

Dept. of Cranio-Maxillofacial and Oral Surgery
Oral Biotechnology & Bioengineering

3D-printed bone substitutes
From pores to adaptive density
minimal surface microarchitectures

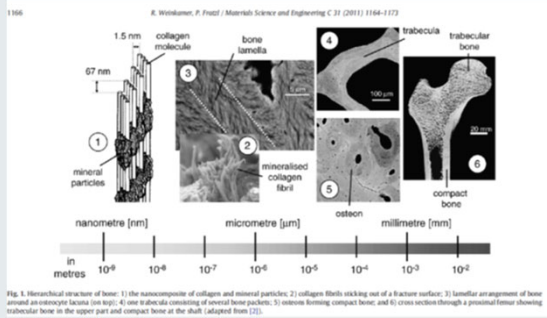
Franz E. Weber
Prof. Dr. rer. nat. habil.



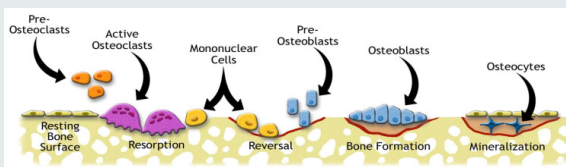
Universität Zürich

USZ Universitäts
Spital Zürich

Hierarchy of bone structure



Bone remodeling



University of Michigan, <http://www.umich.edu/news/index.html?Releases/2005/Feb05/r022005>

Osteoclast

University of Maastricht | <https://www.unima.nl/en/department/physiology>

- RB: ruffled border
- BL: basolateral membrane
- FSD: functional secretory domain
- VT: vesicular transport (transcytosis)

Modified from H.J. Birk, 2003; H.K. Vaheri, 2005

UniversityHospital Zurich | 06.09.2024 | Slide 4

Osteoclast in action

Breakfast, lunch and dinner for an osteoclast!
Alan Boyde, Bone Research Society

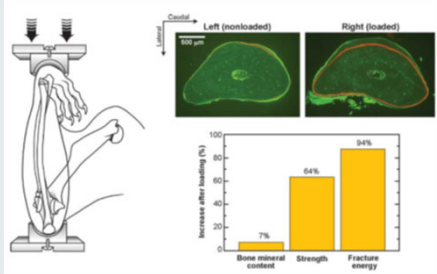
UniversityHospital Zurich | 06.09.2024 | Slide 5

Osteoblasten
Weber FE, Lethaus B (2022) Osteoblast. Cell-to-Cell Communication: Cell-Atlas
- Visual Biology in Oral Medicine ed. Gruber, Stadlinger, Terhyden
QUINTESSENCE PUBLISHING DEUTSCHLAND ISBN: 978-1-78698-107-3 or
QUINTESSENCE PUBLISHING Great Britain ISBN: 978-1-78698-107-3.

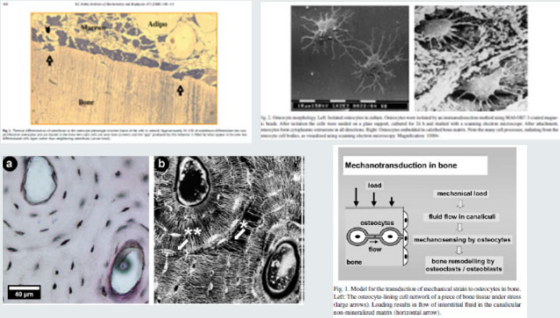
Mineralizing osteoblast

UniversityHospital Zurich | 06.09.2024 | Slide 6

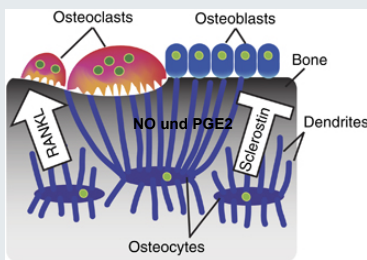
Bone remodeling depends on mechanical load



Osteocyte senses load




Osteocyte orchestrates bone remodeling



Nakashima T, et al. Nat Med 2011;17:1231-1234.

Autologous bone is still the gold standard bone substitute



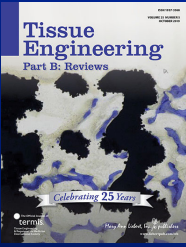
Mandibular reconstruction following tumor resection by using titanium plates and screws

Osteoconduction

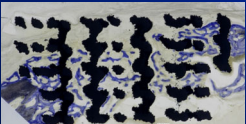
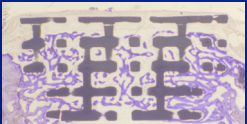
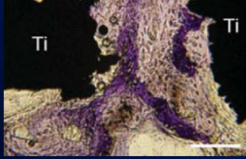
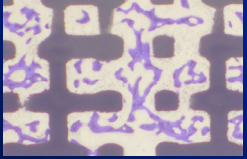
termis
Tissue Engineering & Regenerative Medicine International Society

REVIEW ARTICLE
Reconsidering Osteoconduction in the Era of Additive Manufacturing
Franc E. Weber, PhD^{1,2*}

Osteoconduction:
Three-dimensional process of ingrowth of sprouting capillaries, perivascular tissue, and osteoprogenitor cells from a **bony bed** into the three-dimensional structure of a porous implant to use it as **guiding cue** to **bridge the defect** with bony tissue.



Osteoconduction myths
bone to implant contact (BIC)


<p>Titan</p> 	<p>CaP</p> 
<p>The initial formed woven bone (blue) lays mainly between the titanium surfaces and is covered with later formed lamellar bone (greyish-light blue)</p>	<p>In areas with bone and material, bone to implant contact is only 10-20% of the implant surface</p>
	

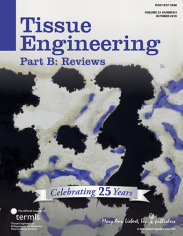
Osteoconduction

REVIEW ARTICLE

Reconsidering Osteoconduction in the Era of Additive Manufacturing



Franz E. Weber, PhD^{1,2,3}








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Autologous bone is still the gold standard bone substitute

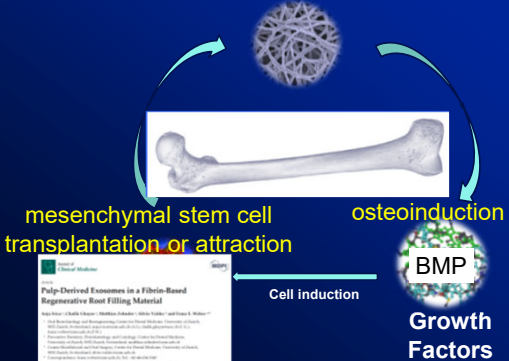
Mandibular reconstruction following tumor resection by using titanium plates and screws


Fibula (Wadenbein)

Principles of bone tissue engineering

Biomaterial Scaffold



mesenchymal stem cell transplantation or attraction



osteoinduction

BMP

Growth Factors

Cell induction

The bone inducing principle

1963 **Urist et al.** 1989 **Wozney et al.** 2002 **FDA approval**

time

Jung, Glauser, Schaefer, Hämmerle, Sailer, Weber FE Clin. Oral Impl. Res. (2003)

Surface fraction of Bio-Oss in direct contact with newly-formed bone

30% (SD 22.6, range 0-66%) * 57% (SD 16.2, range 29-81%)

control * statistically significant (paired t test, p<0.01) test

Synthetic material with cell based regeneration: PEG-Gel

Lutolf, Weber FE, Schmökel, Müller, Hubbell Nature Biotechnology (2003)

control

PEG-Gel with BMP

8 mm defect

Principles of bone tissue engineering

Biomaterial Scaffold

osteoco

2014 - 2024 3D-printed microarchitectures
16 papers 495 citations
2023-2024 zero mesh curvature microarchitectures
4 papers 16 citations in 6 months

meser
transpla

Published October 2023
is already cited 9 times

ORIGINAL ARTICLE

Triply Periodic Minimal Surface-Based Scaffolds for Bone Tissue Engineering: A Mechanical, *In Vitro* and *In Vivo* Study

Ekaterina Mavrikakis, MS¹, Julien Guerrero, PhD¹, Chafik Ghayor, PhD¹, Indrani Bhattacharya, PhD¹, and Franz E. Weber, PhD^{1,2}

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Tissue Engineering & Regenerative Medicine International Society

Open access to all reader and scan code to access the article and other resource online

Additive manufacturing

GrapCap

Source: Rapid manufacturing association

Additive Manufacturing of bone substitutes

Micro architecture

Conventional porous bone substitutes

- > Pores randomly distributed
- > Bottle necks vary in size

bone substitutes by additive manufacturing

- > defined location of pores
- > defined bottle necks

Additive manufacturing


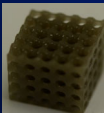
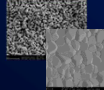
Integration into clinical workflow

Work flow vom CT file to stl-file for AM

Information about the defect dimension = macroarchitecture of the defect

Stl-file with information of the macroarchitecture of the defect enables the production of personalized bone substitutes

Architecture of bone substitutes

Macroarchitecture

e.g. the shape of the bone defect

Can be realized by additive manufacturing


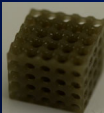
Microarchitecture

Distribution of material in the scaffold defines pore distribution, pore interconnection

Nanoarchitecture

Features of surface and the interior of material
e.g. roughness, microporosity,.....

Architecture of bone substitutes

Macroarchitecture

1. Personalized bone substitute

Additive manufacturing facilitates the control over macro- and microarchitecture and puts bone tissue engineering to the next level

Microarchitecture

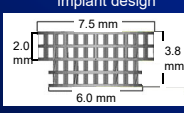
2. Highly osteoconductive bone substitute

Which is the optimal microarchitecture to speed up the healing of a bone defect?

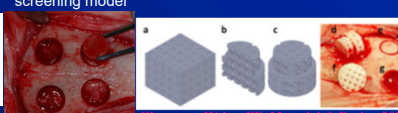
Titanium based scaffold

Rapid prototyping/selective laser melting

implant design

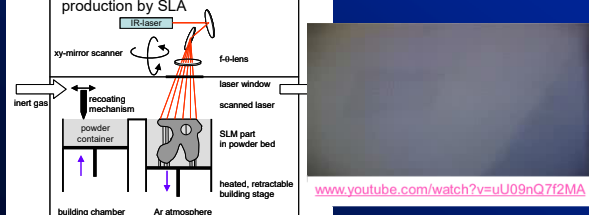


screening model



Ghayer, ..., Weber FE. Material & Design 2021

production by SLA

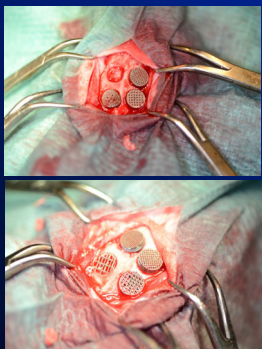



www.youtube.com/watch?v=uU09nQ7f2MA

de Wild, Schumacher, ..., Weber FE. Tissue Engineering 2014

Titanium based scaffold: lattice

Rapid prototyping/selective laser melting

Konstante Strahendurchmesser (S)
S=0.2 mm; Ø=0.2 mm

S=0.2 mm; Ø=0.466 mm

S=0.2 mm; Ø=0.9 mm

S=0.2 mm; Ø=1.3 mm

S=0.2 mm; Ø=1.8 mm

S=0.2 mm; Ø=0.466 mm

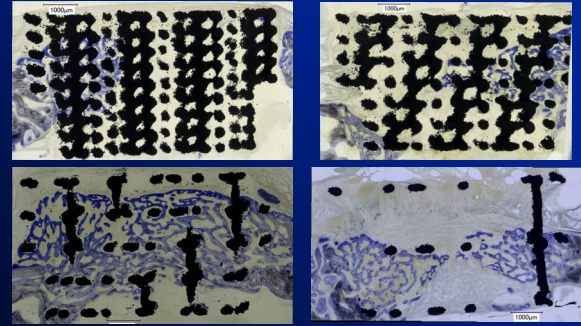
S=0.553 mm; Ø=0.466 mm

S=1.553 mm; Ø=0.466 mm

de Wild, ..Weber 3DPrinting&AM (2018)

Titanium based scaffold: lattice

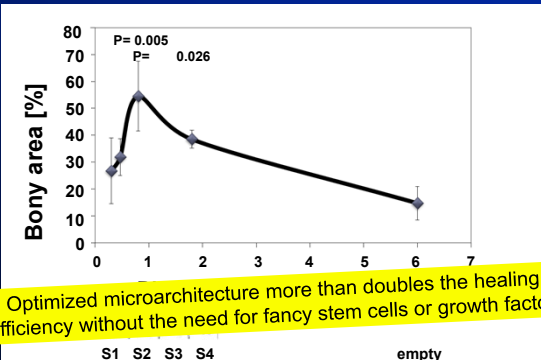
Rapid prototyping/selective laser melting



de Wild, ..Weber 3DPrinting & Additive manufacturing (2018)

Titanium based scaffold: lattice

Rapid prototyping/selective laser melting

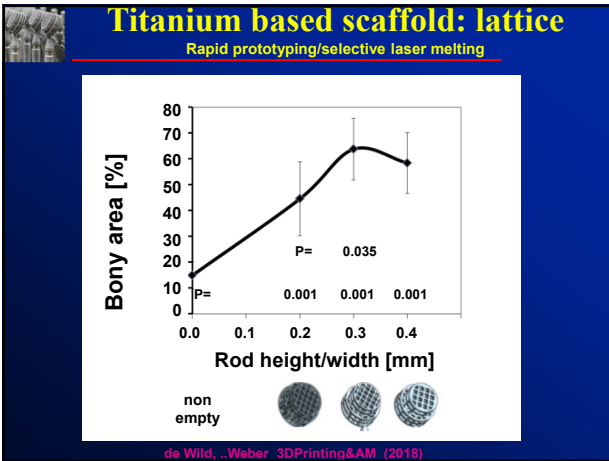


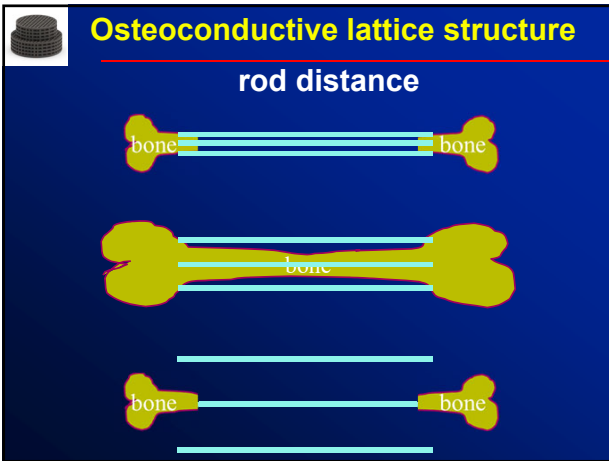
Group	Bony area [%]
S1	~30
S2	~55
S3	~40
S4	~35
empty	~15

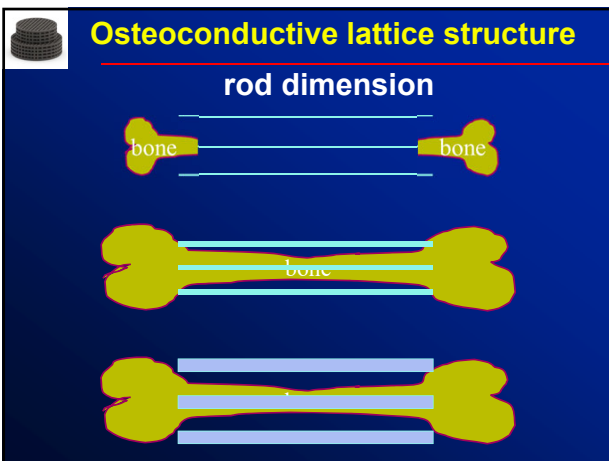
P= 0.005 (S1 vs S2), P= 0.026 (S2 vs S3)

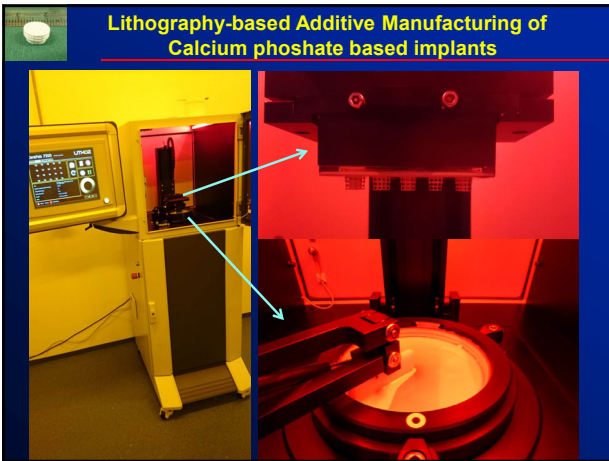
Optimized microarchitecture more than doubles the healing efficiency without the need for fancy stem cells or growth factors

de Wild, ..Weber 3DPrinting & Additive manufacturing (2018)

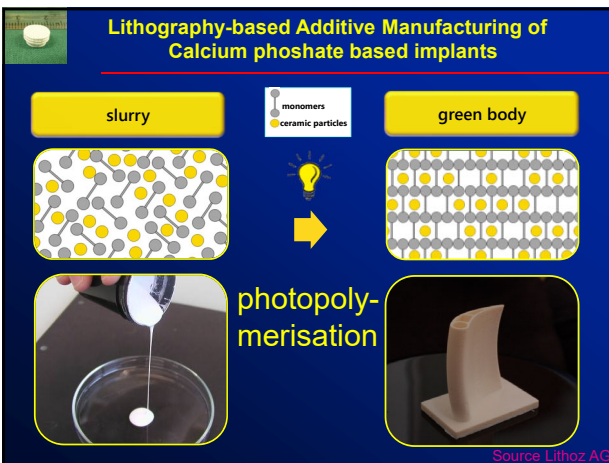












Lithography-based Additive Manufacturing of Calcium phosphate based implants

Post processing of the green body

after building after debinding after sintering

photopolymer ceramic particle (up to 60 vol%) dense material (>99,4 % T.D.)

temperature ↑

time →

Quelle Lithoz AG

Lithography-based Additive Manufacturing of Calcium phosphate based implants

Debinding and sinter yields in:

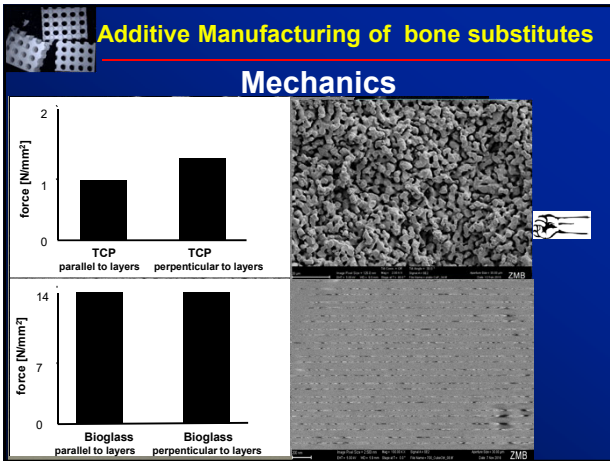
- Initially, no biological materials can be used (proteins, cells, bioactive substances)

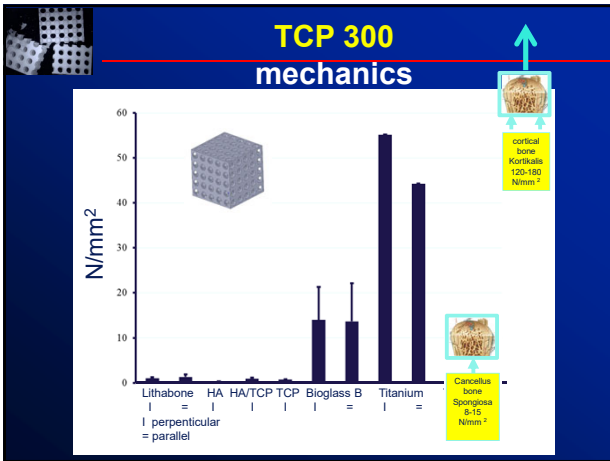
AREA TECH 51
Real tech advice, new, less methods, and the singularity

Lithography-based Additive Manufacturing of Calcium phosphate based implants

Debinding and sinter yields in:

- no biological materials can be used initially (proteins, cells, bioactive substances)
- Bioglass will transform from an amorphous to a crystalline state, will become a glass ceramic, and loose bioactivity .





Lithography-based Additive Manufacturing of Calcium phosphate based implants

Debinding and sintering yields in:

446 T. Goto et al.: Resorption of synthetic porous HA

Table 1. Review of biodegradability of synthetic HA materials and their features

Investigator	Year	Subject	Sintering temperature	Porosity	Pore diameter (µm)	Follow-up period	Biodegradable
Winter et al. ²⁹	1981	Rat	900°C	1%	?	1 m-6 m	Yes
		Rat	1200°C	1%	?	1 m-6 m	Yes
		Rat	1200°C-1300°C	20%	?	1 m-6 m	?
Klein et al. ⁴	1983	Rabbit	1100°C	40%	?	9 m	No
		Rabbit	1300°C	3%	?	9 m	No
Hoogendoorn et al. ¹	1984	Dog	1300°C	56%	480	~3.5 y	No
Renoij et al. ¹³	1985	Dog	1300°C	56%	180	1 y	No
van Blitterswijk et al. ¹⁸	1985	Rat	?	26%	100	1 w-1 y	Yes
van Blitterswijk et al. ¹⁸	1986	Rat	?	<5%	3	1 w-1 y	Yes
		Rat	?	26%	100	1 w-1 y	Yes
Kurosawa et al. ¹⁴	1987	Human	900°C	82%	280	1 y 3 m	Yes
Kurosawa et al. ¹⁴	1989	Dog	900°C	85%	282	2 y	Yes
		Dog	1200°C	85%	230	2 y	Yes
Ushida et al. ¹⁶	1990	Human	1200°C	55%	?	6 m-5 y	Very slightly
Inoue et al. ⁴	1993	Human	900°C	70%	90	1 y 3 m-3 y 4 m	Yes
Ukagawa et al. ¹⁷	1995	Human	900°C	70%	90 or 200	5 y-7 y 9 m	Yes
Yoshida et al. ¹⁵	1995	Human	900°C	70%	90 or 200	5 y-8 y 2 m	Yes
Ubayama et al. ¹⁸	1997	Human	900°C	70%	90 or 200	6 m-8 y 5 m	Yes

HA, Hydroxyapatite; ?, not stated; m, month; y, year; w, week



Lithography-based Additive Manufacturing of Calcium phosphate based implants

Demand for debinding and sinter yields in:

1. no biological materials can be incorporated initially (proteins, cells, bioactive substances)
2. Bioglass will transform from an amorphous to a crystalline state, will become a glass ceramic, and lose bioactivity (above 500°C.)
3. Calcium phosphates (HA) will lose their degradability, since temperatures above 900°C will increase crystal size and favor crystal perfection.

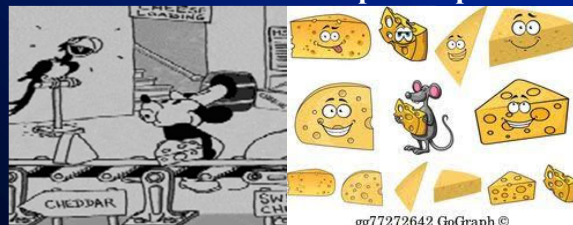
TCP-based scaffolds

Pores and bottlenecks

de Wild, Schumacher, ... Weber FE 3D printing and additive manufacturing (2016)



Switzerland is famous for porous products



Disney.com gg77272642 GoGraph ©

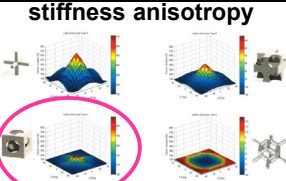
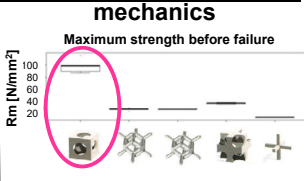
TCP-based scaffolds

Pores and bottlenecks


de Wild, Schumacher, ... Weber FE 3D printing and additive manufacturing (2016)

Basic design elements influence

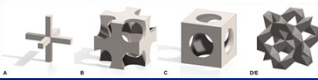
stiffness anisotropy	mechanics
	<p>Maximum strength before failure</p> 

TCP-based scaffolds

Pores and bottlenecks


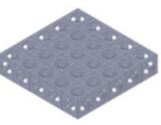
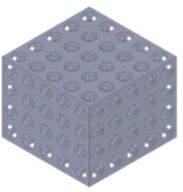
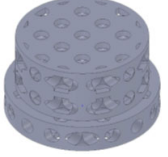


pore Bottleneck



de Wild, Schumacher, ... Weber FE 3D printing and additive manufacturing (2016)

Solid works


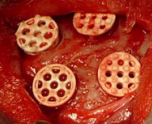
unit cell

Ghayor & Weber FE Frontiers in Physiology (2018); patent pending

TCP-based scaffolds

Pores and bottlenecks


acronym	length of unit cell (mm)	pore diameter (mm)	bottleneck diameter (mm)	porosity (%)	Maximal transparency (%)	
C_19_12_06	C_19_5_5	1.0	0.5	0.5	35.95	19.64
	C_19_07_06	1.0	0.7	0.5	47.40	19.64
	C_19_07_07	1.0	0.7	0.7	52.58	38.48
C_13_10_06	C_13_10_06	1.3	1.0	0.5	47.40	11.61
	C_13_10_07	1.3	1.0	0.7	39.59	22.77
	C_13_10_10	1.3	1.0	1.0	56.00	46.47
C_18_12_07	C_18_12_06	1.5	1.2	0.5	32.04	8.72
	C_18_12_07	1.5	1.2	0.7	37.06	17.10
	C_18_12_10	1.5	1.2	1.0	47.47	34.90
	C_18_12_12	1.5	1.2	1.2	56.96	50.26
	C_18_15_12	1.8	1.5	1.2	47.46	34.90
C_20_17_10	C_20_17_06	2.0	1.7	0.5	35.64	2.42
	C_20_17_07	2.0	1.7	0.7	36.46	9.62
	C_20_17_12	2.0	1.7	1.2	44.87	28.27
	C_20_17_15	2.0	1.7	1.5	52.03	44.17


Ghayor & Weber FE Frontiers in Physiology (2018)

TCP-based scaffolds


Pores and bottlenecks




a



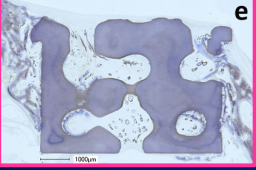
b



c

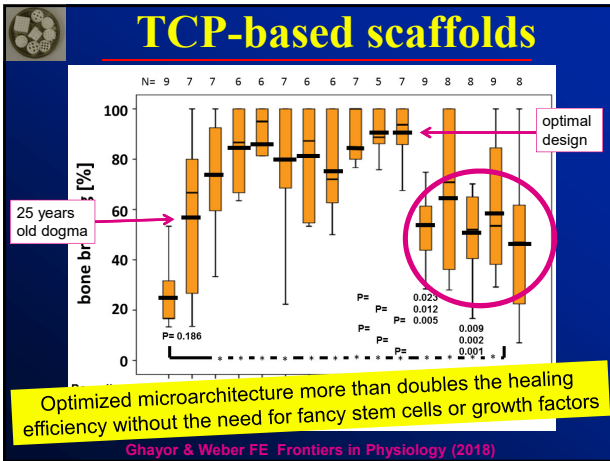


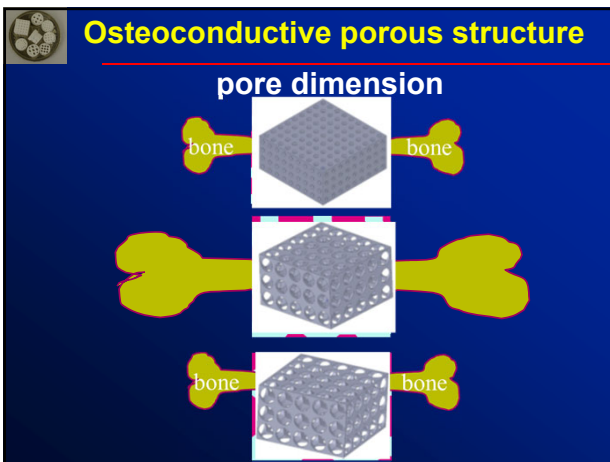
d

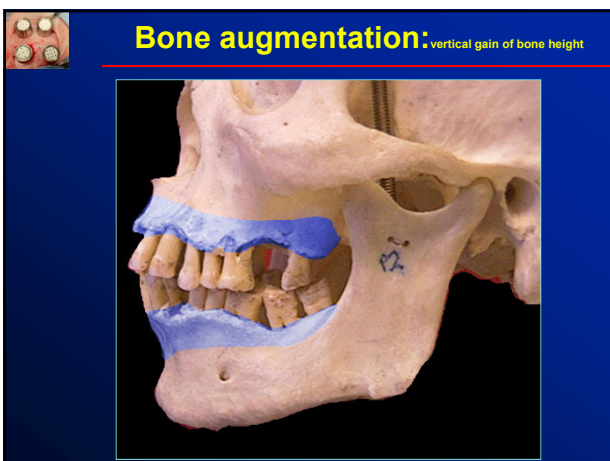


e

Ghayor & Weber FE Frontiers in Physiology (2018)







Bone augmentation

1 // Klassifikation nach Caspod und Howell [4]: 1 bezahnter Kiefer, 2 Kiefer direkt nach Extraktion, 3 abgerundeter Alveolarfortsatz, Höhe und Breite erhalten, 4 Spitzkamm, Höhe erhalten, Breite reduziert, 5 in Höhe und Breite reduzierter Alveolarfortsatz, 6 vollständig, bis unter basalen Knochen atrophiertes Alveolarfortsatz

3 // Zahnlos, extrem stark atrophiertes Ober- und Unterkiefer, retinierter und kariöser Zahn 18

6 // Kontrollröntgenbild nach Augmentation des Ober- und Unterkiefers und der Insertion von zwei provisorischen Implantaten in Regionen 13, 23 sowie operativer Entfernung von Zahn 18

Brown & Torhydon, der Junge Zahnarzt 2/2018

Bone augmentation

Preclinical model for bone augmentation

(1) Bone tissue defect
(2) Additive manufacturing of bone scaffold
(3) Bone augmentation with printed scaffold
(4) Bone regeneration
(5) Placement of dental implant

Rieder et al (2018) IJMS

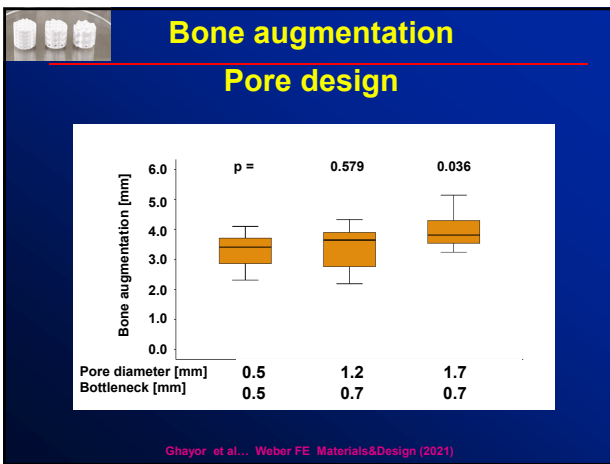
Ghayor et al... Weber FE Materials&Design (2021)

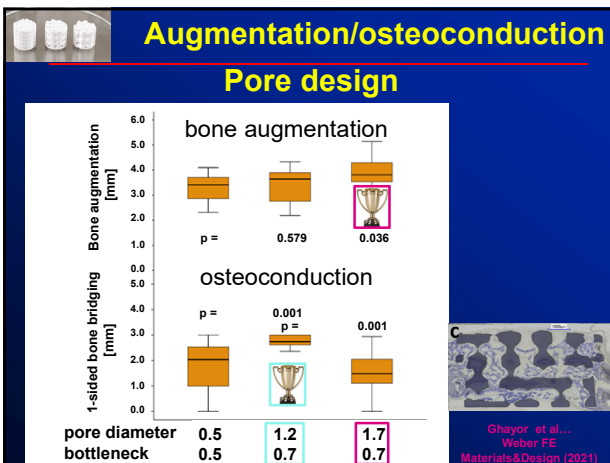
Models for Osteoconduction and bone augmentation

Rabbit Calvaria **Osteoconduction** **Bone Augmentation**

d e g







Pore design microarchitecture

Osteoconduction

bone augmentation

Pore diameter for optimal osteoconduction and optimal bone augmentation are different

Ghayor et al... Weber FE Materials&Design (2021)

Osteoconduction

Lithography-based designs

Filament design

Obregon et al (2015) JDR

All three designs are identical in amount of material, porosity, microporosity and transparency.

Weber FE (2019) Tissue Engineering part B

Osteoconduction directionality

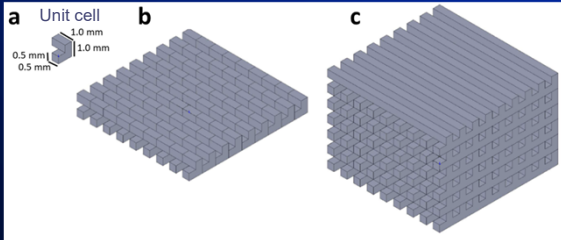
a

b

c



Osteoconduction directionality

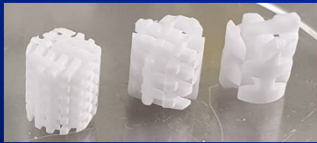




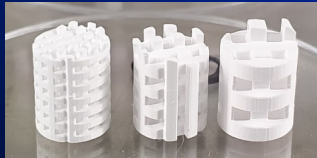
Osteoconduction and directionality



Filament design



Filament (G) design

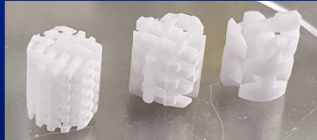




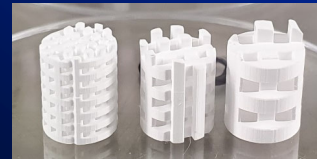
Osteoconduction and directionality



Filament design



Filament (G) design



Osteoconduction and directionality

Filament design

Filaments in x and y-direction

Bone grows in x, y-direction

all beams in direction of bone growth

Filament (G) design

Filaments in y and z-direction

Only half the beams in direction of bone growth

Osteoconduction is independent of rod thickness and distance if 100% of the rods are aligned with bone growth direction

Guerrero J, ...
Weber FE,
Int J Bioprint
(2023)

Bone augmentation

Filament design

Filaments in x and y-direction

Bone augmentation

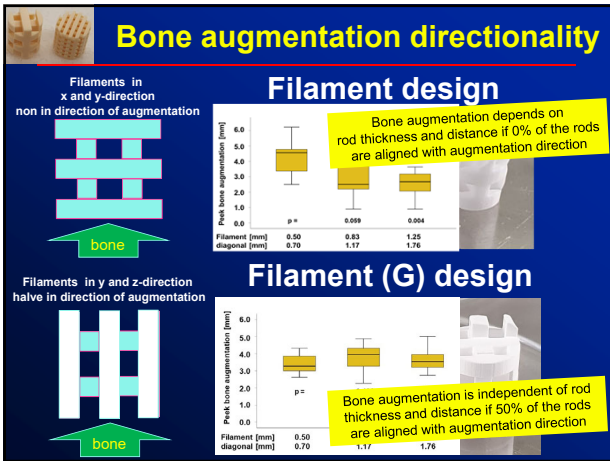
Filament (G) design

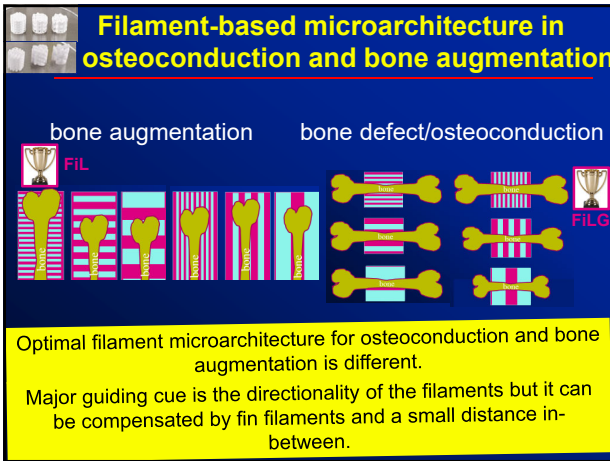
Filaments in y and z-direction

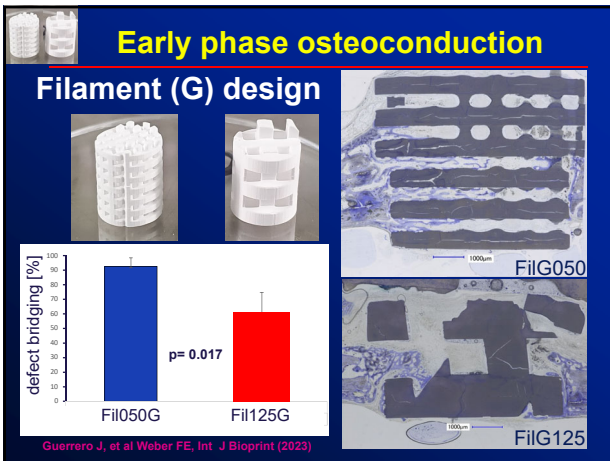
Bone augmentation and directionality

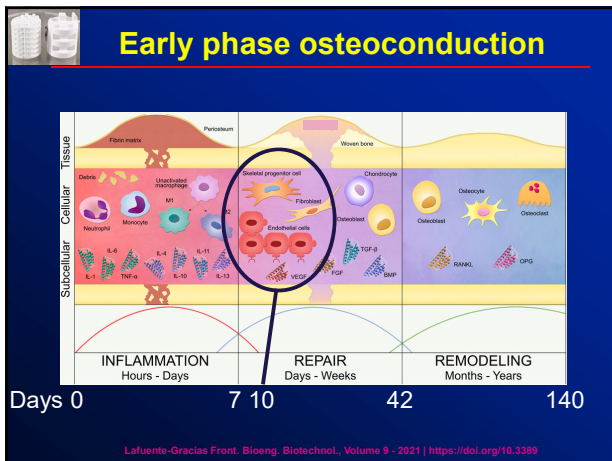
Filament design

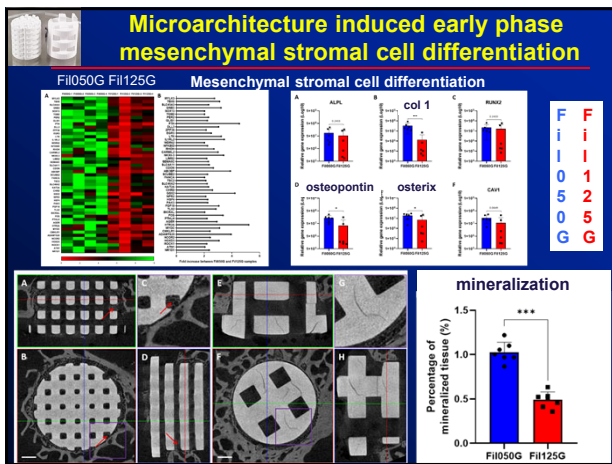
Filaments in x and y-direction are not aligned to bone augmentation

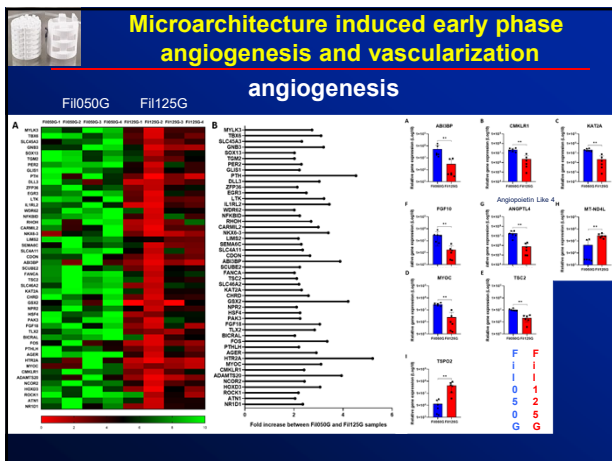


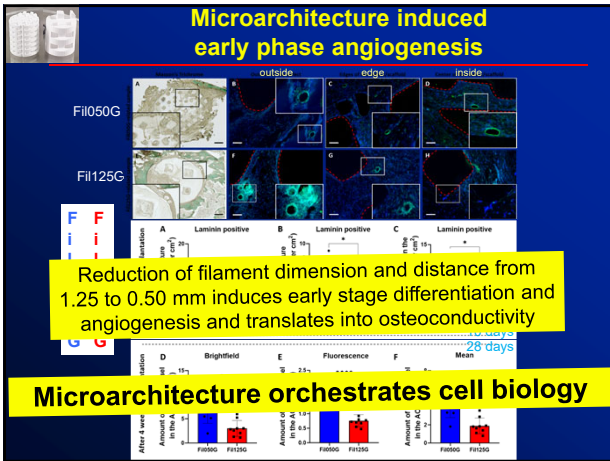


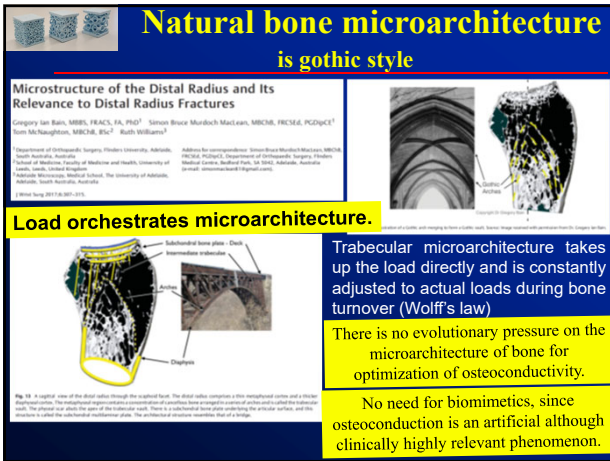


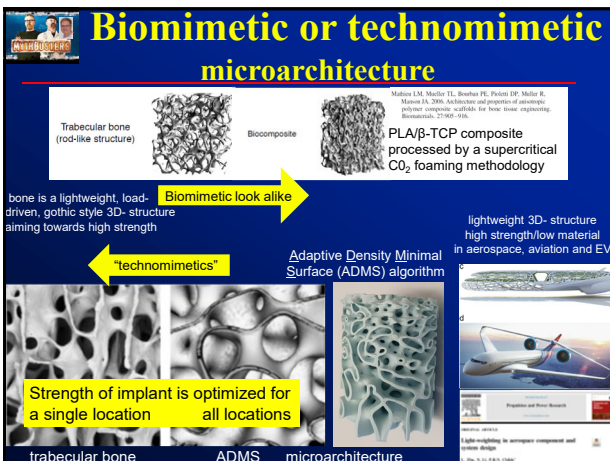












ADMS Adaptive Density Minimal Surface algorithm

ADMS autonomous design algorithm calculates structures using minimal resources while providing maximum strength. This image shows the development of a satellite bracket as part of the European Space Agency's Open Space Innovation Platform (Courtesy sphere AG)

Simplified Complexity: sphere Parameter Driven Design Tools

ADMS based shoe sole design

ADMS-lightweight microarchitectures

Adaptive Density Minimal Surface geometry

a

ADMS 500µm

b

ADMS 800µm

c

ADMS 1100µm

d

6 mm 15 mm

ADMS is periodic and adaptable to predefined load

Maevskaia et al. ...Weber FE 3D Printing & Additive Manufacturing (2022)

Osteoconduction

"natural" pores or "artificial" microarchitectures

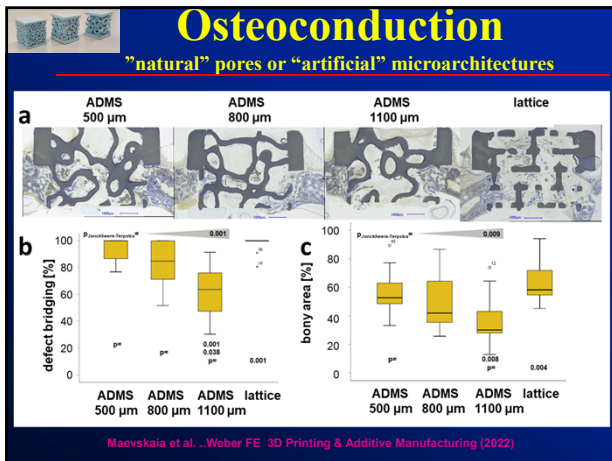
ADMS channel 500µm

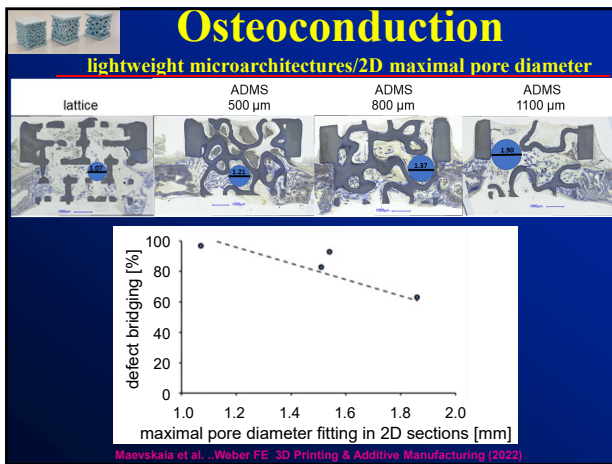
ADMS channel 800µm

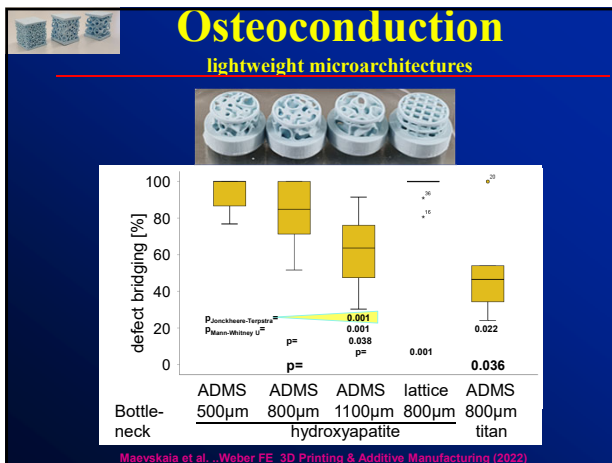
ADMS channel 1100µm

lattice

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Osteoconduction

lightweight microarchitectures

a

b

In osteoconductive ADMS and TPMS microarchitectures single 2D-spheres fitting the maximal pore should not exceed 1.53 mm.

Maximal pore diameter [mm]	Bridging [%]	Material
1.0	100	HA
1.2	~95	HA
1.4	~90	HA
1.6	~85	HA
1.8	~75	HA
1.8	~50	TI

Pore diameter is more important than bottle-neck or percolation

Mechanics

"natural" pores or "artificial" microarchitectures

Adaptive Density Minimal Surface geometry (ADMS) lattice

Geometry	Material	P-value
Bottle neck	ADMS	0.009
500µm	ADMS	0.004
800µm	ADMS	0.015
1100µm	ADMS	0.009
800µm	lattice	0.009

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ADMS-lightweight microarchitectures

Adaptive Density Minimal Surface geometry

a

b

c

d

e

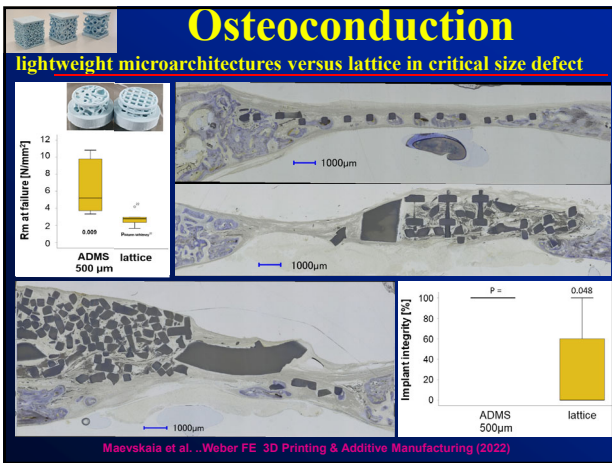
ADMS 500µm

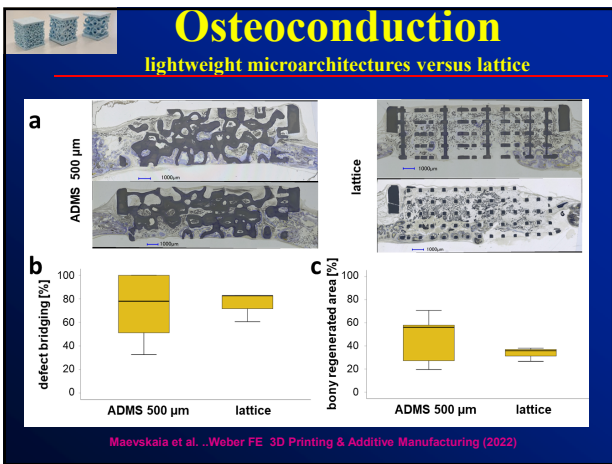
ADMS 800µm

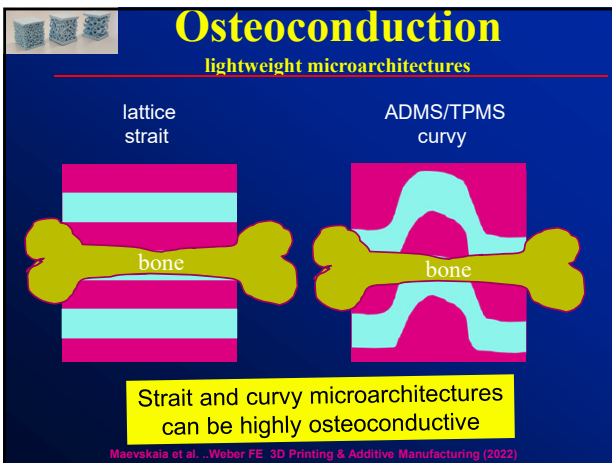
ADMS 1100µm

ADMS is periodic and adaptable to predefined load


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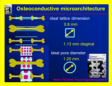
Microarchitecture orchestrates osteoconduction and bone augmentation



Reduction of filament dimension and distance from 1.25 to 0.50 mm induces early stage differentiation and angiogenesis and translates into osteoconductivity



Straight and curvy microarchitectures can be highly osteoconductive. No need for biomimetics



The choice of the microarchitecture matters for osteoconduction and bone augmentation.

University Hospital Zurich Center of Dental Medicine

Thank you

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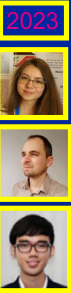
Lithoz
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for your attention

Oral Biotechnology & Bioengineering 2018



2023



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