

Figure S1. Representative images of a micro X-ray computed tomography system immediately after injection of sodium alginate. (Above) 0.2 mL injected onto the parietal periosteum. (Middle) 0.1 mL injected intradermally. (Below) 0.5 mL injected subcutaneously. Scale bars = 30 mm.

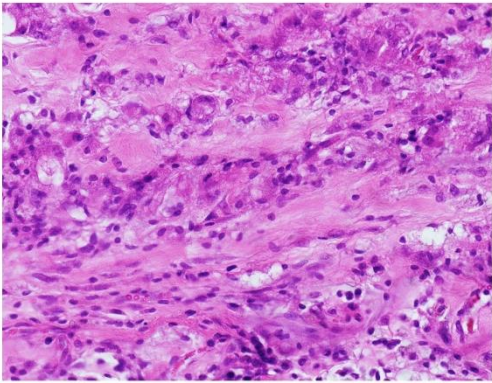
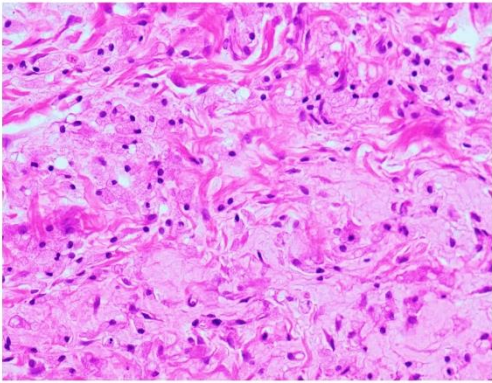
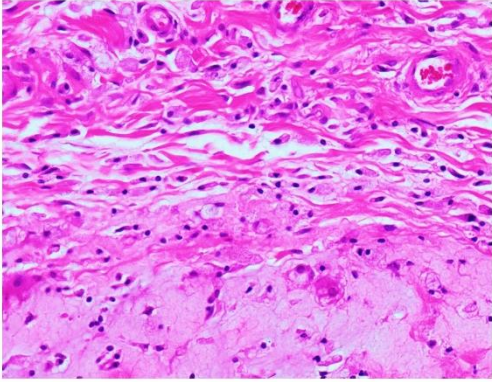
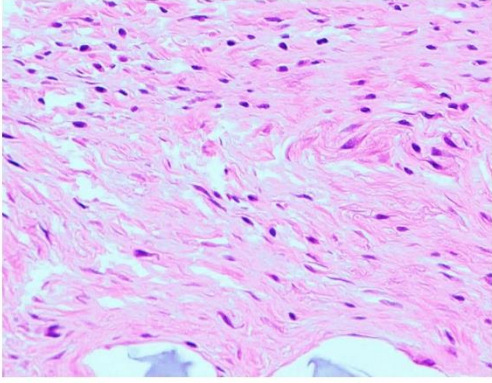
Severe	
Moderate	
Mild	
Absent	

Figure S2. Visual scoring scale for granulomatous changes

Table S1. The results are shown as means \pm standard error. The numbers are rounded off to the first decimal place. Four rats for each test substance (n = 4). Some bulges were flattened, and their diameters could not be measured (*n = 3; †n = 1; N/A, n = 0). SA: sodium alginate, SH: sodium hyaluronate.

		Diameter [mm]				
		Day 0	4 weeks	8 weeks	12 weeks	24 weeks
A1	Onto the periosteum	12.3 \pm 0.3	15.8 \pm 1.6	16.8 \pm 1.7	15.2†	N/A
	Intradermally	10.8 \pm 0.5	13.9 \pm 0.6	13.8 \pm 0.9	14.4 \pm 1.7	13.4 \pm 0.9
	Subcutaneously	17.7 \pm 0.3	29.6 \pm 0.7	27.0 \pm 0.7	28.8 \pm 1.3	29.2 \pm 1.6
A2	Onto the periosteum	12.5 \pm 0.2	16.6 \pm 0.8	16.5 \pm 1.4	14.9†	N/A
	Intradermally	10.4 \pm 0.4	14.3 \pm 0.5	13.9 \pm 1.1	15.4 \pm 1.0	16.3 \pm 0.3
	Subcutaneously	18.3 \pm 0.1	29.7 \pm 1.0	30.1 \pm 0.7	31.8 \pm 0.8	33.1 \pm 1.2
A3	Onto the periosteum	12.7 \pm 0.2	14.8 \pm 0.8	14.2 \pm 0.8	17.0†	N/A
	Intradermally	11.3 \pm 0.2	13.7 \pm 0.4	15.7 \pm 1.2	14.5 \pm 1.4*	14.1 \pm 0.7*
	Subcutaneously	18.6 \pm 0.1	29.9 \pm 0.4	29.5 \pm 0.7	34.6 \pm 1.1	30.9 \pm 1.1
A4	Onto the periosteum	11.6 \pm 0.5	17.8 \pm 0.9	16.7 \pm 0.4	15.4 \pm 0.5	14.9 \pm 0.9
	Intradermally	10.8 \pm 0.2	13.7 \pm 0.3	12.9 \pm 0.7	13.4 \pm 1.0	12.0 \pm 0.9
	Subcutaneously	18.2 \pm 0.3	26.9 \pm 0.4	27.0 \pm 0.8	26.0 \pm 0.8	24.7 \pm 1.1
A5	Onto the periosteum	12.5 \pm 0.1	17.1 \pm 1.1	14.8 \pm 0.7	15.1 \pm 0.5*	11.3†
	Intradermally	10.9 \pm 0.3	14.5 \pm 0.5	15.8 \pm 0.7	16.2 \pm 1.4	16.1 \pm 0.6
	Subcutaneously	18.1 \pm 0.4	30.6 \pm 0.3	31.6 \pm 0.8	34.2 \pm 1.0	30.1 \pm 1.8
A6	Onto the periosteum	12.5 \pm 0.3	16.8 \pm 0.5	15.0 \pm 0.6	N/A	N/A
	Intradermally	10.4 \pm 0.5	14.8 \pm 0.4	16.1 \pm 1.0	16.0 \pm 0.5	16.6 \pm 0.9
	Subcutaneously	18.0 \pm 0.4	30.0 \pm 0.7	29.4 \pm 0.4	33.2 \pm 0.6	30.8 \pm 1.8
A7	Onto the periosteum	12.6 \pm 0.1	18.4 \pm 1.0	17.8 \pm 0.7	15.9 \pm 1.2	14.1 \pm 0.8*
	Intradermally	10.3 \pm 0.3	13.4 \pm 0.5	12.9 \pm 0.5	13.0 \pm 0.6	11.6 \pm 0.8
	Subcutaneously	18.0 \pm 0.4	27.5 \pm 1.4	28.2 \pm 2.1	26.5 \pm 1.5	25.8 \pm 3.4
A8	Onto the periosteum	12.8 \pm 0.4	18.6 \pm 0.5	18.2 \pm 0.7	16.2 \pm 0.9	16.3 \pm 0.7*
	Intradermally	10.9 \pm 0.2	14.3 \pm 0.5	14.7 \pm 0.9	14.7 \pm 1.1	13.6 \pm 0.8
	Subcutaneously	18.0 \pm 0.5	29.0 \pm 0.5	29.4 \pm 0.6	31.5 \pm 0.7	26.1 \pm 2.0
A9	Onto the periosteum	12.2 \pm 0.2	17.1 \pm 1.1	17.1 \pm 0.6	13.4†	N/A
	Intradermally	10.8 \pm 0.2	15.8 \pm 0.5	16.8 \pm 1.4	18.3 \pm 1.0	15.3 \pm 1.0
	Subcutaneously	18.3 \pm 0.4	31.7 \pm 0.9	30.6 \pm 1.4	33.5 \pm 1.1	28.7 \pm 1.1
SH	Onto the periosteum	12.4 \pm 0.4	14.2 \pm 0.6	13.6 \pm 0.8	12.1 \pm 0.4	10.0 \pm 0.2
	Intradermally	10.6 \pm 0.6	11.4 \pm 0.9	9.9 \pm 0.6	8.9 \pm 0.5	7.6 \pm 0.5
	Subcutaneously	17.4 \pm 1.0	19.4 \pm 1.3	18.3 \pm 1.1	17.9 \pm 2.0	16.8 \pm 1.2

Table S2. The results are shown as means \pm standard error. The numbers are rounded off to the second decimal place. Four rats for each test substance (n = 4). Some boundaries of the injected substances were unclear in the CT images, and their volumes could not be measured (*n = 3; ‡ n = 2; †n = 1; N/A, n = 0). SA: sodium alginate, SH: sodium hyaluronate.

		Volume [mL]				
		Day 0	4 weeks	8 weeks	12 weeks	24 weeks
A1	Onto the periosteum	0.52 \pm 0.03	N/A	N/A	N/A	0.25†
	Intradermally	0.25 \pm 0.01	0.17 \pm 0.02 ‡	0.10†	0.12†	N/A
	Subcutaneously	1.23 \pm 0.08	0.53 \pm 0.01*	0.72 \pm 0.11 ‡	0.62 \pm 0.14 ‡	0.54 \pm 0.04 ‡
A2	Onto the periosteum	0.56 \pm 0.03	N/A	N/A	N/A	N/A
	Intradermally	0.25 \pm 0.01	N/A	N/A	N/A	N/A
	Subcutaneously	1.23 \pm 0.05	0.41†	0.80 \pm 0.11*	N/A	0.73 \pm 0.11 ‡
A3	Onto the periosteum	0.55 \pm 0.02	N/A	N/A	N/A	N/A
	Intradermally	0.25 \pm 0.02	N/A	N/A	N/A	N/A
	Subcutaneously	1.22 \pm 0.09	0.67†	0.71†	0.46†	0.76 \pm 0.05 ‡
A4	Onto the periosteum	0.51 \pm 0.03	0.47 \pm 0.08*	0.33 \pm 0.09*	0.45 \pm 0.02 ‡	0.27 \pm 0.10 ‡
	Intradermally	0.26 \pm 0.01	0.14 \pm 0.03	0.17 \pm 0.04	0.14 \pm 0.02	0.08 ‡
	Subcutaneously	1.17 \pm 0.09	0.87 \pm 0.06	0.85 \pm 0.09	0.66 \pm 0.03	0.93 \pm 0.09
A5	Onto the periosteum	0.53 \pm 0.04	N/A	N/A	N/A	N/A
	Intradermally	0.26 \pm 0.01	0.16 \pm 0.01	0.16 \pm 0.03 ‡	0.10†	N/A
	Subcutaneously	1.29 \pm 0.14	0.76 \pm 0.12 ‡	0.96 \pm 0.02*	0.67 \pm 0.19 ‡	0.89 \pm 0.17*
A6	Onto the periosteum	0.58 \pm 0.03	N/A	N/A	N/A	N/A
	Intradermally	0.25 \pm 0.01	0.11*	N/A	N/A	N/A
	Subcutaneously	1.14 \pm 0.08	0.80 \pm 0.07 ‡	0.57†	0.73†	1.01 \pm 0.03 ‡
A7	Onto the periosteum	0.63 \pm 0.01	0.45 \pm 0.03 ‡	0.42 \pm 0.02 ‡	0.44 \pm 0.02 ‡	0.30 \pm 0.02 ‡
	Intradermally	0.21 \pm 0.01	0.11 \pm 0.01*	0.10 \pm 0.01	0.20 \pm 0.01 ‡	0.16 \pm 0.06 ‡
	Subcutaneously	1.17 \pm 0.10	0.82 \pm 0.20*	0.67 \pm 0.12	0.67 \pm 0.05*	0.74 \pm 0.15
A8	Onto the periosteum	0.51 \pm 0.02	0.47 \pm 0.05 ‡	0.36 ‡	0.38 \pm 0.08 ‡	0.17†
	Intradermally	0.24 \pm 0.02	0.22 \pm 0.05	0.15 \pm 0.03	0.18 \pm 0.02*	0.19†
	Subcutaneously	1.05 \pm 0.04	0.94 \pm 0.07	0.92 \pm 0.16	0.71 \pm 0.10*	1.20 \pm 0.02*
A9	Onto the periosteum	0.55 \pm 0.05	N/A	0.46†	N/A	N/A
	Intradermally	0.26 \pm 0.01	0.20†	0.25†	N/A	N/A
	Subcutaneously	1.16 \pm 0.08	0.81 \pm 0.02 ‡	0.79 \pm 0.14 ‡	N/A	0.68†
H	Onto the periosteum	0.22 \pm 0.01	0.18 \pm 0.03*	0.20 \pm 0.01*	0.18 \pm 0.03*	0.13 \pm 0.01
	Intradermally	0.12 \pm 0.01	0.11 \pm 0.01	0.08 \pm 0.01	0.08 \pm 0.02	0.12 \pm 0.01
	Subcutaneously	0.68 \pm 0.10	0.41 \pm 0.08	0.30 \pm 0.05	0.33 \pm 0.04	0.35 \pm 0.04