Designing Degradable Implant Materials

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Collaborating Medical and Veterinary Units

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Gregor Zünd	Cardiovascular Surgery, University of Zürich

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Why New Medical Implant Materials? What Should Be Their Characteristics?

- most of the polymers currently used in implants were not initially designed for medical use — **rapidly increasing awareness of potential risks**

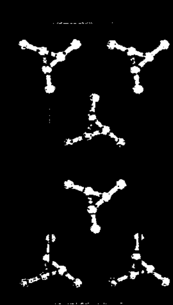
- each implant application calls for a specific set of properties; hence, **materials are needed in which the most important characteristics can be modified independently from the others (materials with orthogonal properties)**

Blockcopolymers: Materials with Orthogonal Properties

Natta, Mazzanti, Crespi & Moraglio *La Chimica e l'Industria* **1957**, *39*, 275
"Stereoblock copolymers of polypropylene (PP)"

isotactic isotactic

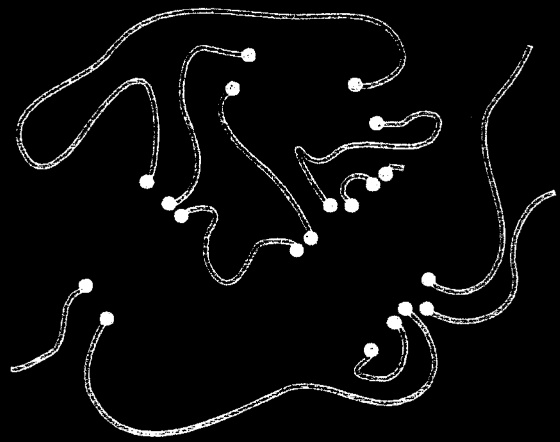
crystalline α-form of isotactic PP



Materials Properties — **Findings:**

- The isotactic blocks crystallize, the atactic blocks form a continuous amorphous phase (T_g as in atactic PP)
- The crystal T_m depends on the length of the isotactic blocks
- Between T_g and T_m, the material is a (thermoplastic) **ELASTOMER**
- The material's modulus is determined by the number of crystals (often by the volume fraction of crystalline blocks)

Approach to Degradable Block-Copolymers



hard segments form domains that are crystalline or glassy (→ THERMO-MECHANICS)

soft segments form domains that are amorphous and "rubbery" (→ DEGRADE FIRST)

junction units

macrodiol 1 + macrodiol 2 + junction unit ——→ block-copolymer

PHB-diol

diisocyanate or diaciddichloride

copolyesterurethane or copolyester

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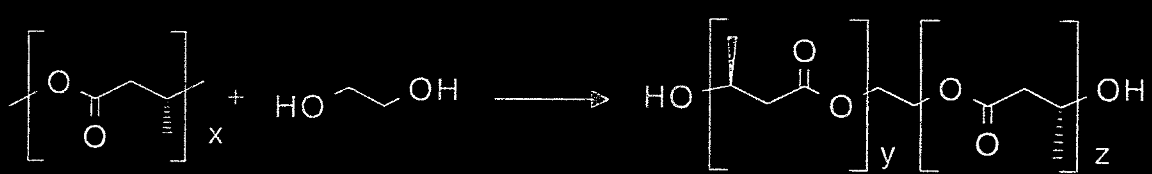
Hard Segments: Telechelic PHB-diols by Transesterification of Bacterial PHB with a Diol



catalyst
dibutyl-Sn(II)-dilaurate

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T. Hirt

PHB-diol (M_n 2'500) + Poly(ε-caprolactone) (M_n 2'500) + (*S*)-2,6-Diisocyanato methylcaproate

PHB-diol (hard segment) [wt-%]	PCL-diol (soft segment) [wt-%]	tensile modulus [MPa]	tensile strength [MPa]	elongation at break [%]	T_m [°C]
29	58	60	6	830	116
44	44	200	7	610	122
69	21	500	11	21	134
92	0	1260	14	2	131

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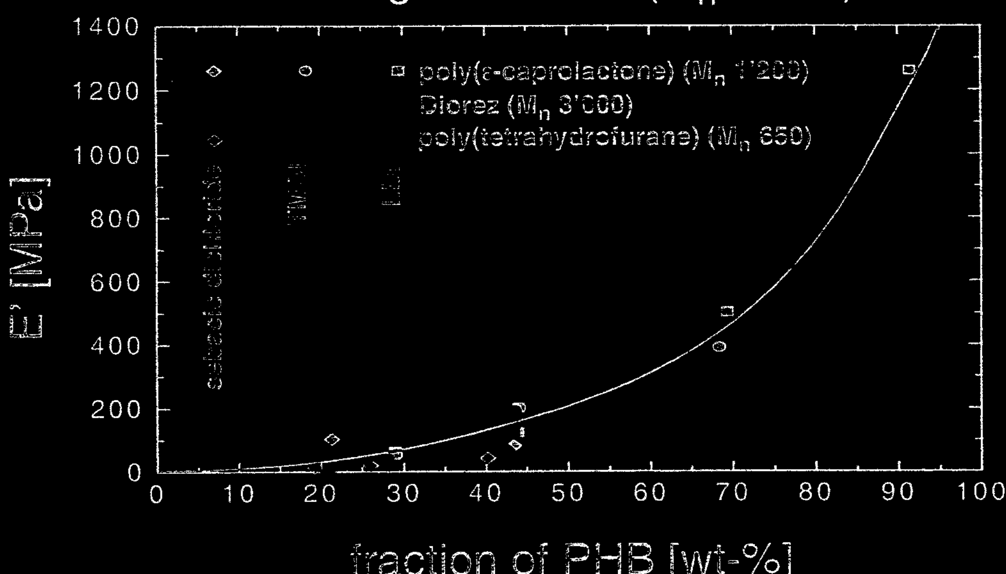
T. Hirt

The Modulus is Mainly Dependent on the Fraction of Hard Segment

hard segment: PHB (M_n 2'500)



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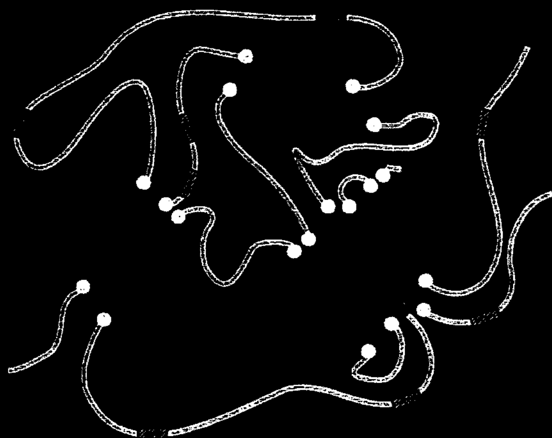
R. Stoll

Control of Degradation Rates: Introduction of "Weak Links"



hard segments
(→ THERMO-MECHANICS)

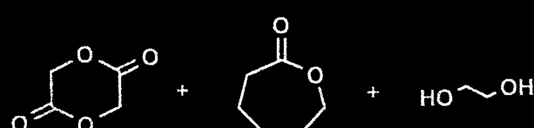
soft segments
(→ ELASTOMERIC PROPERTIES)

"weak links" (readily hydrolizable groups)
(→ DEGRADATION RATE)

"weakest link": glycolyl glycolate

A. Lendlein

Soft Segments by Ring-Opening Polymerization from Diglycolide and ε-Caprolactone

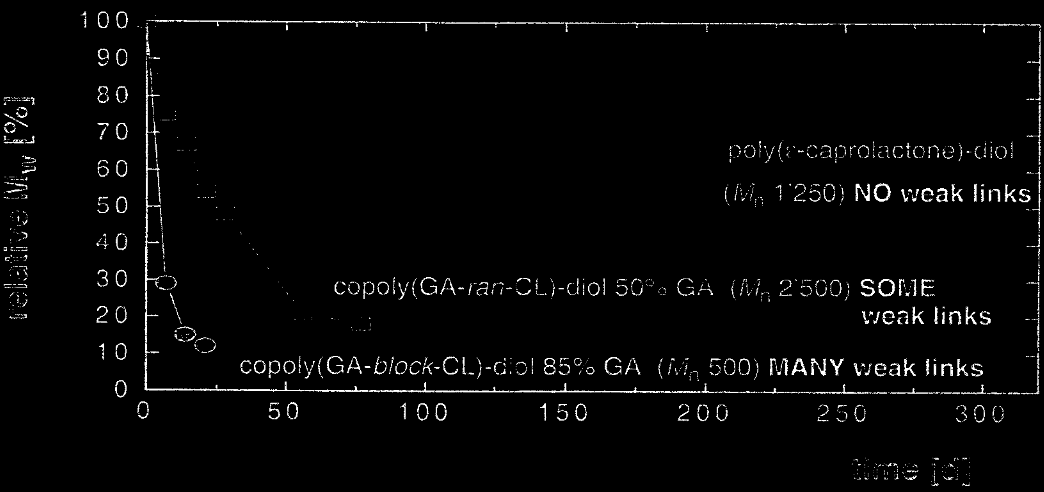


catalyst → ring-opening polymerization → telechelic diol with structure

catalyst → ring-opening polymerization + transesterification → telechelic diol with structure

A. Lendlein

Hydrolysis of Block-Copolyesterurethanes with 44 wt-% PHB and Different Soft Segments



pH 7 — 37 °C

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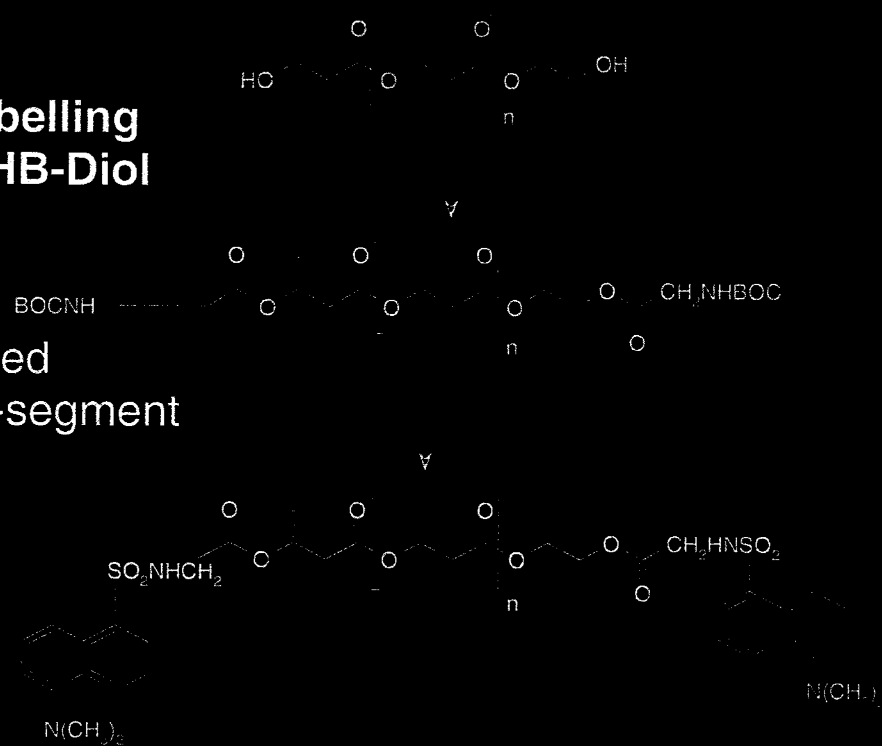
Fluorescent Labelling of Telechelic PHB-Diol with a Dye



The dansyl-labelled blocks form hard-segment crystals that can be traced by their fluorescence

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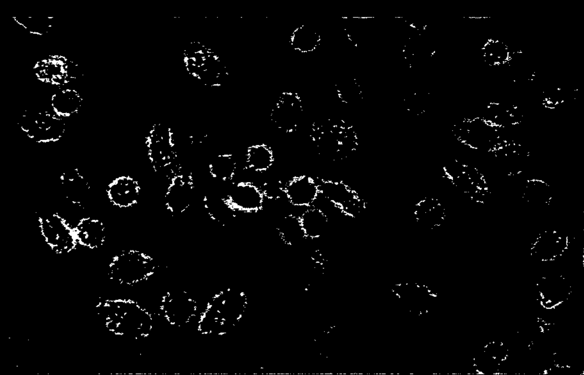
G. Ciardelli

Phagocytosis of Fluorescent-labelled PHB Particles in Rat Macrophages

macrophage cell line J774 — 2 µg/ml DPHB particles
optical micrographs after 4 hours

phase-contrast image

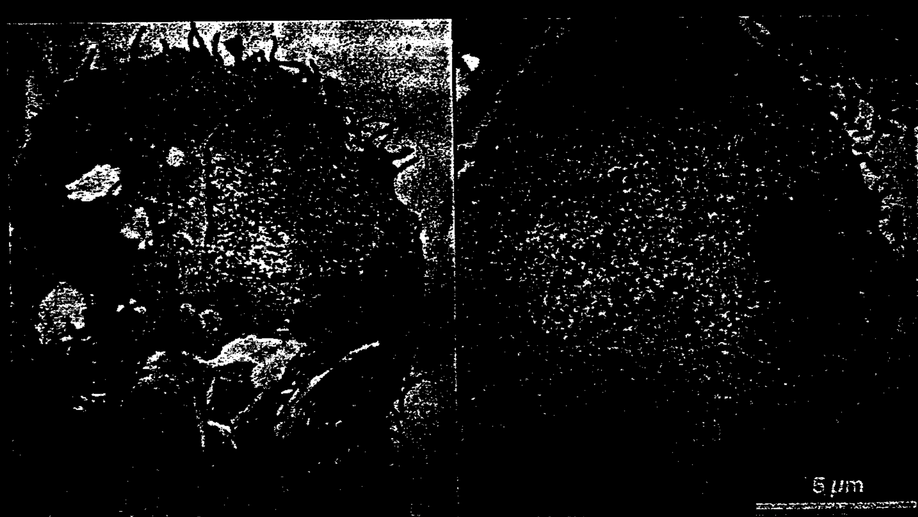


fluorescence image

ETH Materials

B. Saad

Macrophage Cell Cultures that Were Exposed to PHB Particles as They Result from Significantly Degraded DegraPol®



M. Müller

PHB (2 µg PHB/ml) PHB

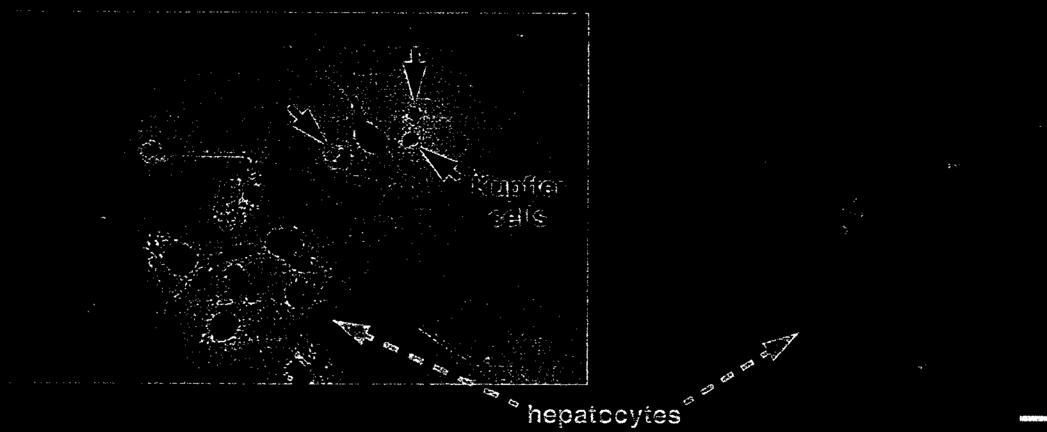
ETH Materials

B. Saad. G.K. Uhlschmid

Phagocytosis of Fluorescent-labelled PHB Particles in Co-cultures of Hepatocytes and Kupffer Cells

1 µg/ml of DPHB particles, after 4 hours

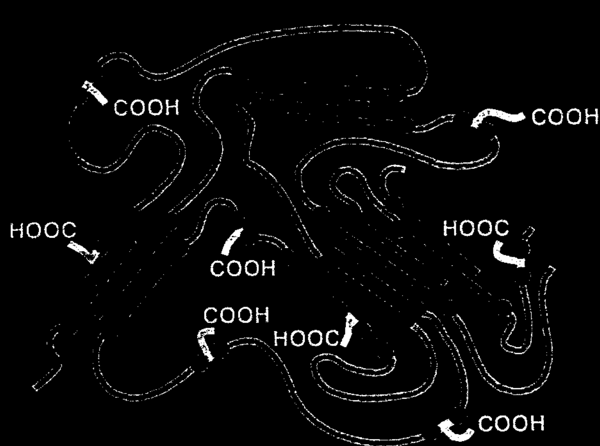
phase-contrast image | fluorescence image

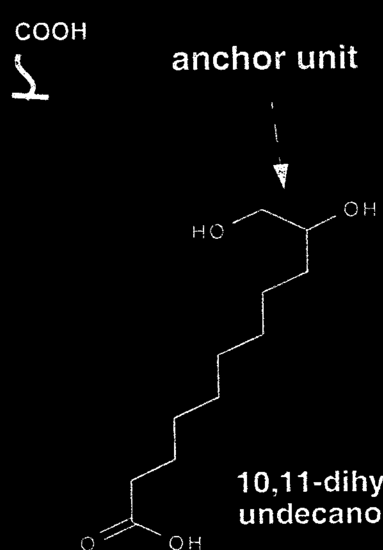


Kupffer cells phagocytose PHB particles, hepatocytes are unaffected

P. Schmutz

Functionalization of Copolyesterurethanes: Adding Carboxylic Side Groups



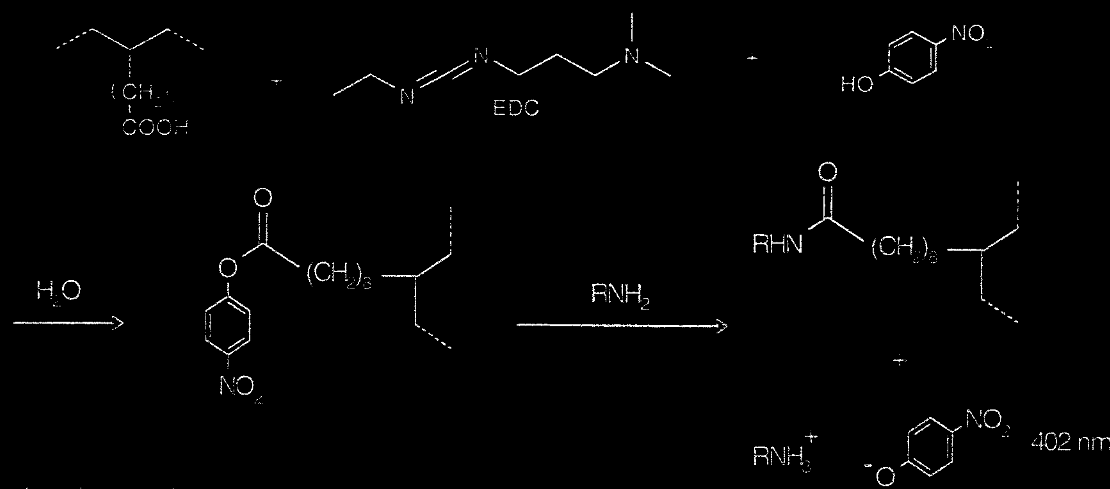


10,11-dihydroxy-undecanoic acid

G. Ciardelli

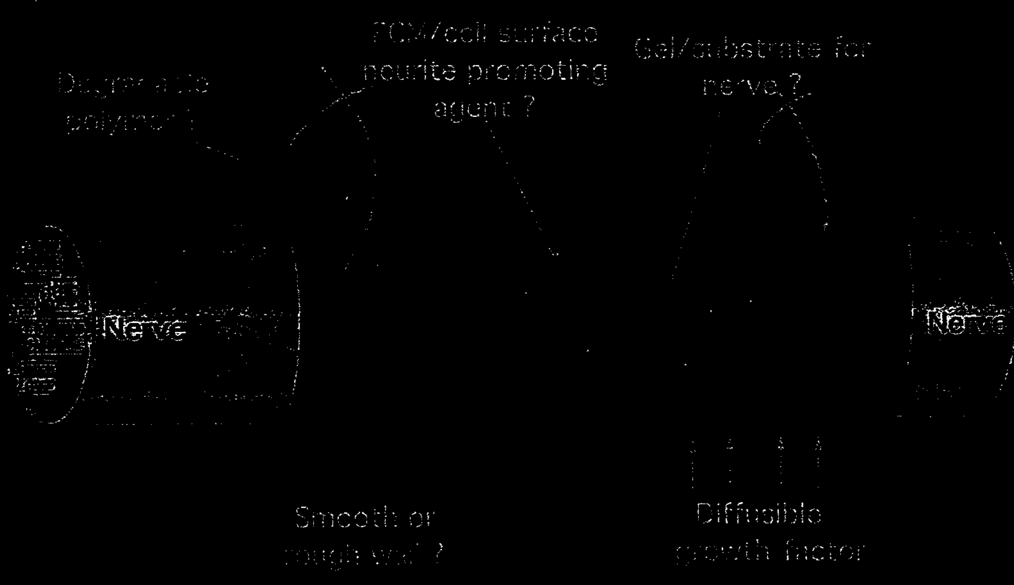
Reaction of Polymer-bound COOH with "Any" Amine Through Activation with *p*-Nitrophenol

1. Formation and isolation of the
2. Reaction with amines — no further activation necessary



G. Ciardelli

Nerve Conduits — Operating Principle



P. Aebischer

Nerve Conduits Made from DegraPol® with Varying PHB Content

R. Stoll

Nerve Conduits Made from DegraPol

Number of axons is not significantly different than in a normal sciatic nerve

P. Aebischer

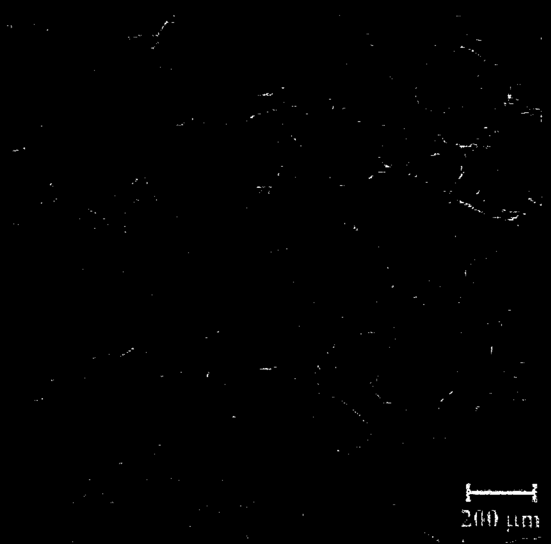
Production of Open-pored Scaffolds

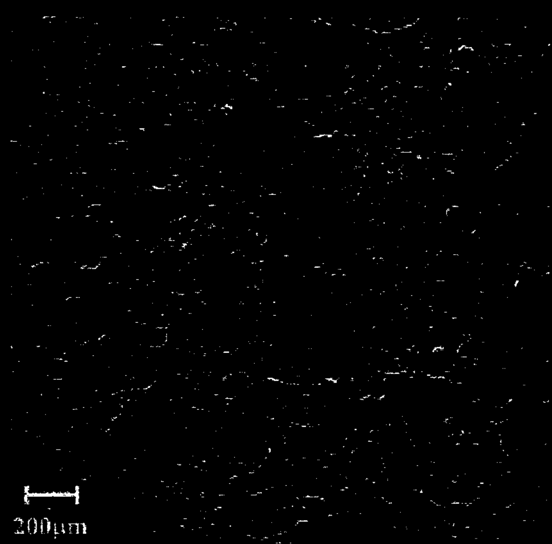
DegraPol solution in 1,4-Dioxane → phase segregation into polymer-rich and polymer-poor phase

→ 3D structure of polymer-rich phase is fixed → open-pored DegraPol scaffold

S. Matter

Porous Foams with Different Pore Size



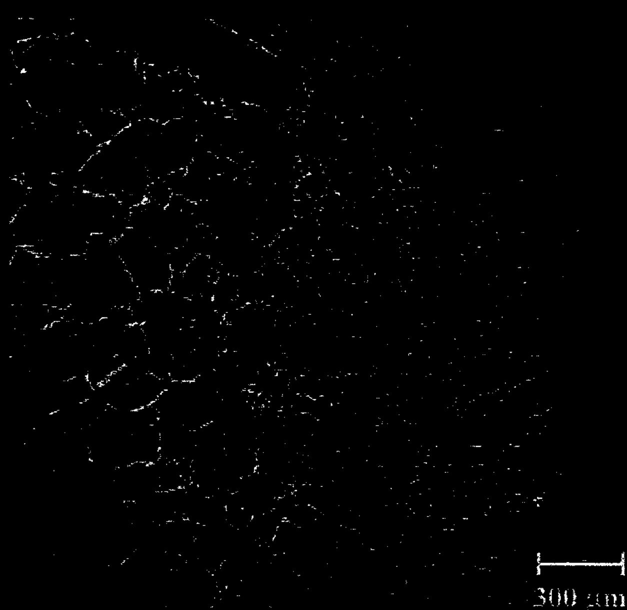


"normal"

the smallest pores practical

S. Matter, M. Camus

Porous Foams with Different Pore Sizes in One Object

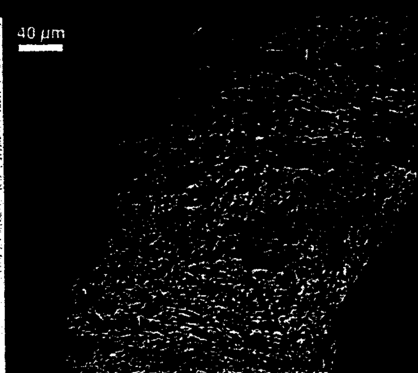


structures with small and large pores can be joined through an abrupt transition region, without “skin” between the regions

M. Camus

Porous Tubes from DegraPol® (Obtained by Extrusion of a Gel in 1,4-Dioxane into Liquid N_2 and Freeze Drying)

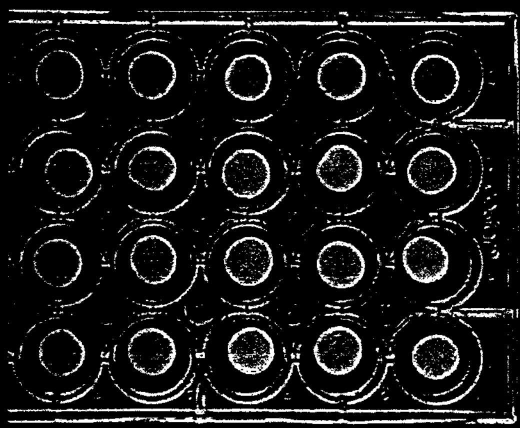
optical micrograph
(tube appears white because of light scattering)

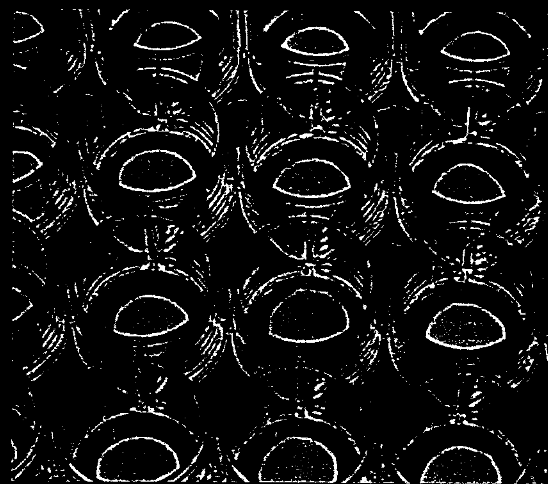


SEM

R. Stoll, Ph. Kern

Application: Foams as Tissue-culture Substrates





DegraPol® Scaffold disks, diameter 10 mm, thickness 0.5 or 1 mm
24 pieces packed in a 24-well tissue-culture plate

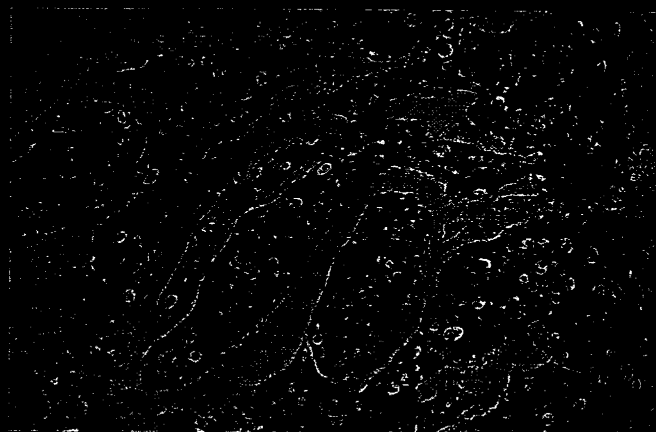
M. Camus

An Application: Cartilage Repair

adult pig chondrocytes, cultured on DegraPol foam for 2 weeks, then stained with Alcain blue for Collagen II
→ **the correct intercellular matrix is produced**

B. von Rechenberg, B. Saad

An Application: Cartilage Repair



adult pig chondrocytes, cultured on DegraPol foam for 4 weeks, then stained with toluidine blue to visualize cells

→ **chondrocytes proliferate in the interstitial spaces of the foam**

B. von Rechenberg, B. Saad

An Application: Cartilage Repair

[illegible] of DegraPol sponge, seeded with chondrocytes and cultured for 2 weeks, then glued to a conical plug of hard [illegible] cement with liquid bone cement.

The plug will be inserted in a conical hole drilled into the bone and is fixated with liquid bone cement.

B. von Rechenberg

An Application: Cartilage Repair

pig chondrocyte-cultured
DegraPol sponge (slowly
degradable variety),
implanted in the trochlea
ossis femoris (knee) of a pig
for 3 weeks

The implants form a smooth surface with the joint, no abbrasion, also at the counterpart (femour condyles). DegraPol foam is yellow because of small contamination with blood

B. von Rechenberg

Conclusions

- Multi-Blockcopolymers allow the design of a large variety of polymeric, tissue-compatible materials with a number of continuously tunable, orthogonal properties
- Independently variable are: softening point, mechanical moduli, degradation rates, functionalizability
- Functionalization can be achieved through attachment of any amine-terminated compound
- The polymeric materials described here (DegraPol©) have been extensively tested in vitro and in vivo and are highly tissue compatible
- The DegraPol©-foam structures are the first available elastomeric tissue-culture scaffolds