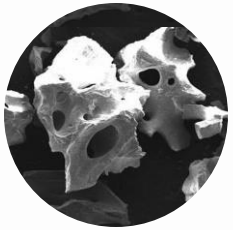
Large Granules
(1.00 – 2.00 mm)

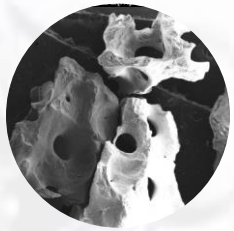


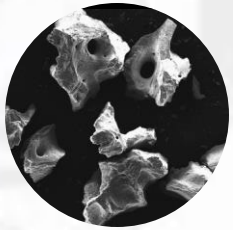
SigmaGraft, Inc.

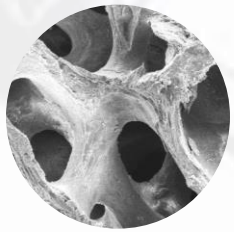
The Bone Graft Substitute Specialists

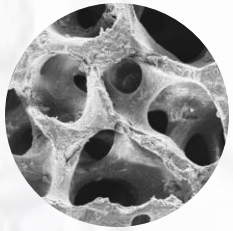
A comparison between SigmaGraft's Bovine Derived Xenograft and Bio-Oss®

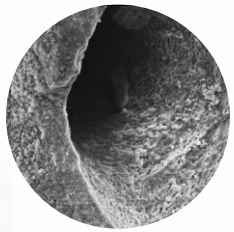
Small Granules
(0.25 – 1.00 mm)

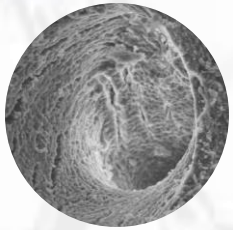


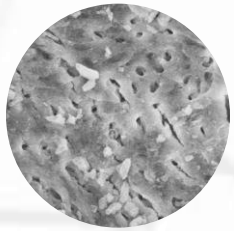


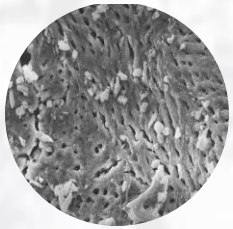






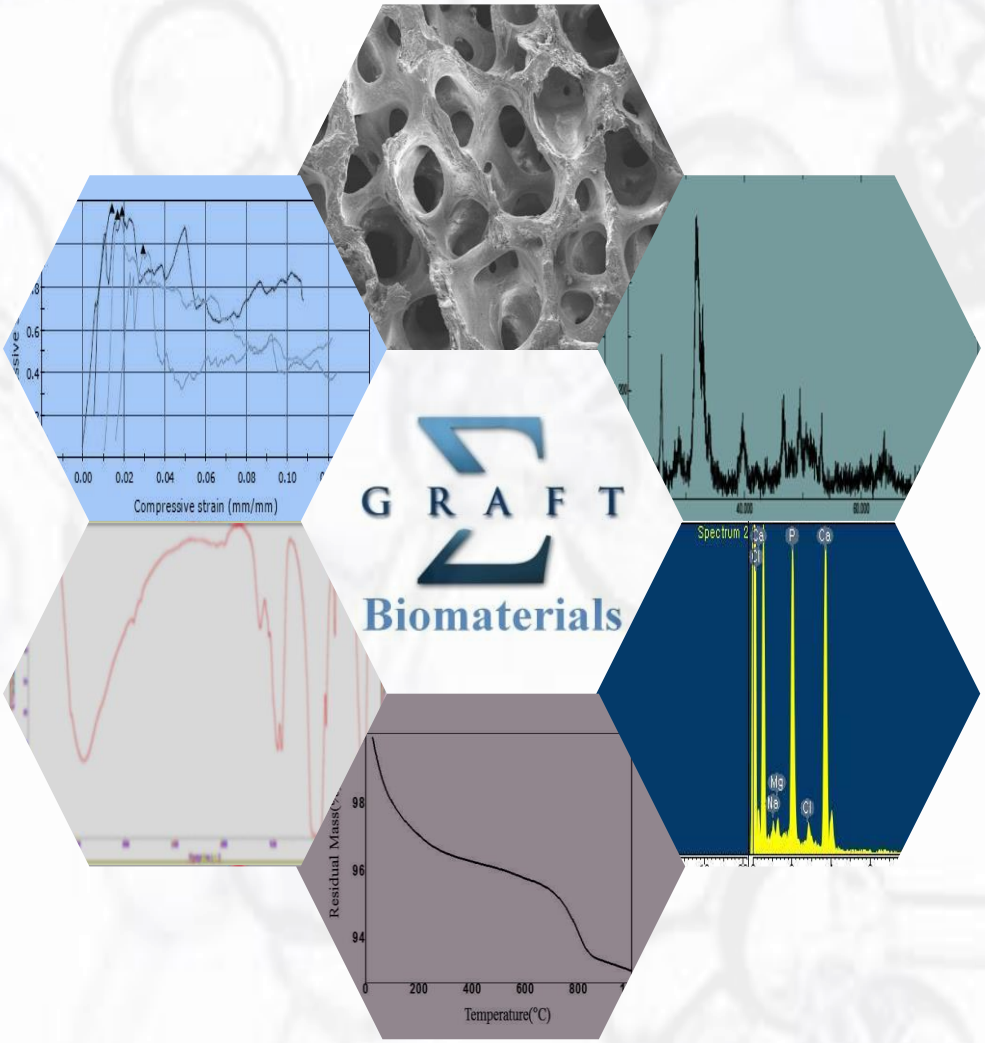






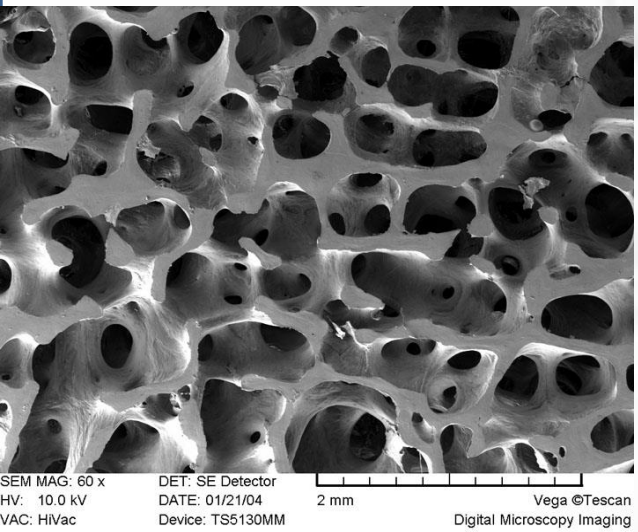
Physiochemical Data

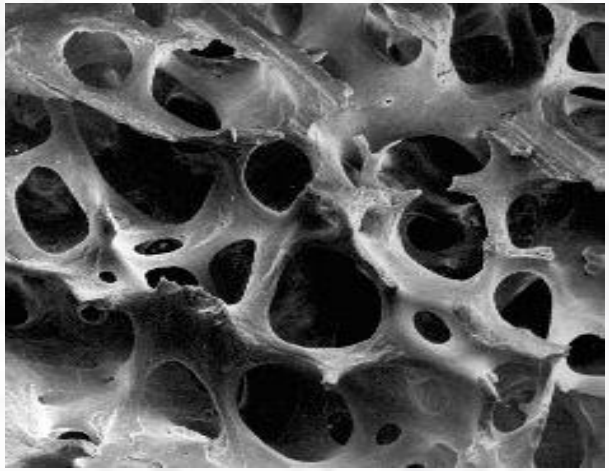
- SEM
- EDS
- XRD
- TGA
- Fat/Protein
- Surface Area
- FTIR



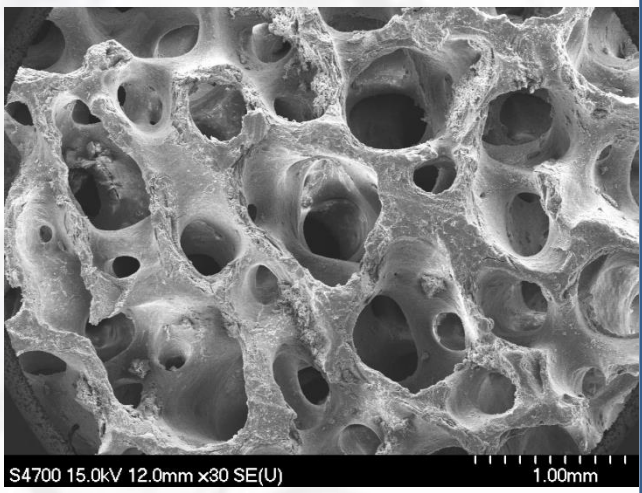
Scanning Electron Microscopy (SEM)

Human Bone





SigmaGraft Bone

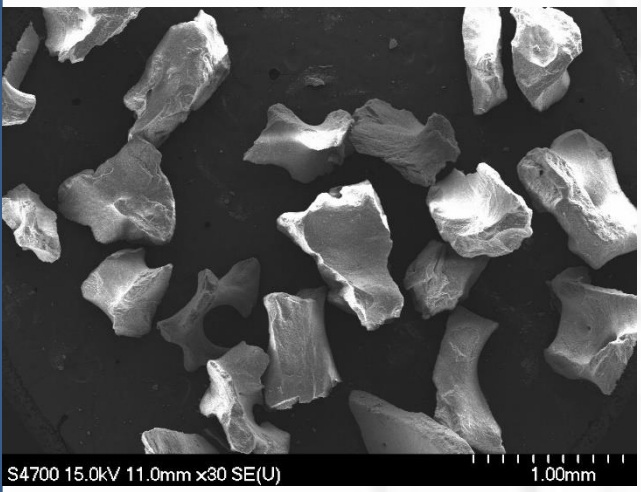


- Similar pore structure to that oh human bone

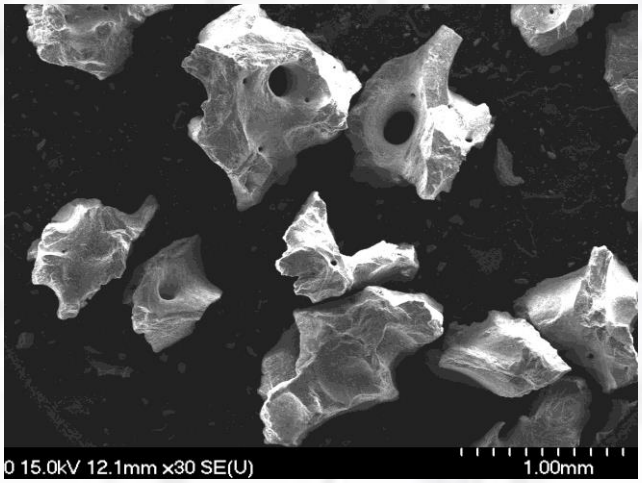
GRAFT Biomaterials

Scanning Electron Microscopy (SEM)

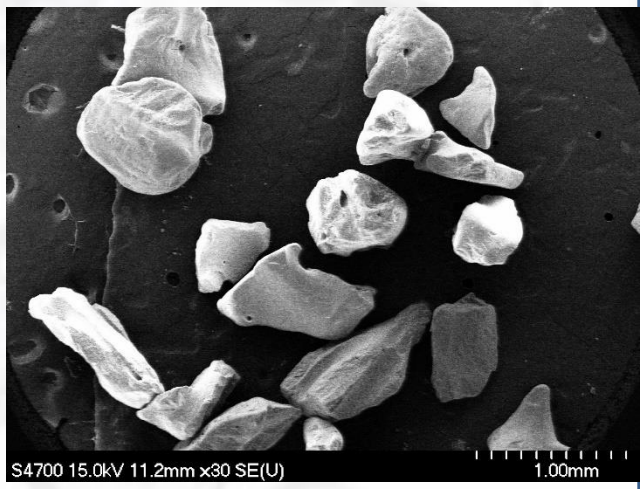
Geistlich



SigmaGraft



Nibec

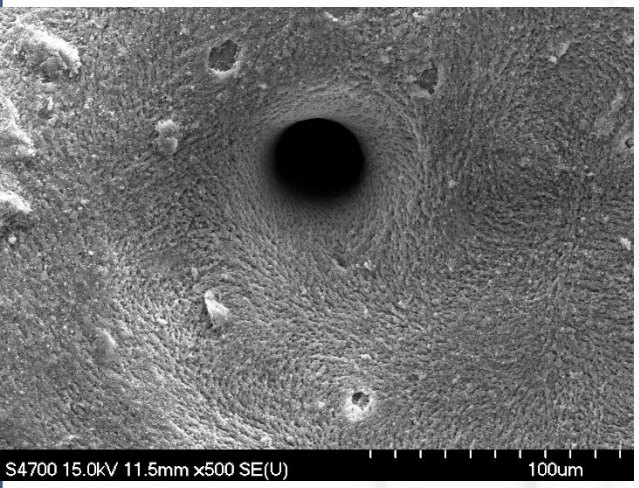


- Irregular porous shape to promote angiogenesis and migration of osteoblasts

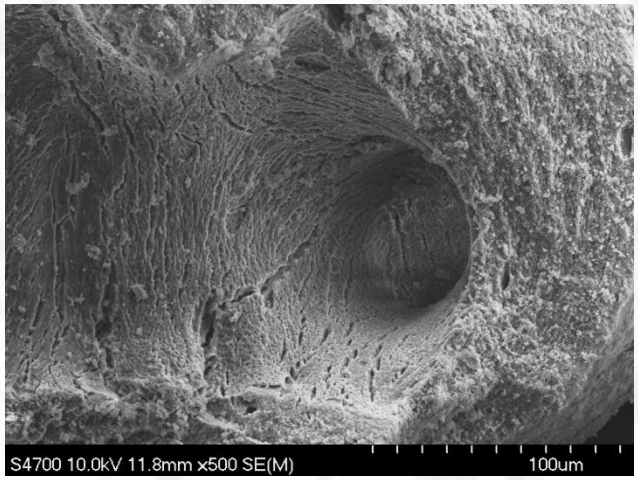
GRAFT Biomaterials

Scanning Electron Microscopy (SEM)

Geistlich



SigmaGraft



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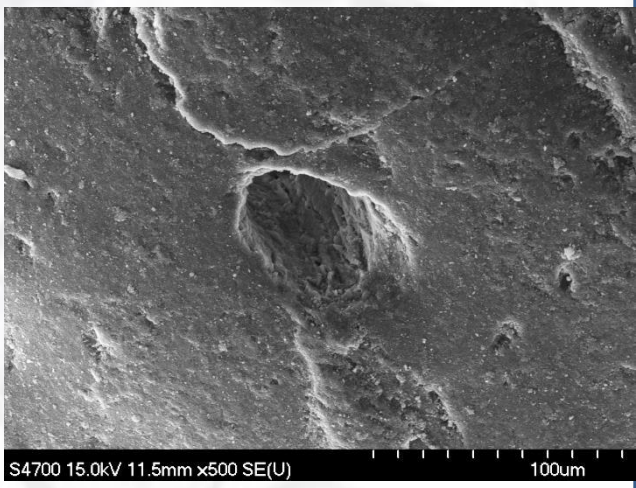
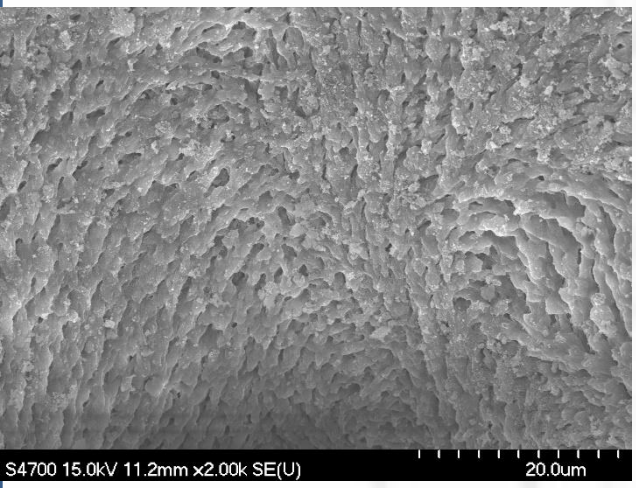


- Well shaped micropores with a large number of micropores
  - 40-60 µm for InterOss and 30-40 µm for Bio-Oss

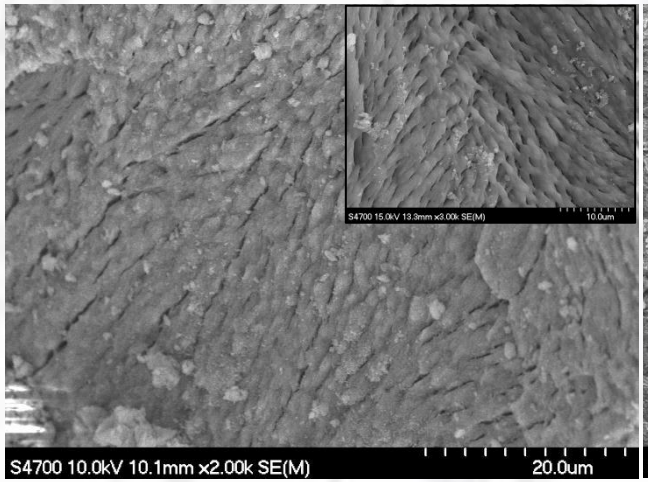
GRAFT Biomaterials

Scanning Electron Microscopy (SEM)

Geistlich



SigmaGraft



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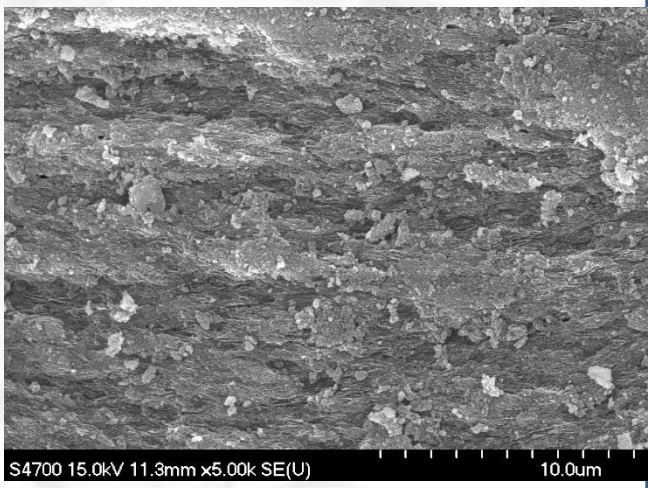
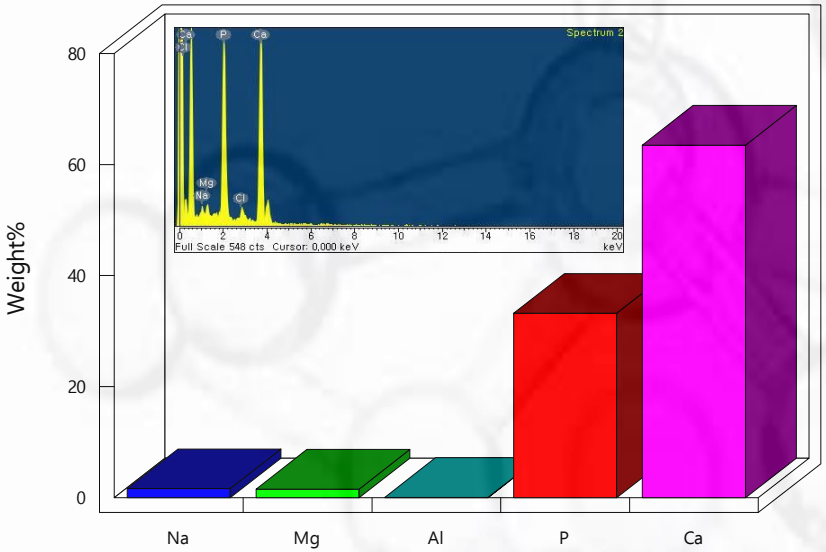


- Well defined micropores
  - ≤ 1.5 µm for InterOss and ≤ 3.0 µm for Bio-Oss

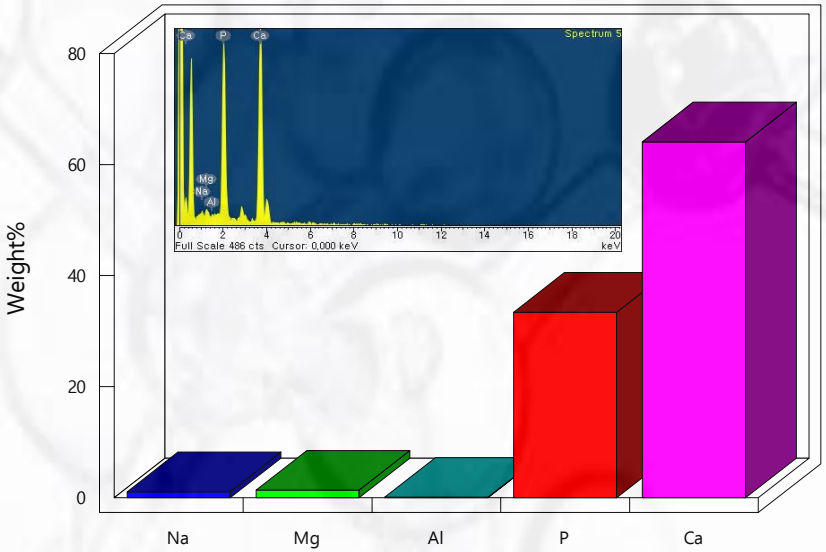
GRAFT Biomaterials

Energy Dispersive Spectroscopy (EDS)

Geistlich



SigmaGraft



- Elemental composition
- Ca/P = 1.48

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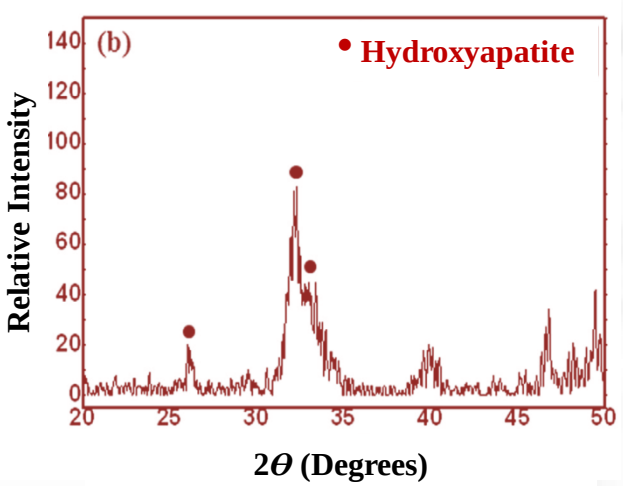
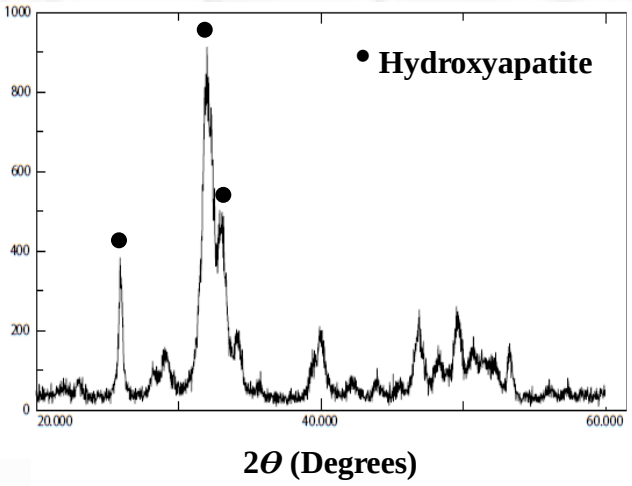
X-ray Powder Diffraction (XRD)

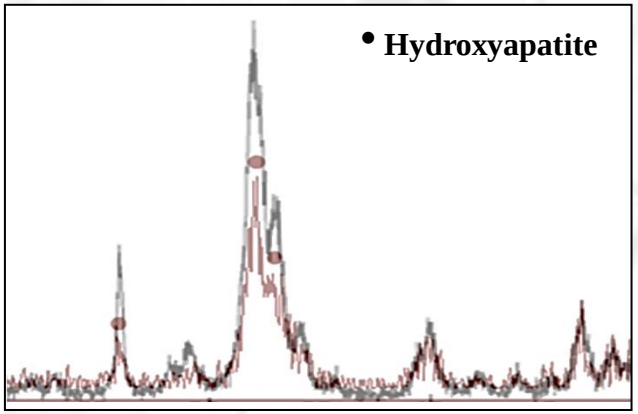
Geistlich



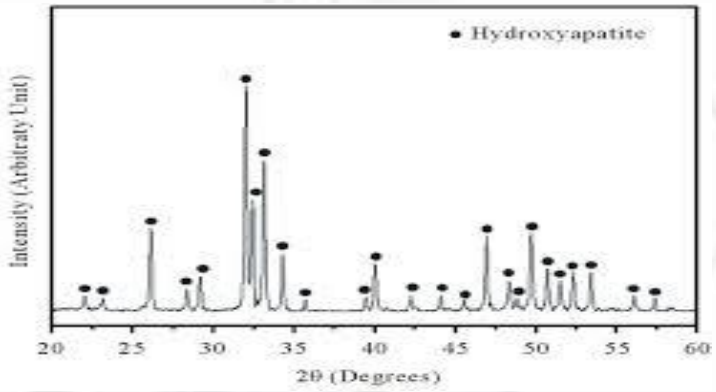
SigmaGraft



Hydroxyapatite



- Identification of a crystalline material and crystal structure



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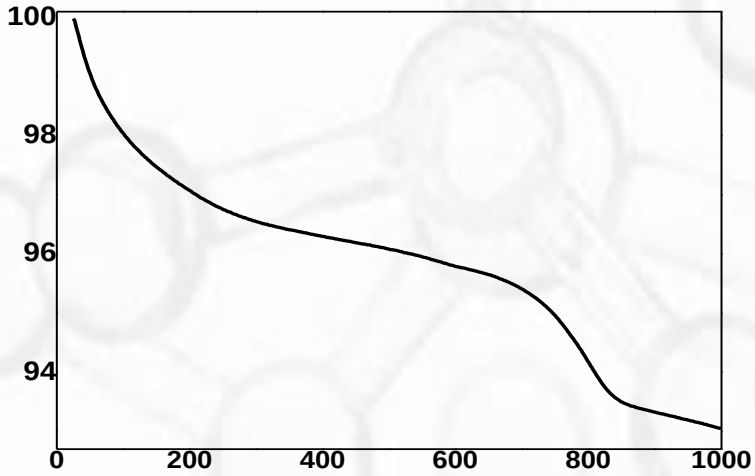
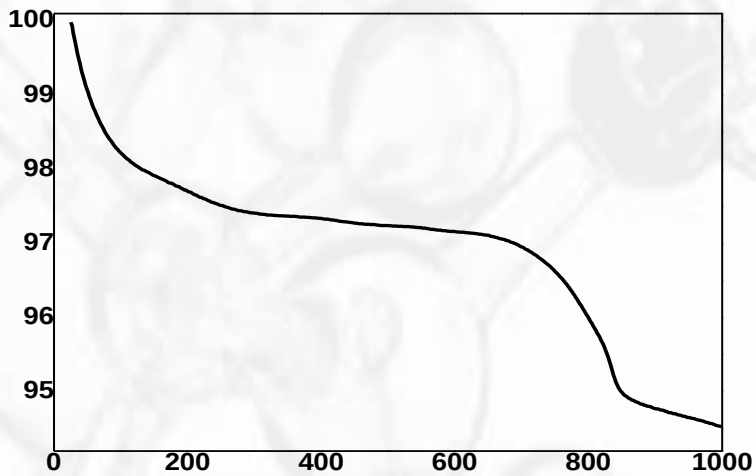
Thermogravimetric Analysis (TGA)

SigmaGraft



Geistlich



SigmaGraft		Geistlich	
H_2O(%) (30~220°C)	Organic (%) (220~635°C)	H_2O(%) (30~220°C)	Organic (%) (220~635°C)
2.69	2.38	2.83	2.86

GRAFT Biomaterials

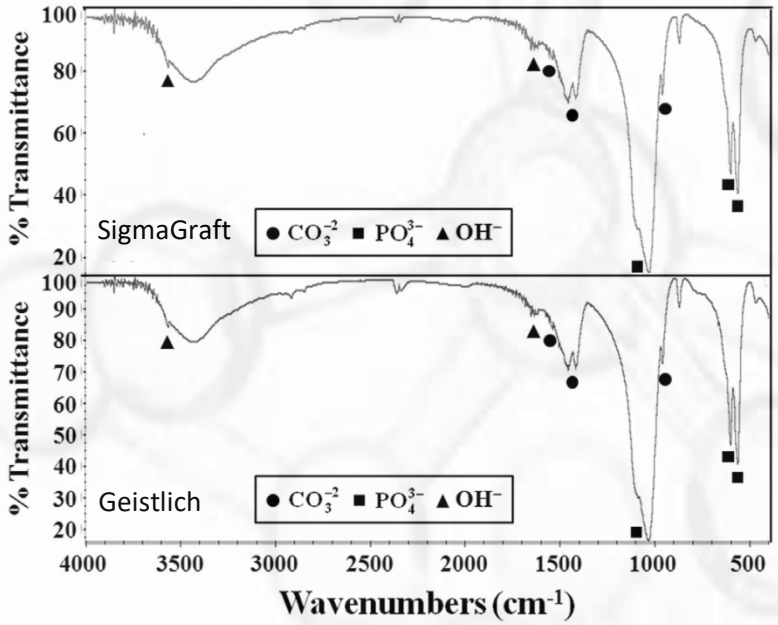
Fat, Protein, and Surface Area

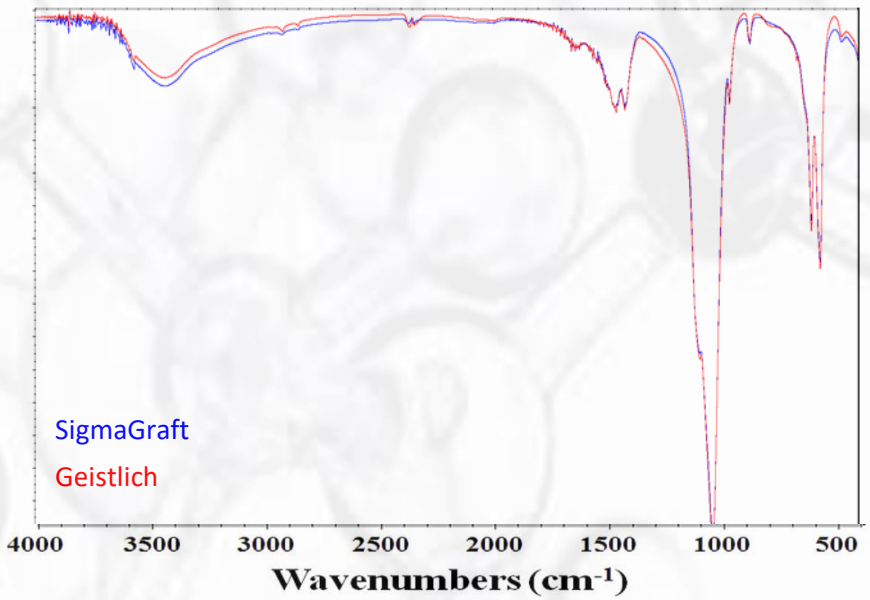
	SigmaGraft	Geistlich
Fat	**0.60 %**	**1.54 %**
Crude Protein	**0.04 %**	**0.07 %**
Surface Area	**88.2 m^2/g**	**77.5 m^2/g**
Porosity	**70.2 %**	**63.5 %**

- Fat reduces biocompatibility and wettability
- Protein can decrease biocompatibility and increase inflammation
- Higher porosity and surface are more biologically active

GRAFT Biomaterials

Fourier Transform Infrared Spectroscopy (FTIR)





- Carbonate bands at 1506-1570 cm^{-1}, 1400-1477 cm^{-1}, 953-989 cm^{-1}
- Hydroxyl bands at 3572 cm^{-1} and 1638 cm^{-1}
- Orthophosphate bands at 960-1120 cm^{-1}, 602 cm^{-1}, 570 cm^{-1}

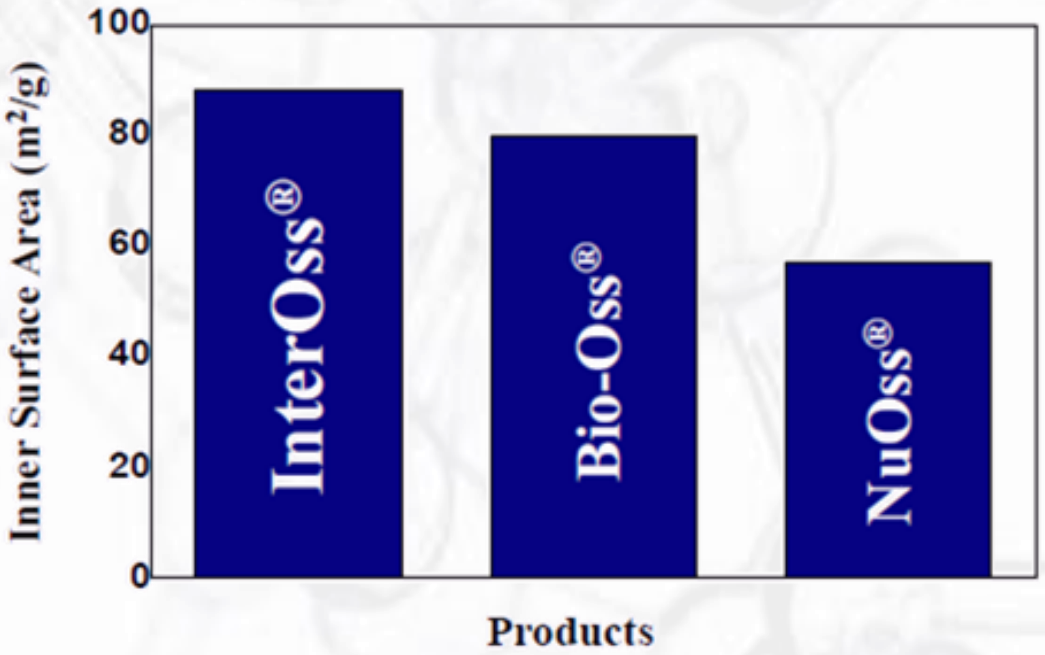
GRAFT Biomaterials

BET (Surface Area) Comparison

Inner Surface Area (m^2/g)

InterOss®	Bio-Oss®	NuOss®
88.2	79.7	57.0

Ref.) NuOss, a Bone Grafting Material for Oral Surgery: A Comparative Study with BioOss by Collagen Matrix Inc.
Ref.) Bio-Oss Product Brochure by Geistlich



GRAFT Biomaterials

Biocompatibility

- Extractable Test
- Sensitization
- Genotoxicity
- Intracutaneous Reactivity
- Acute Systemic Toxicity
- Cytotoxicity
- Pyrogen
- Hemolysis
- Sterility
- Endotoxin
- Subchronic Toxicity
- Implantation

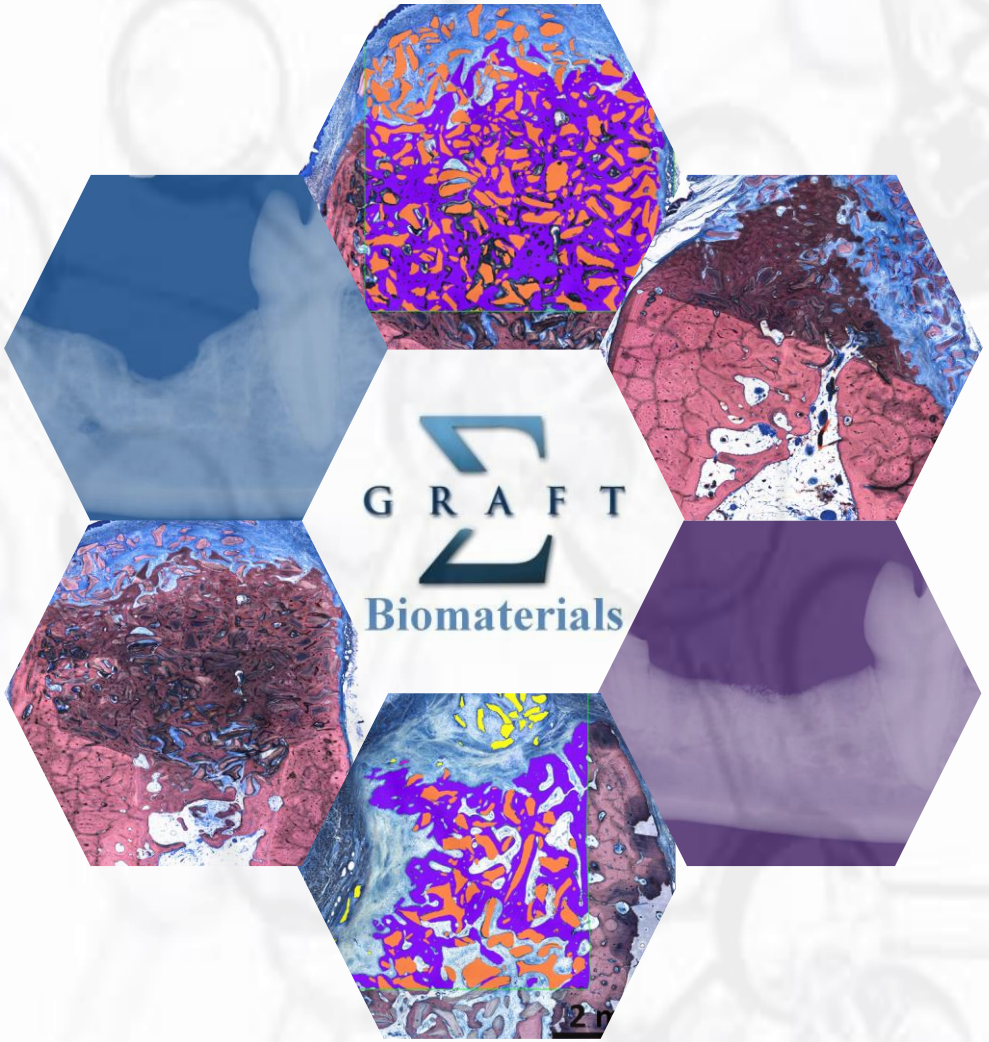
GRAFT Biomaterials

Biocompatibility

Test	Method	Criteria	Result
Extractable Test	USP <661>	< 15 mg	Pass
Sensitization	ISO 10993-10	No signs of sensitization	Pass
Genotoxicity	ISO 10993-3	No significant increase in micronucleated polychromatic erythrocytes, number of revertant colonies, chromosome aberrations	Pass
Intracutaneous Reactivity	ISO 10993-10	No Signs of erythema or edema	Pass
Acute Systemic Toxicity	ISO 10993-11	No signs of toxicity	Pass
Cytotoxicity	ISO 10993-5	No detectable zone of inhibition around or under specimen	Pass
Pyrogen	ISO 10993-11	< 5°C increase in body temperature	Pass
Hemolysis	ISO 10993-4	< 5% hemolysis	Pass
Sterility	ISO 11737-2	No evidence of microbial growth	Pass
Endotoxin (LAL)	ANSI/AAMI ST72, USP <161>, USP <85>	<0.00500 EU/mL	Pass
Subchronic Toxicity	ISO 10993-11	No signs of toxicity	Pass
Implantation	ISO 10993-6	No signs of tissue reactivity or inflammation	Pass
Virus Inactivation	ISO 22442-3	Steps in manufacturing process must inactivate select viruses	Pass

Evaluation Of The Bone Regenerating Effects of SigmaGraft Bone Graft as Compared to Geistlich Bone Graft In A Critical Sized Supra-alveolar Defect Model

- 2-wall defect
  - 4, 8, and 12 weeks
  - 9 animals per group
  - SigmaGraft, Geistlich, empty
- 5-wall defect
  - 12 weeks
  - 6 animals
  - SigmaGraft, Geistlich, empty



GRAFT Biomaterials

Surgical Procedure

- Access the bone
- Removal of the third and fourth mandibular premolars
- Drilled a 6 mm depth by 6 mm diameter hole
  - Stop for group 4
- Removed residual bone on the buccal or lingual aspect of the drill hole and squared the mesial and distal wall create a 6 mm deep by 6 mm long defect

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Empty	SigmaGraft	Geistlich
		
		
		

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5-Wall Defect

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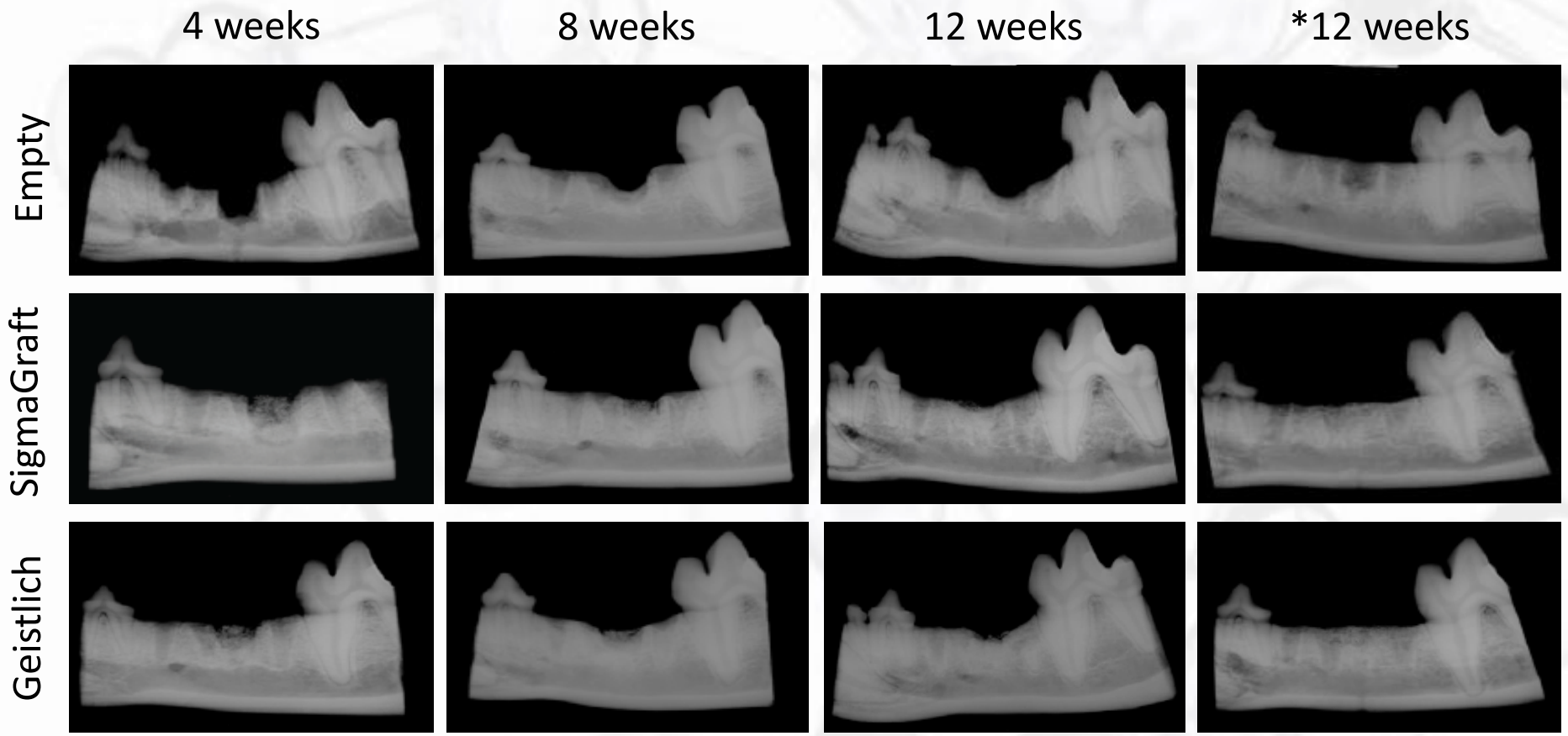
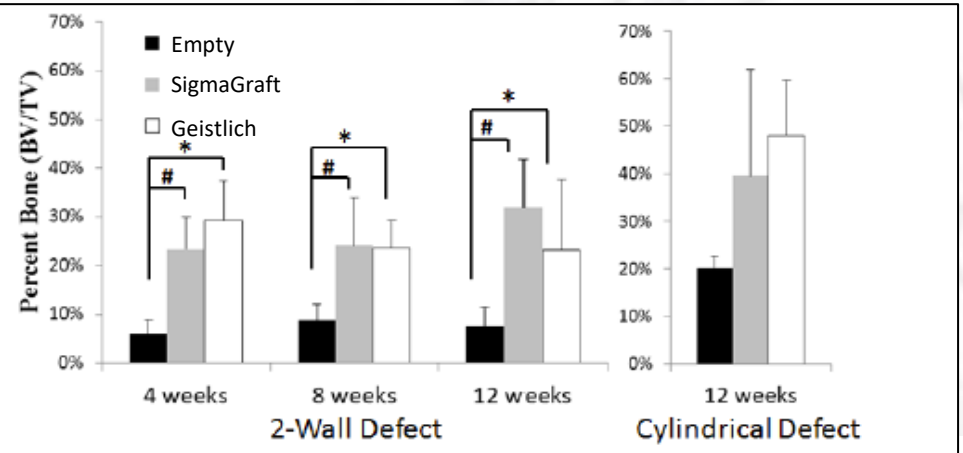
Mean Faxitron Scores

	4 Weeks	8 Weeks	12 Weeks	*12 Weeks
SigmaGraft	0.167	0.833	1.000	1.500
Geistlich	0.167	0.667	0.833	2.000
P-value	1.00	0.545	0.531	1.00

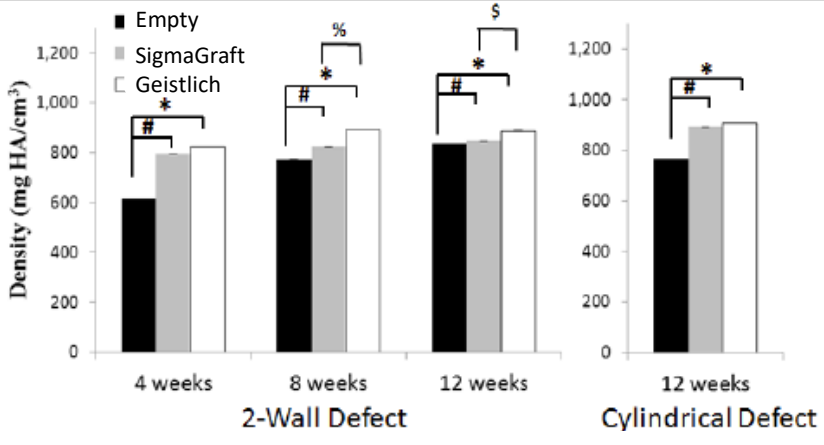


GRAFT Biomaterials

Micro-CT

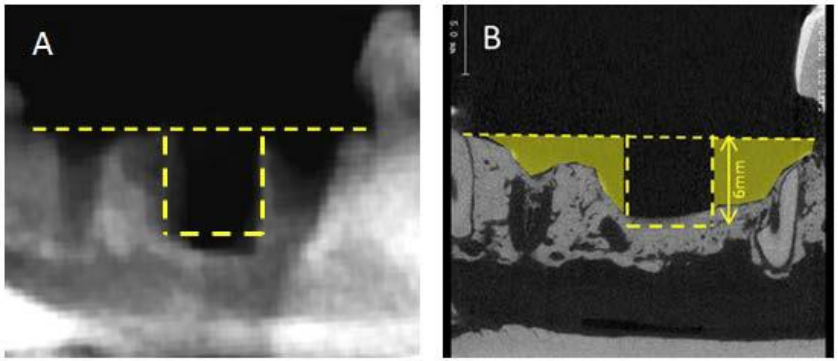


Average percent Bone (Bone + Graft). Statistical differences were observed for the following: # SigmaGraft and the empty control (P<0.01). *Geistlich and the empty control (P<0.01).



Mean mineralized density. Statistical differences were observed for the following: #SigmaGraft and the empty control (p <0.0), *Geistlich and the empty control (p < 0.05), %SigmaGraft and Geistlich at 8 weeks (p < 0.01) and $SigmaGraft and Geistlich at 12 weeks.

- Lack of a bone void filler in the empty controls led to excessive erosion of the mesial and distal alveolar bone surrounding the defect



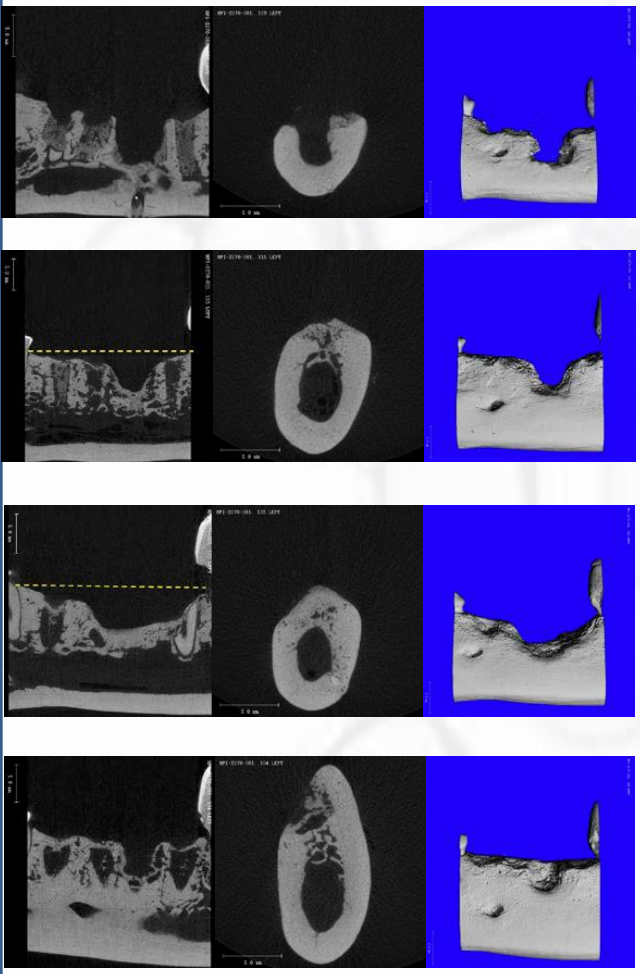
GRAFT Biomaterials

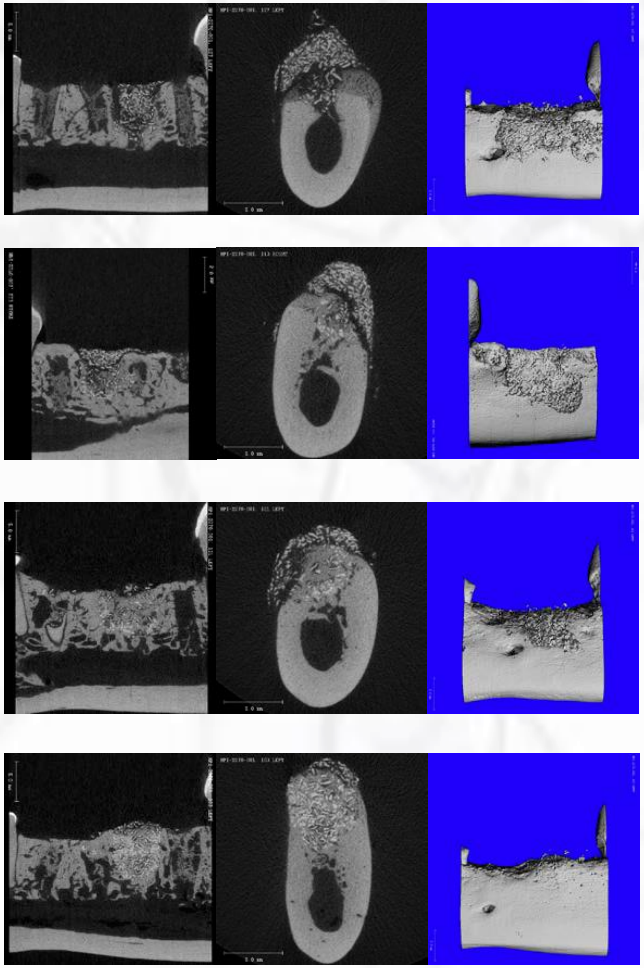
Micro-CT

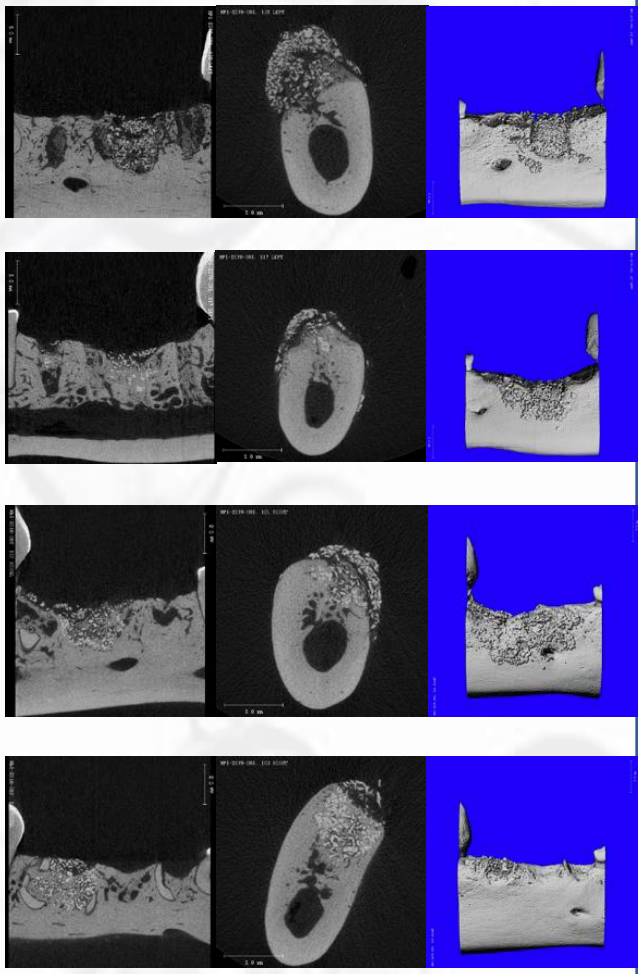
Empty

SigmaGraft

Geistlich



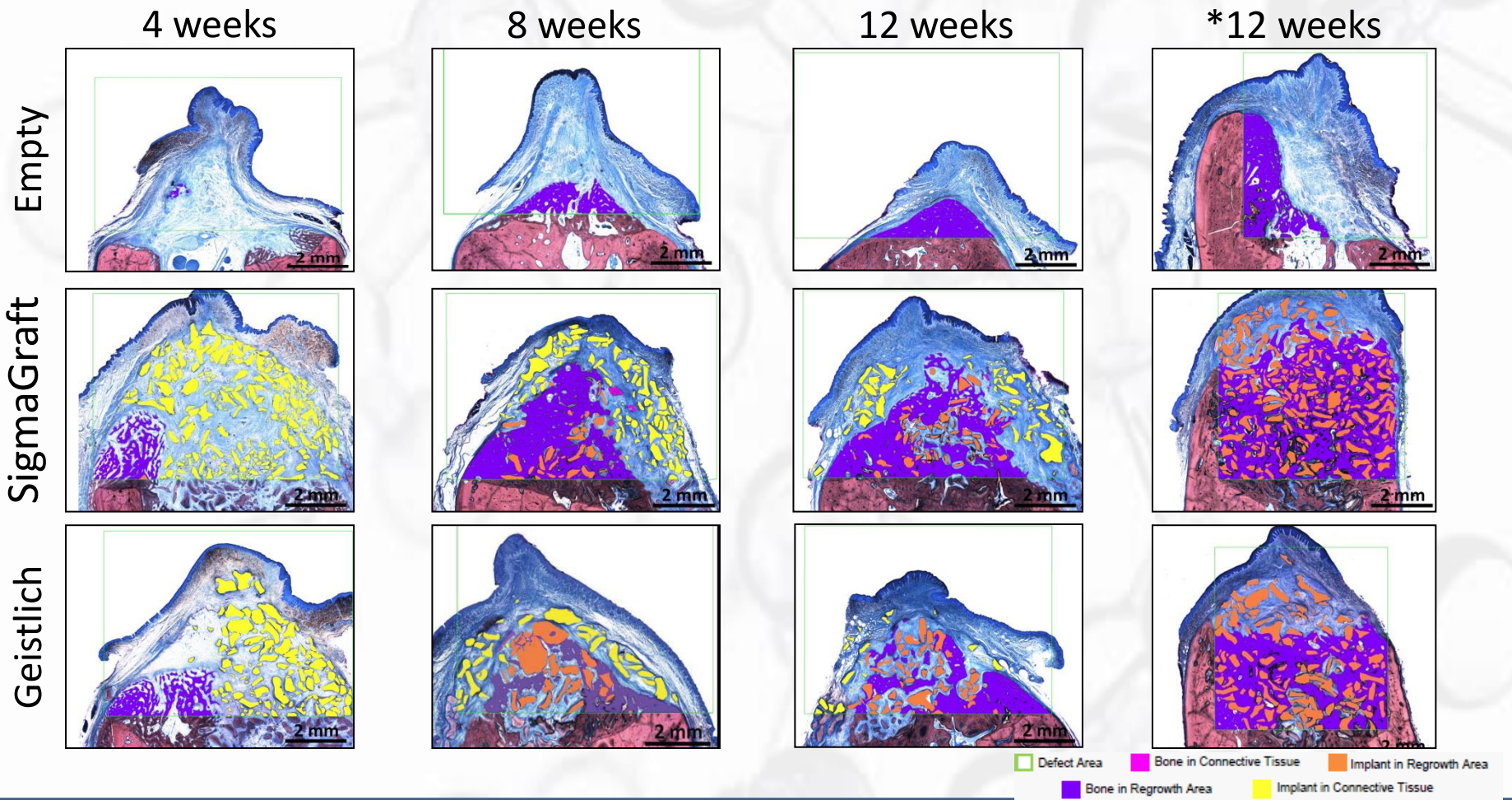




GRAFT Biomaterials

Residual Implant Material

	4 Weeks	8 Weeks	12 Weeks	*12 Weeks
SigmaGraft	2.8 ± 0.4	2.7 ± 0.5	2.5 ± 0.8	2.3 ± 0.6
Geistlich	3.0 ± 0.0	2.3 ± 0.5	2.5 ± 0.5	2.5 ± 0.5
P-value	0.283	0.713	1.000	0.140



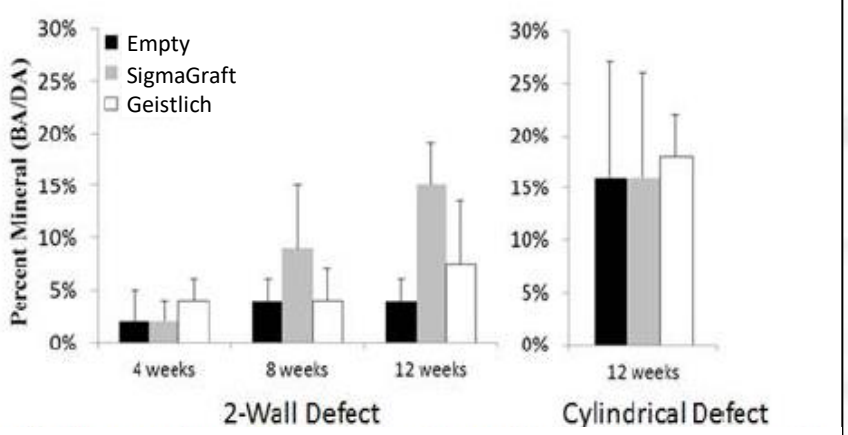
GRAFT Biomaterials

Inflammatory Response

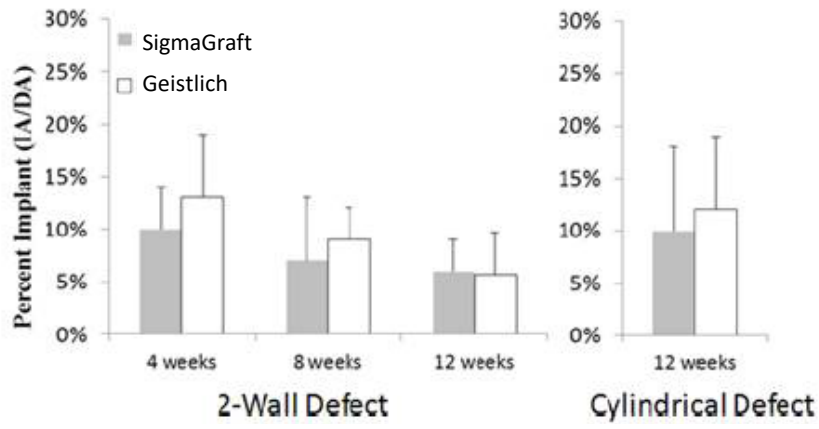
n=6	SigmaGraft (4)	Geistlich (4)	Empty (4)		SigmaGraft (8)	Geistlich (8)	Empty (8)
Polymorphonuclear (PMN) Leukocytes	0.2 ± 0.4	0.0 ± 0.0	1.0 ± 0.9		0.0 ± 0.0	0.2 ± 0.0	0.0 ± 0.0
Lymphocytes	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Plasma Cells	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Macrophages	1.0 ± 0.0	1.2 ± 0.4	0.8 ± 0.8		1.5 ± 0.5	1.5 ± 0.5	0.3 ± 0.8
Giant Cells	1.2 ± 0.4	1.0 ± 0.6	0.0 ± 0.0		1.2 ± 0.4	0.3 ± 0.5	0.2 ± 0.4
Necrosis	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Fibrosis	3.0 ± 0.0	3.0 ± 0.0	3.3 ± 0.8		2.5 ± 0.5	2.3 ± 0.5	2.3 ± 0.8
Fatty Infiltrate associates with Fibrosis	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Neovascularization associates with Fibrosis	1.8 ± 0.4	2.0 ± 0.0	2.2 ± 0.4		2.0 ± 0.0	2.0 ± 0.0	1.8 ± 0.4

n=6	SigmaGraft (12)	Geistlich (12)	Empty (12)		SigmaGraft (*12)	Geistlich (*12)	Empty (*12)
Polymorphonuclear (PMN) Leukocytes	0.3 ± 0.8	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Lymphocytes	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Plasma Cells	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Macrophages	1.2 ± 0.4	1.0 ± 0.0	0.2 ± 0.4		1.0 ± 0.0	1.0 ± 0.0	0.0 ± 0.0
Giant Cells	1.0 ± 0.0	1.0 ± 0.0	0.2 ± 0.4		1.0 ± 0.6	1.0 ± 0.0	0.0 ± 0.0
Necrosis	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Fibrosis	2.7 ± 0.5	2.0 ± 0.0	1.8 ± 0.4		2.3 ± 0.5	2.0 ± 0.0	2.3 ± 0.6
Fatty Infiltrate associates with Fibrosis	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Neovascularization associates with Fibrosis	2.0 ± 0.0	2.0 ± 0.0	1.8 ± 0.4		2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0

Percent Bone and Percent Residual Implant by Area



Histomorphometry. Percent bone by area for the treatment group. No statistical differences were observed between treatments.



Histomorphometry. Percent residual implant by area for the test article and predicate groups. No statistical differences were observed between treatments.

- SigmaGraft bone graft had higher or equal to percent bone by area compared to Geistlich
- SigmaGraft bone graft had less than or equal to percent residual implant by area compared to Geistlich

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Conclusion

- By all parameters assessed, SigmaGraft bone graft treated defects were indistinguishable from those treated with the Geistlich bone graft
- When compared to empty controls, both grafts showed statistically greater amounts of bone present within the defect sites
- Both bone grafts contributed to alveolar ridge preservation
- Histomorphometry supports the similarity in performance of SigmaGraft and Geistlich bone grafts
  - No statistically significant differences were observed with regards to percent bone, percent residual implant and percent bone marrow values
- While not significantly different, SigmaGraft bone graft had a higher mean percent bone value as compared to Geistlich bone graft at 4, 8 and 12 weeks.
- The amount of inflammation present was on the low end of the spectrum and is indicative of a good biocompatibility response that would not interfere with healing

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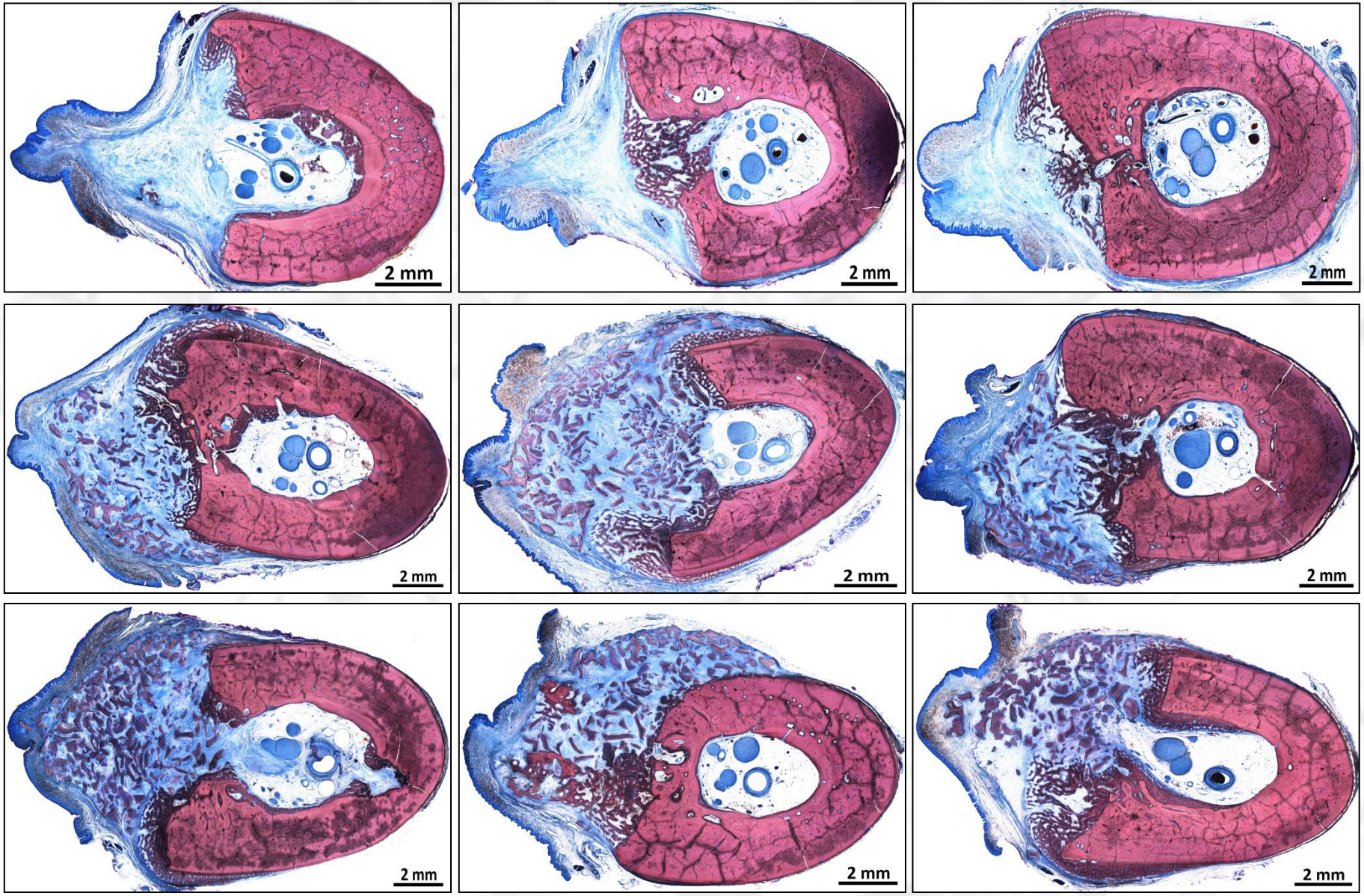
4 Weeks



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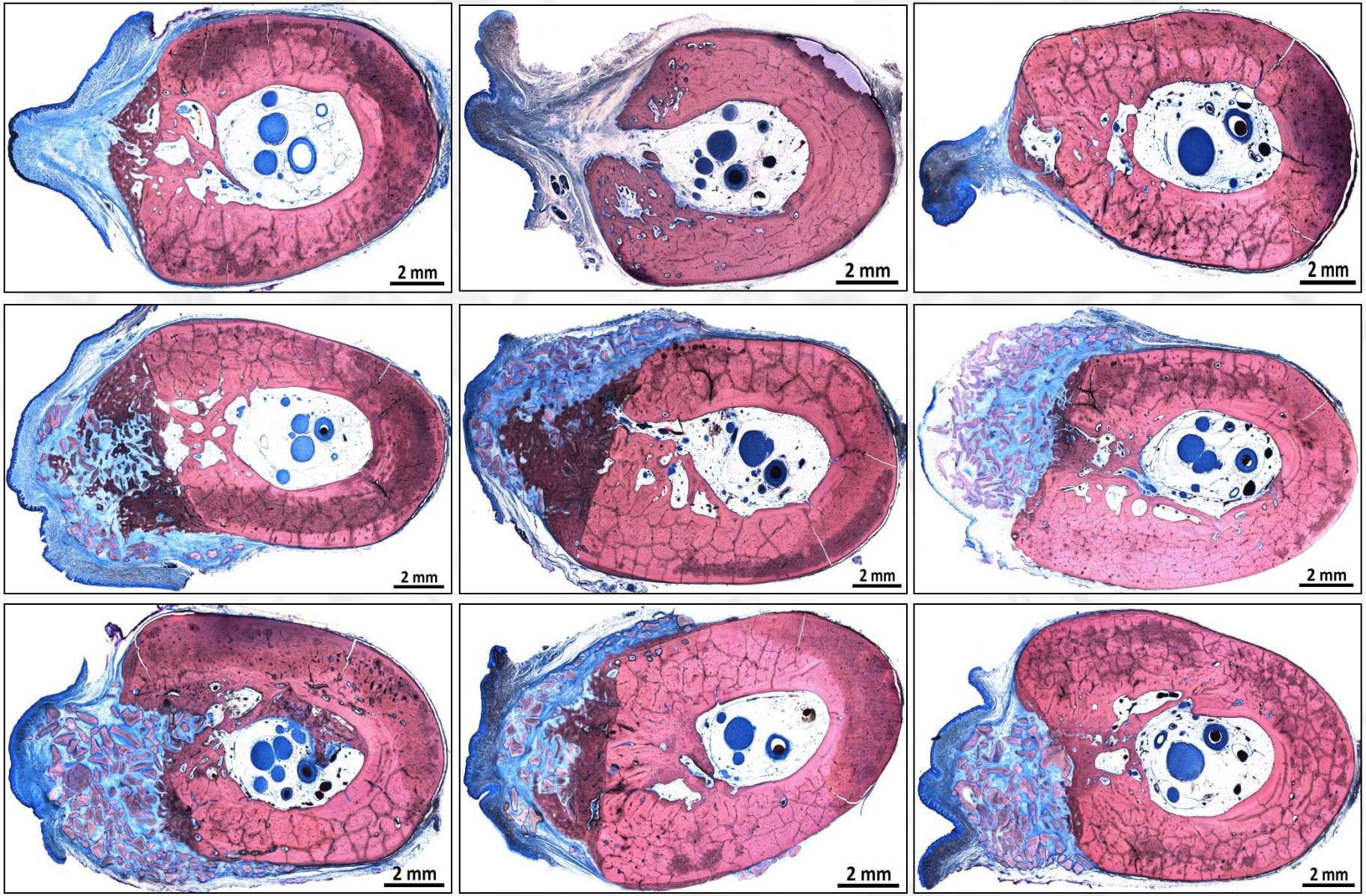
8 Weeks



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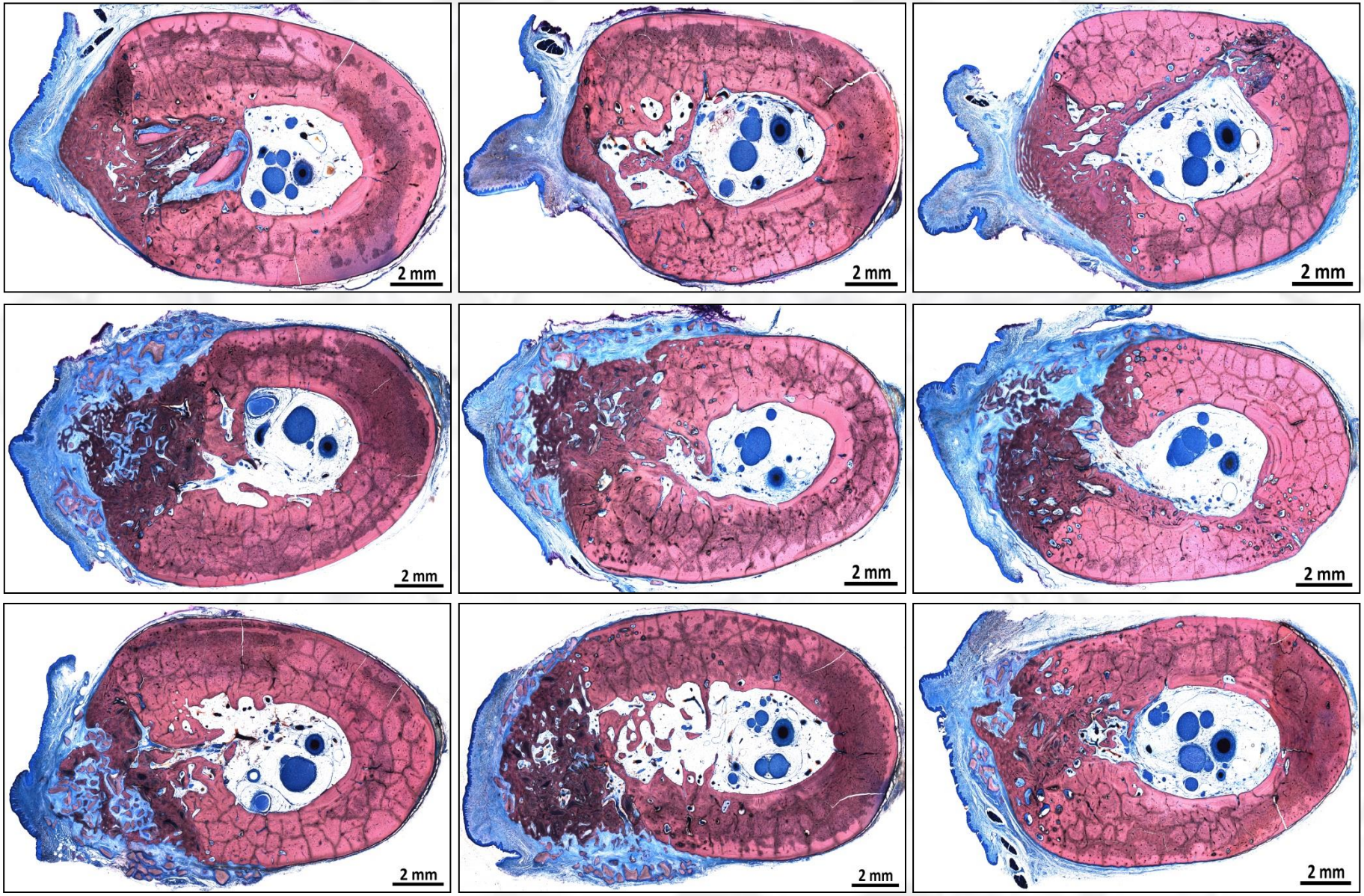
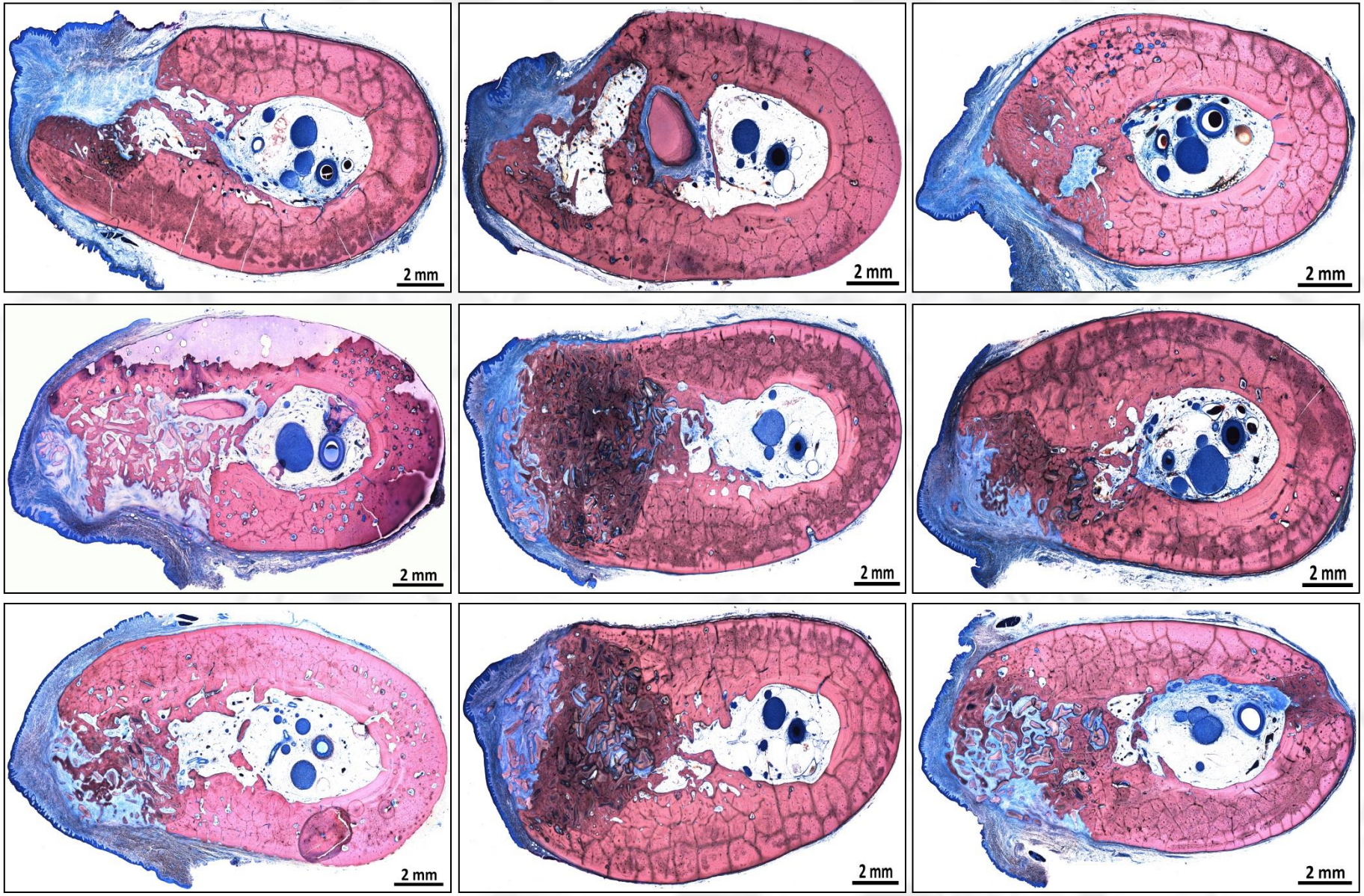
12 Weeks



GRAFT Biomaterials

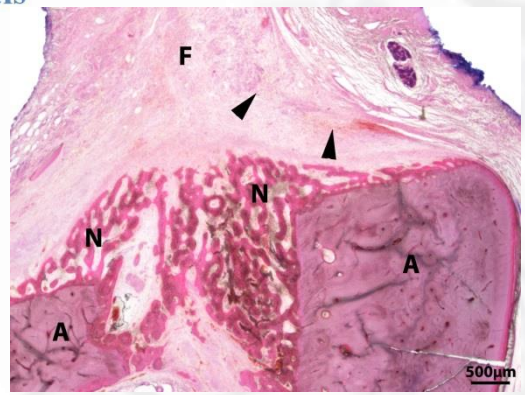
*12 Weeks

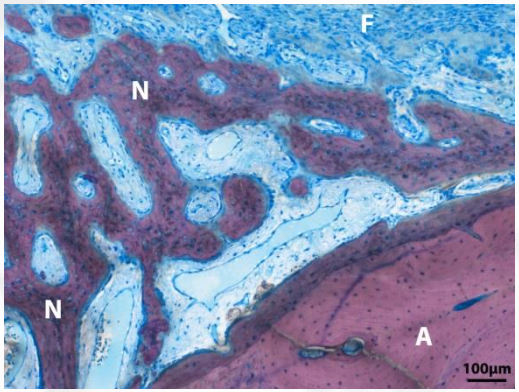


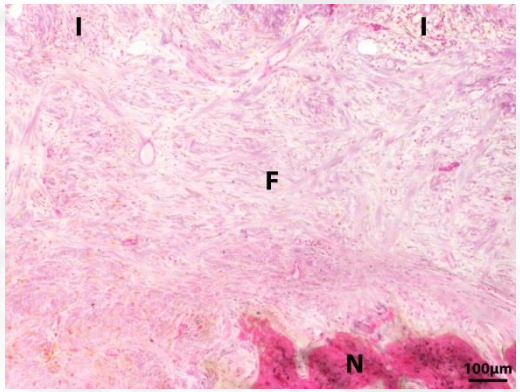
GRAFT Biomaterials

4 Weeks

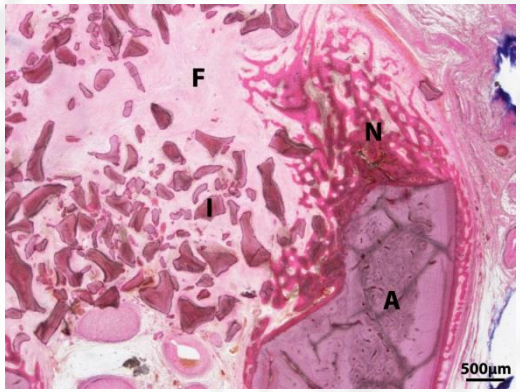
Empty

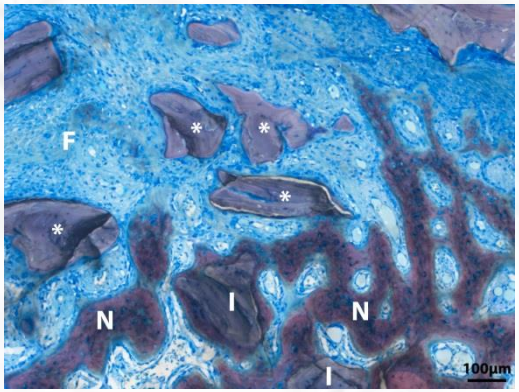


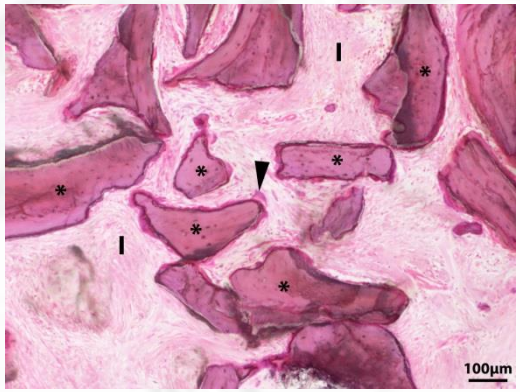




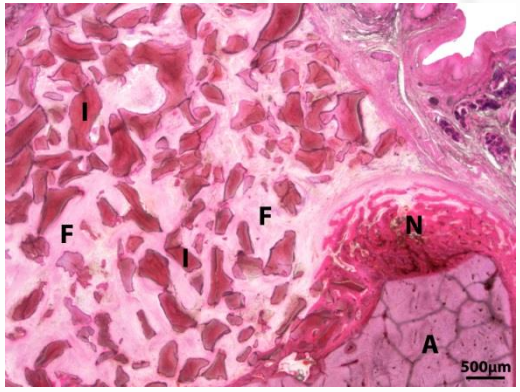
SigmaGraft

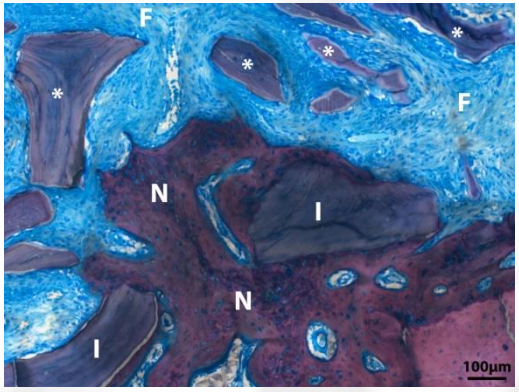


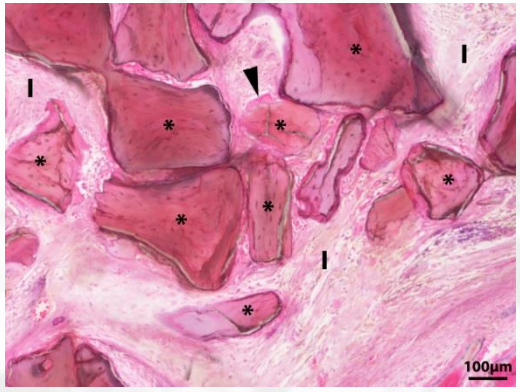




Geistlich







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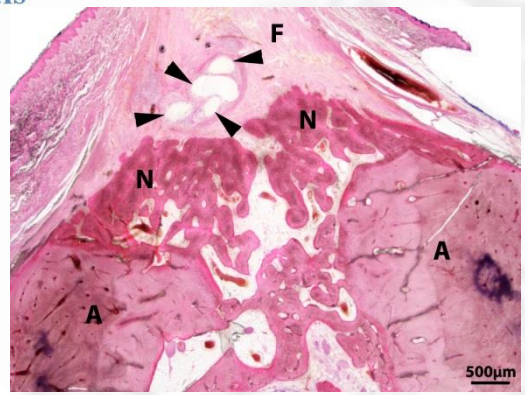
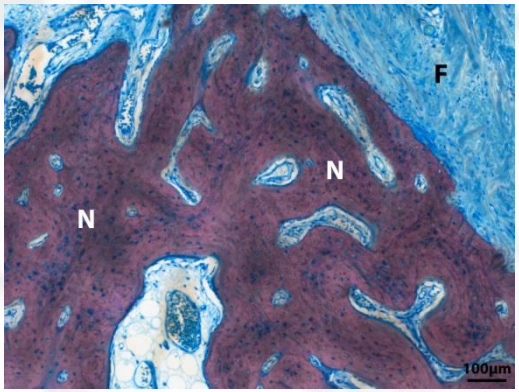
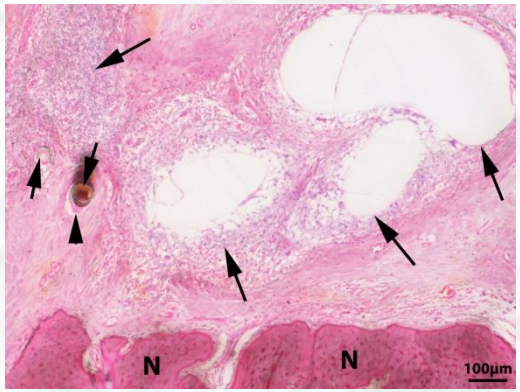
8 Weeks

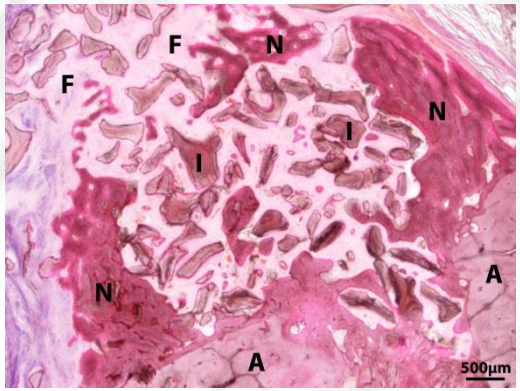
Empty

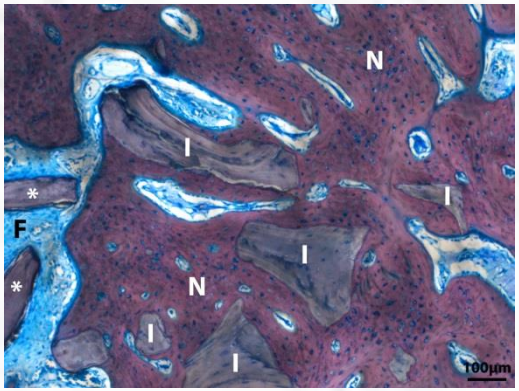




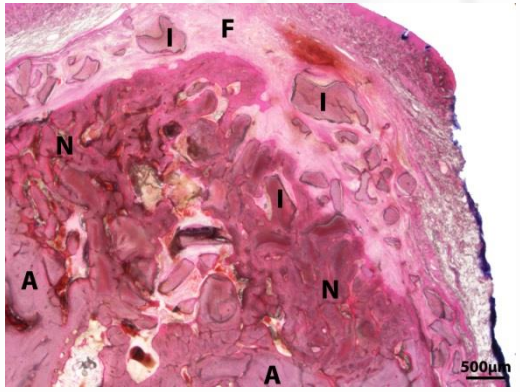


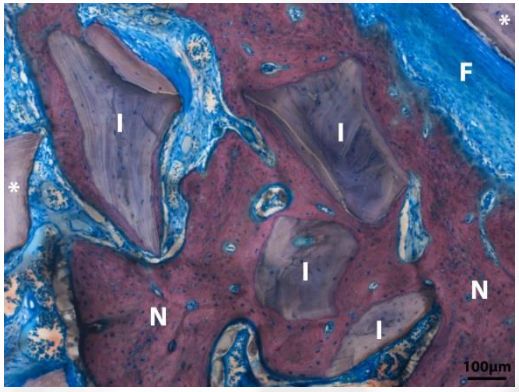
SigmaGraft





Geistlich

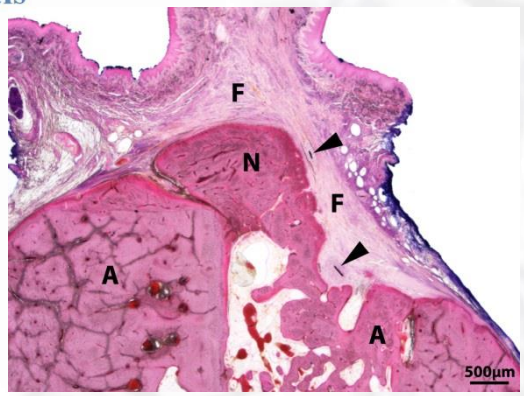


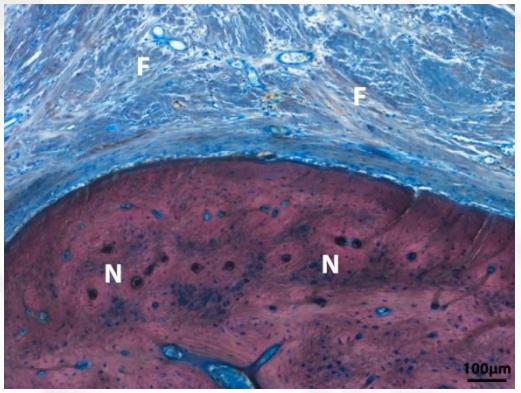


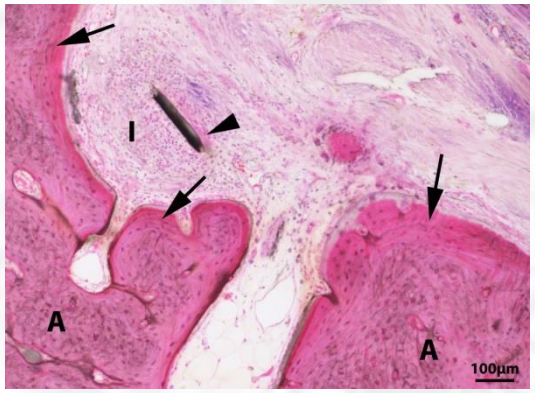
GRAFT Biomaterials

12 Weeks

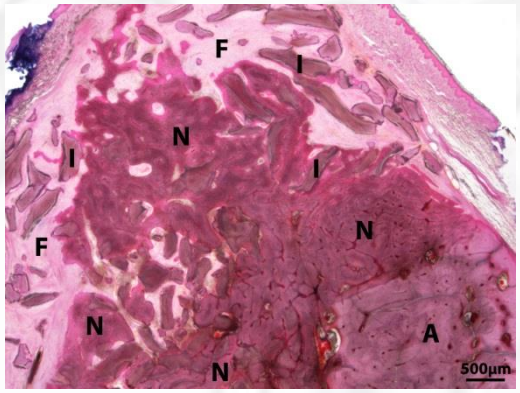
Empty

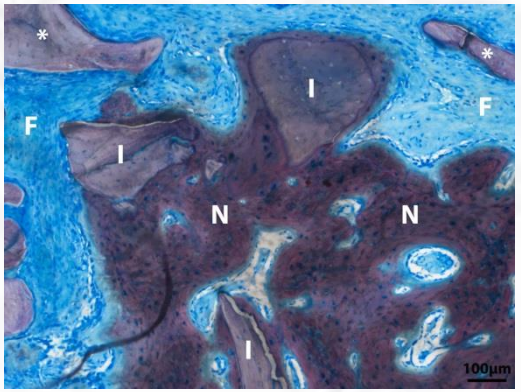




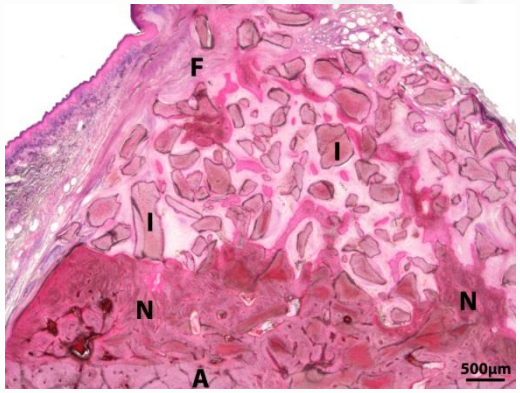


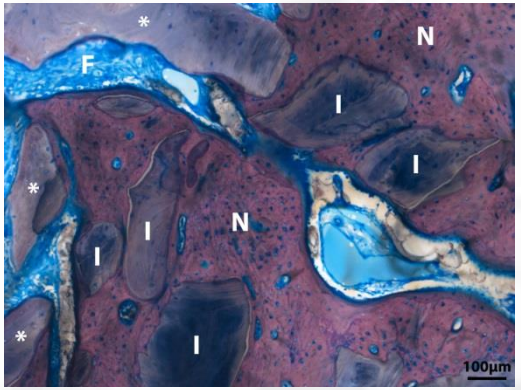
SigmaGraft

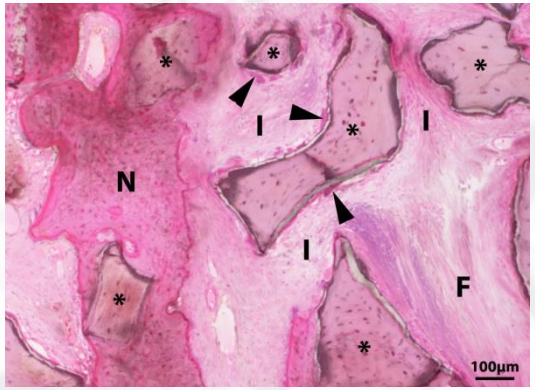




Geistlich



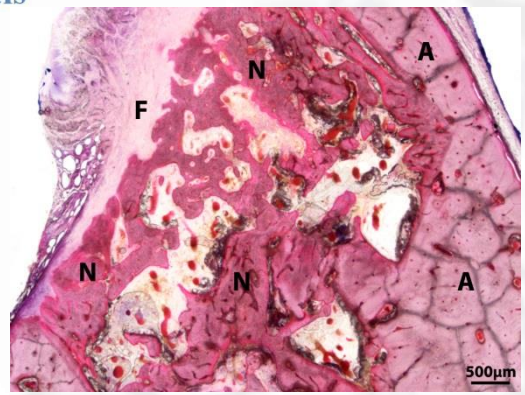


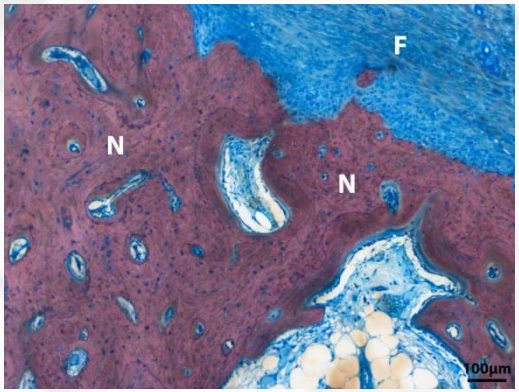


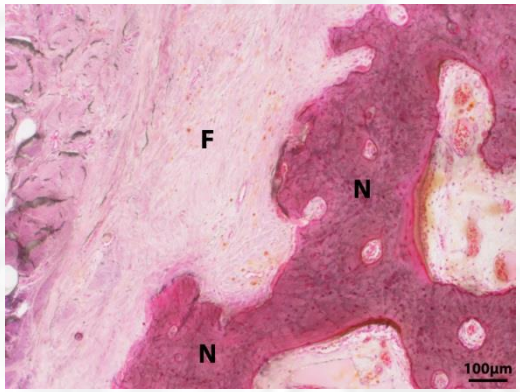
GRAFT Biomaterials

12* Weeks

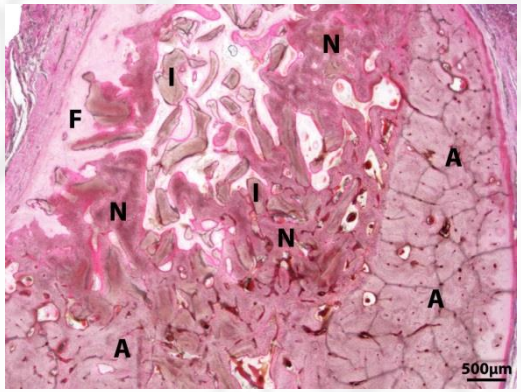
Empty

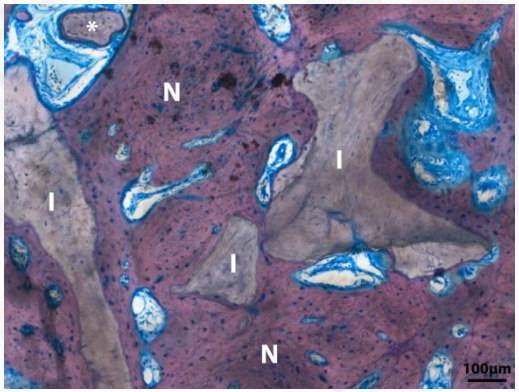


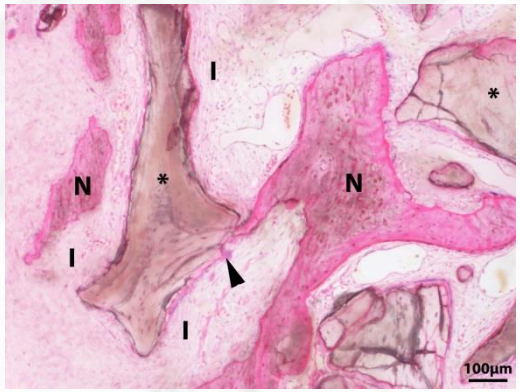




SigmaGraft







Geistlich