capsule thickness in C57BL/6 models (main Fig. 5a). Red hash lines demarcate fibrotic capsules at 3wk (4X mag); blue arrows, capsule at 6wk (2X mag). Scale bar = 2000 μm (2X), 1000 μm (4X), 400 μm (10X), and 200 μm (20X). Images are representative across N = 5 mice/group per time point. Experiments repeated at least twice, three times for early 3- and 6-week time points.

a) 3wk & 6wk FACS plots, Macrophage response:

3wks: Reduction in Macrophages (by ~80% compos

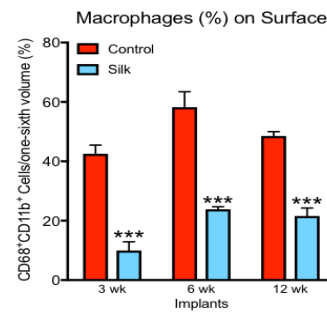
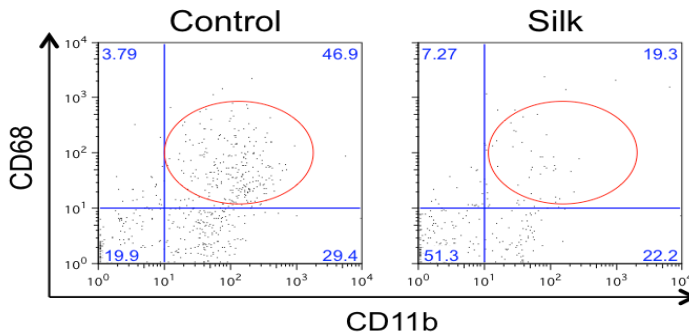


6 weeks: significant reduction is maintained



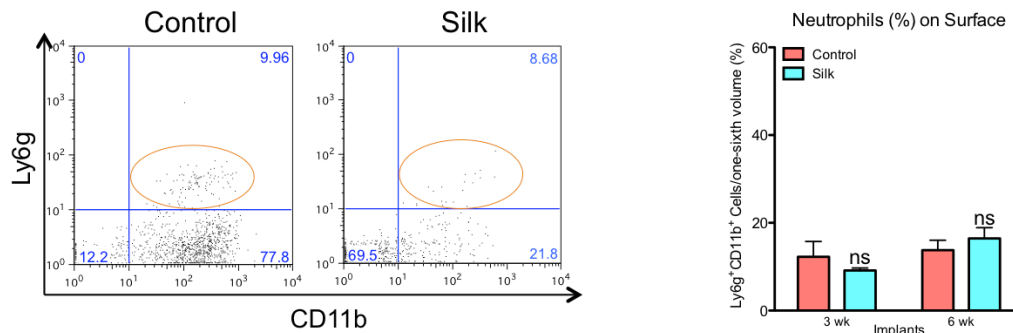
12 weeks (left) and summary graph (by %, right):

Reduction in Macrophages (by ~65-85% by #):

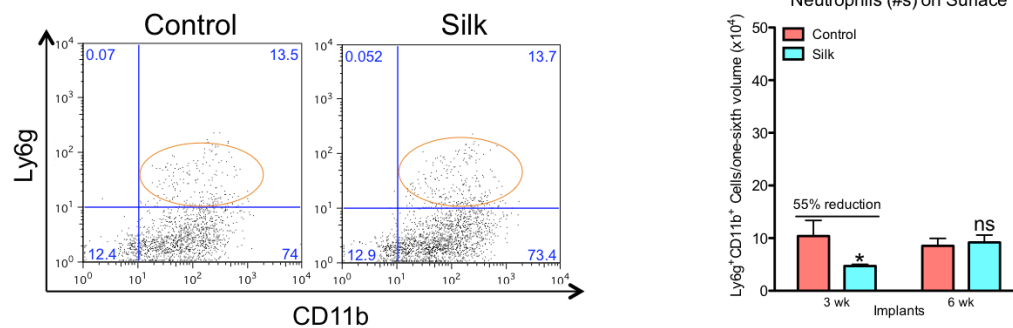


b) 3wk & 6wk FACS plots (left) and graphs (by % & #, right), Neutrophil response

3 wks: No difference in Neutrophils by % composition, but presence ~55% reduced by number:

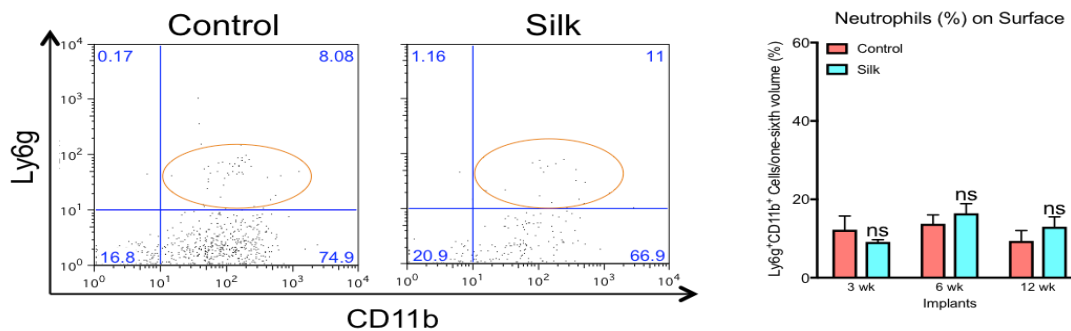


6 wks: No difference.

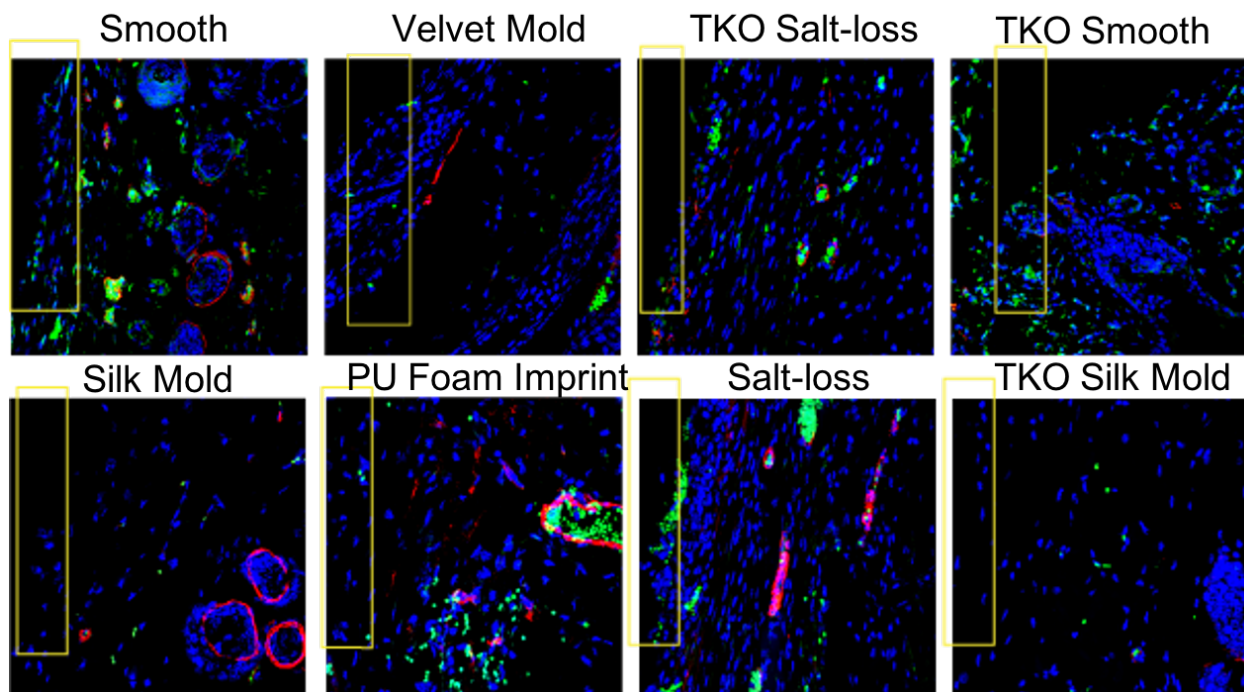


c) 12wk FACS plots (left) and updated graph (% , right), Neutrophil response

No significant difference in Neutrophils:



Supplemental Figure 21. Quantitative FACS analysis performed on cells dissociated from retrieved implant capsules – Capsules were retrieved from control (0 μ m) vs. 4 μ m miniaturized implant mimics at 3, 6, 12, and 24 weeks (6 months) post-implantation in wildtype female C57BL/6 mice for innate immune macrophage (a) and neutrophil (b-c) analysis (complete cell number-adjusted wildtype data in main Fig. 5b; T cell deficient (B6-nude) data in main Fig. 5f). Subpanels reflect data from N = 5 animals/group.

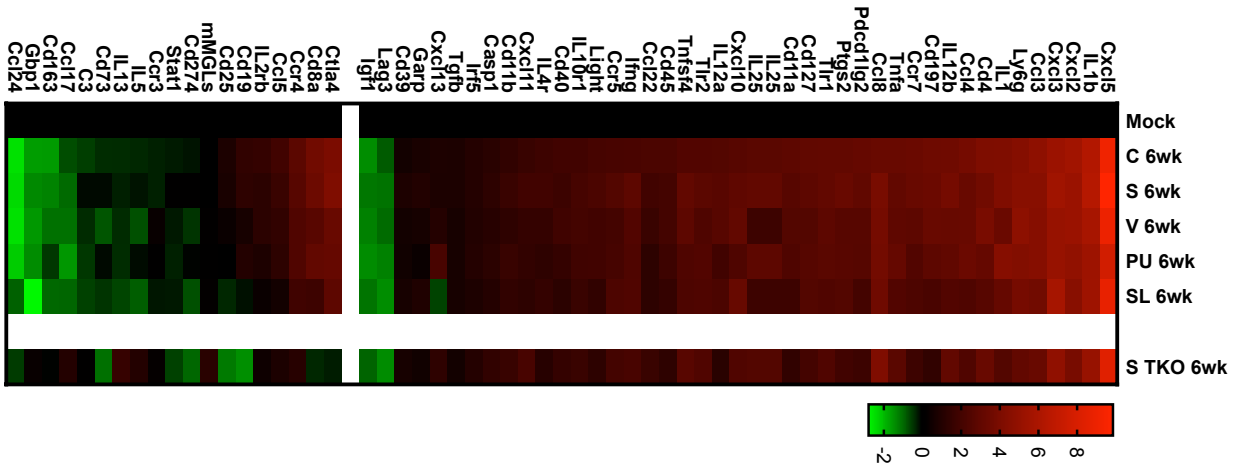


Supplemental Figure 22. Confocal of (6-week) implantations reflecting presence or lack of fibrosis and immune cell responses – Confocal microscopy images showing reduced or no fibrotic overgrowth and macrophage presence in the case of 4 μ m and 15 μ m miniaturized implant mimics. Data collected at 6 weeks post-subcutaneous implantation in wildtype or T cell deficient (nude) female C57BL/6 mice. (Blue, DAPI nuclear stain; Green: Macrophage CD68; and Red: Fibrosis marker α -smooth muscle actin). All subpanels reflect data from N = 5 animals/group.

T cell deficient (B6-nude) model retrievals, 3wk:



Supplemental Figure 23. Retrieval photo of implant capsules retrieved from T cell deficient C57BL/6-nude mice – Image showing both control 0 μm and 4 μm miniaturized implant mimics explanted after 3-week subcutaneous incubations. Images are representative across N = 5 mice/group per time point.



Supplemental Figure 24. NanoString analysis of 6-week breast implant capsules surrounding different mini implant mimics (C = smooth control (0 μm), S = SmoothSilk®-like (4 μm), V = VelvetSurface®-like (15 μm), PU = polyurethane foam imprint (30 μm), and SL = salt-loss (90 μm)) in wildtype and T cell deficient (nude) C57BL/6 mice, implanted subcutaneously for assessing cell and cytokine marker responses, as compared to mock (saline-injected) controls. This overall gene set includes the remaining factors that showed no significant difference in expression levels between breast capsule tissue retrieved for control 0 μm vs. 4 μm breast implants. We further divided this panel into 2 groupings based on whether or not T cell deficiency left expression levels unchanged (top) or significantly altered (bottom). Otherwise, patterns of down- and up-regulation in the 4 μm group are represented in main Fig. 5g-h. Samples were collected from multiple rounds of mouse implantation procedures.

3) Supplementary Videos -

Supplementary Video 1. Double capsules for Mentor Siltex®. The video is representative for experiments repeated 5 times across all rabbits receiving this implant and incubating for 3 weeks.

Supplementary Video 2. Double capsule for Allergan Microcell®, also Velcro effect. The video is representative for experiments repeated 5 times across all rabbits receiving this implant and incubating for 3 weeks.

Supplementary Video 3. Double capsule for Allergan BIOCELL®, also Velcro effect. The video is representative for experiments repeated 5 times across all rabbits receiving this implant and incubating for 3 weeks.

4) Supplementary References –

- 60 in *ISO 14607:2018* (ed International Organization for Standardization) 41 (ISO
copyright office, Switzerland, 2018).
- 61 Munhoz, A. M., Clemens, M. W. & Nahabedian, M. Y. Breast Implant Surfaces and
Their Impact on Current Practices: Where We Are Now and Where Are We Going? *Plast*
Reconstr Surg Global Open, doi:10.1097/GOX.0000000000002466 (2019).
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- 63 Sforza, M. *et al.* Preliminary 3-Year Evaluation of Experience With SilkSurface and
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doi:10.1093/asj/sjx150 (2018).
- 64 Quiros, M. C., Bolanos, M. C. & Fassero, J. J. Six-Year Prospective Outcomes of
Primary Breast Augmentation With Nano Surface Implants. *Aesthet Surg J* **39**, 495-508,
doi:10.1093/asj/sjy196 (2019).
- 65 FDA Update on the Safety of Silicone Gel-Filled Breast Implants. (U.S. Food & Drug
Administration <https://www.fda.gov/media/80685/download>, 2011).

5) Conflict of Interest listing for R. Langer –

2021 Competing Interests Disclosure

From FY 2015 to the present, Dr. Robert Langer receives licensing fees (to patents in which he was an inventor on) from, invested in, consults (or was on Scientific Advisory Boards or Boards of Directors) for, lectured (and received a fee), or conducts sponsored research at MIT for which he was not paid for the following entities:

1. 7th Sense;
2. Abpro Labs;
3. Abpro-Korea;
4. Acorda (Formerly Civitas Therapeutics);
5. Aleph Farms;
6. Alivio Therapeutics;
7. Alkermes;
8. Allevi;
9. Alnylam Pharmaceuticals, Inc;
10. Amoon
11. Apotex;
12. Arcadia Biosciences, Inc;
13. Arsenal Medical;
14. Artificial Cell Technology, Inc;
15. Avalon-Gilbocare;
16. BASF Corporation;
17. Bayer;
18. Bilayer Therapeutics
19. Biogen;
20. BioInnovation Institute (Novo Nordisk Founden);
21. Blackstone (Formerly Clarus);
22. Boston Children's Hospital;
23. CBC Group Investment Mgmt Group;
24. Celanese;
25. Celero;
26. Cellink
27. Cellomics Technology, LLC;
28. Cellular Biomedical;
29. Charles River Laboratories, Inc.;
30. Clontech Laboratories;
31. Combined Therapeutics ("CTx");
32. Conference Forum;
33. Cornell University;
34. Crispr Therapeutics Ag;
35. Crown Bioscience Inc.;
36. Cygnal Therapeutics, Inc.;
37. Daré Biosciences (Formerly Microchips Biotech, Juniper Pharmaceuticals, and Columbia Laboratories);
38. Daros, Inc.
39. DeepBiome;
40. Dewpoint Therapeutics;
41. Dispendix
42. Domain;
43. Eagle Pharmaceuticals;
44. Earli;
45. Edigene Biotechnology, Inc.;
46. Editas Medicine, Inc.;
47. Eli Lilly;
48. Eisai Inc.;
49. Entrega;
50. EpiBone
51. Establishment Labs, SA.
52. Everlywell;
53. Evox Therapeutics, Ltd.;
54. Flagship Pioneering;
55. Frequency Therapeutics, Inc.;
56. GeneLeap Biotech
57. Genemedicine Co Lmtd;
58. GenScript USA Inc;
59. GENUV;
60. Glaxosmithkline LLC;
61. Glycobia;
62. Glympse Bio;
63. Goldman Sachs
64. Greenlight Biosciences;
65. HCR (HealthCare Royalty Partners);

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66. Hopewell Therapeutics;
67. Horizon Discovery Group Plc;
68. Humacyte, Inc.;
69. IBEX Pharmaceuticals, Inc.;
70. Immunai;
71. ImmuneXcite Inc.;
72. Indivor;
73. Institute of Immunology Co. Ltd;
74. Integrated Dna Technologies, Inc.;
75. InVivo Therapeutics;
76. IxBio;
77. J.R. Simplot Company;
78. Jnana Therapeutics;
79. Kala Pharmaceuticals;
80. Kallyope, Inc.;
81. Kendall Capital;
82. Kensa;
83. Kodikaz Therapeutics
84. Ksq Therapeutics, Inc.;
85. Landsdowne Labs;
86. LikeMinds;
87. Lonza;
88. Luminopia, Inc.;
89. Luye (Shandong luye);
90. Lyndra Therapeutics;
91. Lyra Therapeutics (Formerly "480 Biomedical");
92. McGovern Institute;
93. Medikinetix Co., Ltd.;
94. Merck;
95. MGH Ragon Institute;
96. Micelle;
97. Moderna Therapeutics;
98. Momena;
99. Muse Biotechnologies Inc.
100. Mylan;
101. N2Tech;
102. Nanobiosym;
103. Nanobiotix;
104. Nextma;
105. Newbridge Ventures LLC;
106. Noveome Biotherapeutics, Inc.;
107. Novo Nordisk;
108. Particles for Humanity;
109. Pfizer, Inc.;
110. Pioneer Hi-Bred International, Inc.;
111. Placon Therapeutics
112. Polaris Partners;
113. Portal Instruments;
114. Preceres, LLC (Acquired by Monsanto);
115. PrognomiQ Inc.;
116. Pulmatrix;
117. PureTech;
118. Quris
119. ReLive;
120. Reprocell Usa, Inc. (Formerly Stemgent);
121. Rubius Therapeutics;
122. Secant Medical, Inc.;
123. Seer, Inc.;
124. Selecta Biosciences;
125. Senses LLC;
126. Setsuro Tech Inc.;
127. Seventh Sense Biosystems, Inc.;
128. Shenzhen Rice Life Technology, Ltd;
129. Shire Ag;
130. Sigilon;
131. Sigma Aldrich Co. LLC;

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132. Sio2;
133. Ske S.R.L.;
134. Soil Culture Solutions Llc (Dba Soilcea);
135. SQZ Biotechnologies;
136. StemBioSys, Inc.;
137. SuonoBio;
138. T2 Biosystems;
139. Taconic Biosciences, Inc. (formerly Taconic Farms);
140. TARA;
141. Tarveda Therapeutics;
142. Teal Bio
143. Tesio Pharmaceuticals
144. Third Rock Ventures;
145. Tiba Biotech LLC;
146. Tissium (formerly "Gecko");
147. Transgenic Inc.;
148. Translate Bio (Formerly Rana Therapeutics, Inc.);
149. Trilink Biotechnologies, Inc.;
150. Unilever (Living Proof);
151. VasoRX;
152. Verseau Therapeutics, Inc.;
153. Vitakey;
154. Vivtex Corporation;
155. Whitehead Institute;
156. Wiki Foods;
157. Yz Biosciences (Guangzhou) Inc.;
158. Zenomics;

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Note: for up-to-date COI listing, please see active URL:

www.dropbox.com/s/yc3xqb5s8s94v7x/Rev%20Langer%20COI.pdf?dl=0