Close to the Heart – Biomaterial Developed to Serve Vascular Applications

Presented by Dr. George Mihov, Ph.D.

July 2024

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Presentation Focus

- Company overview
- Introduction to TheraPEA™ polymer platform
- Drug eluting coating on cardiovascular stent – inspiration for biomaterial development
- Addressing challenges with TheraPEA™
  - Polymer chemistry, structural features and material properties
  - Unique biodegradation
  - Biocompatibility and fit for intravascular applications
  - Drug release kinetics
  - Pre-clinical and clinical research examples
- Conclusions

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We're a trusted partner to global companies operating in high-growth and resilient markets. We bring progress to life as innovators in nutrition, health, and beauty.

150+ years
of combined scientific discovery and innovation heritage

~30,000
employees

€12+ bn
revenue

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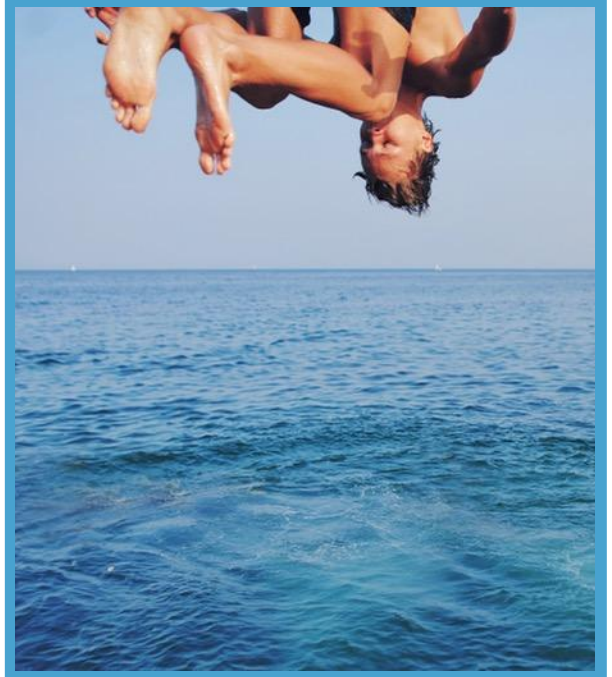
Perfumery
& Beauty

Taste, Texture
& Health



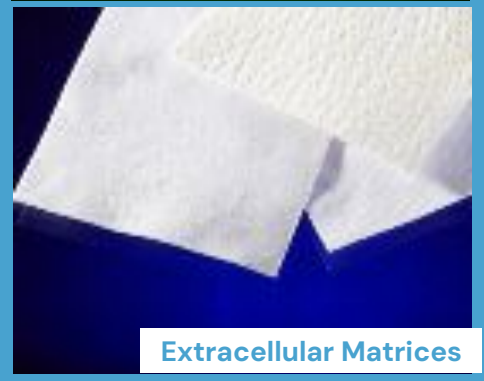
Health, Nutrition
& Care

About DSM Biomedical

Taking biomaterials FURTHER

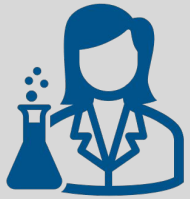
DSM Biomedical aspires to *solve the world's healthcare needs through sustainable science*

Through our extensive biomaterials portfolio and world-class capabilities, we empower our global partners to create and deliver transformative solutions that *elevate patient well-being, enable healthcare professionals, and foster sustainability*



DSM's Core Strengths in Polymeric Drug Delivery Solutions

Full support from feasibility to cGMP manufacturing



Extensive expertise in polymer technologies for biomedical applications

Formulation development with APIs to achieve the desired therapy profile

Custom process development for different polymeric drug delivery forms

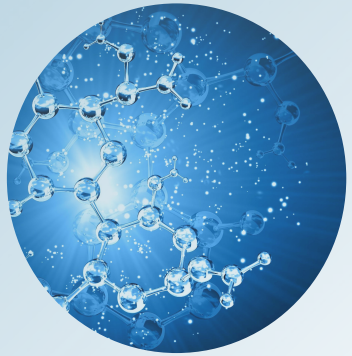
A broad IP portfolio that enables life cycle management opportunities in branded products

Why sustained delivery?

At DSM we strongly believe in doing well by doing good, which is why our company's strategies are aligned with the UN's Sustainable Development Goals (SDGs).

TheraPEA™ Sustained Drug Delivery Platform

Enabling Innovative Long-Acting Therapies

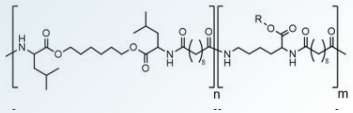


Near Linear Release Rates
Slow and controlled release enables possibility of less frequent administration for the patient

Sustainability
Enables a solution that is good for the planet by minimizing sharps and other plastics use

TheraPEA™

Biodegradable Polyester Amide Platform



No Acidic Microenvironment During Degradation
Enables controlled release per design and provides protection for sensitive API payload

Broad IP Portfolio
Enables partners opportunities for branded sales protection and life cycle management

Processing Flexibility
Enables multiple therapeutic forms; low melt temperature and solubility in low MW alcohols for ease of processing

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TheraPEA™ – A Proven Biodegradable Platform Solution for Sustained Drug Delivery

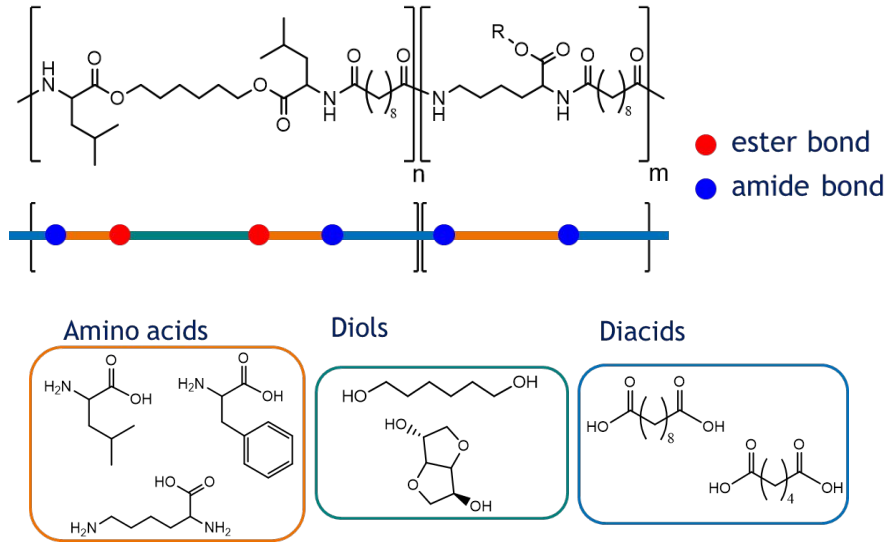
DSM Biomedical's Competitive Qualifiers

- Excellent biocompatibility proven in multiple settings including ophthalmic[1], intravascular[2] and intra-articular[3] applications
- Material Master Files and GMP Manufacturing

Our Competitive Differentiators

- Broad compatibility with wide range of small molecules and biological drugs[4]
- Controlled degradation kinetics (weeks to multiple months); no acidification of micro-environment[4]
- Unique solubility properties (incl. low hydrocarbon alcohols) provides for ease of processing with active pharmaceutical ingredients incl. low temperature melt processing into multiple product forms (fibers, microparticles, films, foams, coatings)[4]
- Broad IP protection provides opportunities for lifecycle extension

TheraPEA™ Polyester Amide (PEA)



DSM offers polymer solutions tailored to sustain drug elution over the lifetime of the therapy, while allowing ease of processing with active pharmaceutical ingredients (APIs).

[1]Polymers 2014, 6, 243
[2]EXPERT REVIEW OF MEDICAL DEVICES, 2017, 14, (9), 669
[3]Pharmaceutics 2021, 13(3), 372
[4]Internal reports, data on file

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Cardiovascular Drug Eluting Stents

Innovation driven therapeutic area

- Revolution of the Bare Metal Stents (BMS) and restenosis incidents
- Drug Eluting Stents (non-degradable coating) reduced restenosis but revealed the issue of late stage thromboses
- Raising the barrier for biomaterials in stent coating
- Ideally the coating should be:
  - Non-thrombogenic
  - Hemocompatible
  - With good adhesion and integrity (no particulates)
  - Non-inflammatory
  - Biodegradable
  - To maintain the target release kinetics
- Inspire many material developments including in TheraPEA™ technology

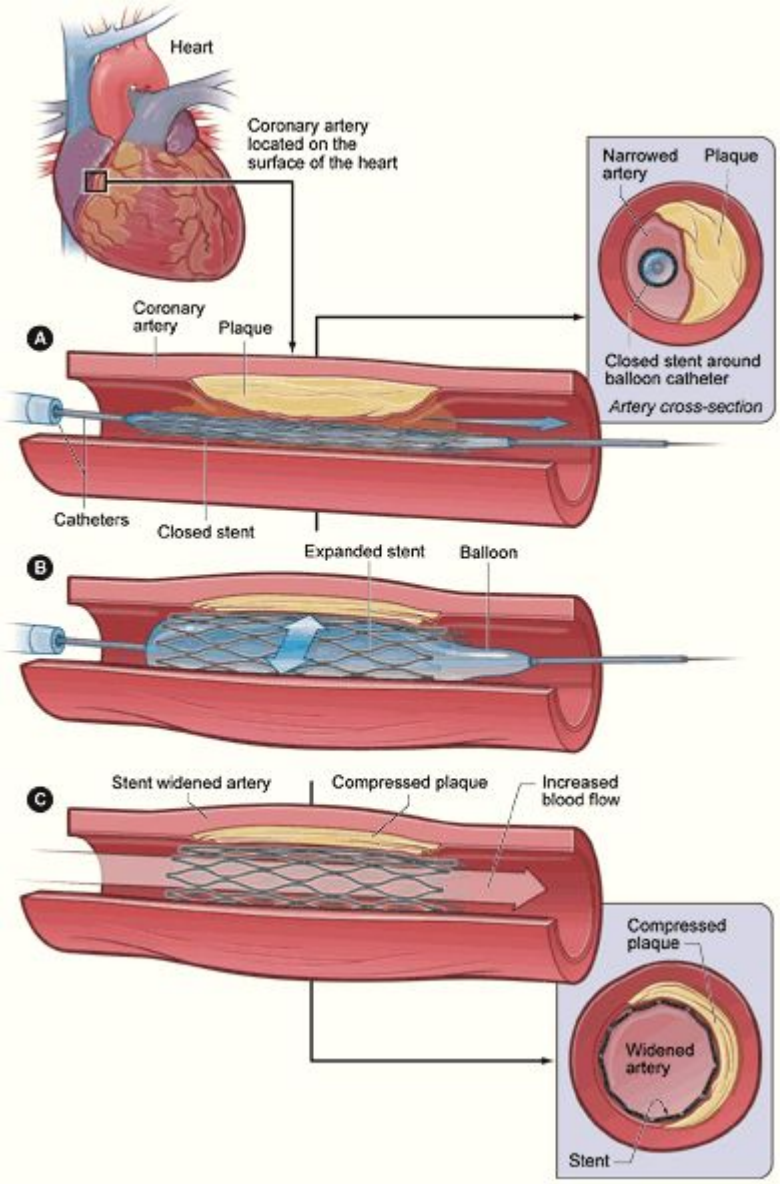

Image reference: PTCA_stent_NIH.gif (390×592) (wikimedia.org)

Polymer chemistry, structural features and material properties

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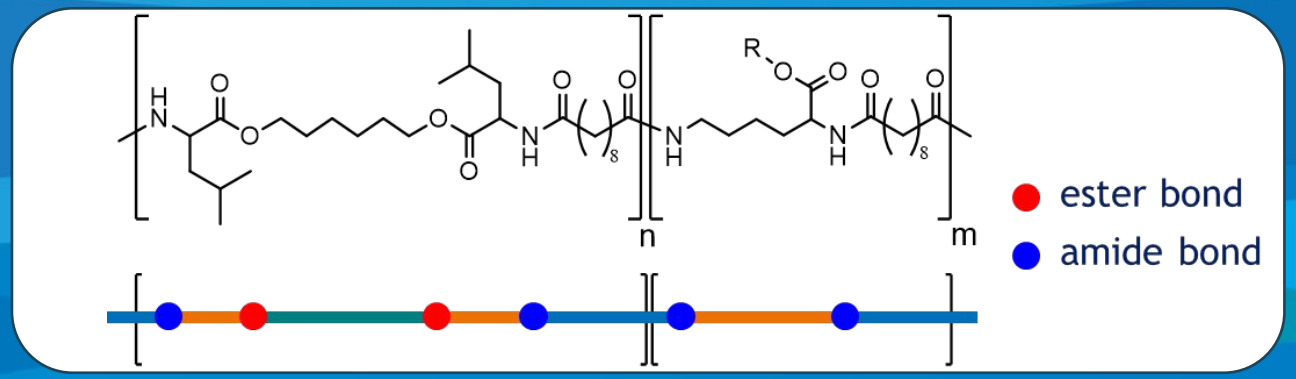
Programmable material and functional properties

Side functions for attachment of targeting and bio-active moieties as well as for tuning the polymer properties

Unique biodegradability properties

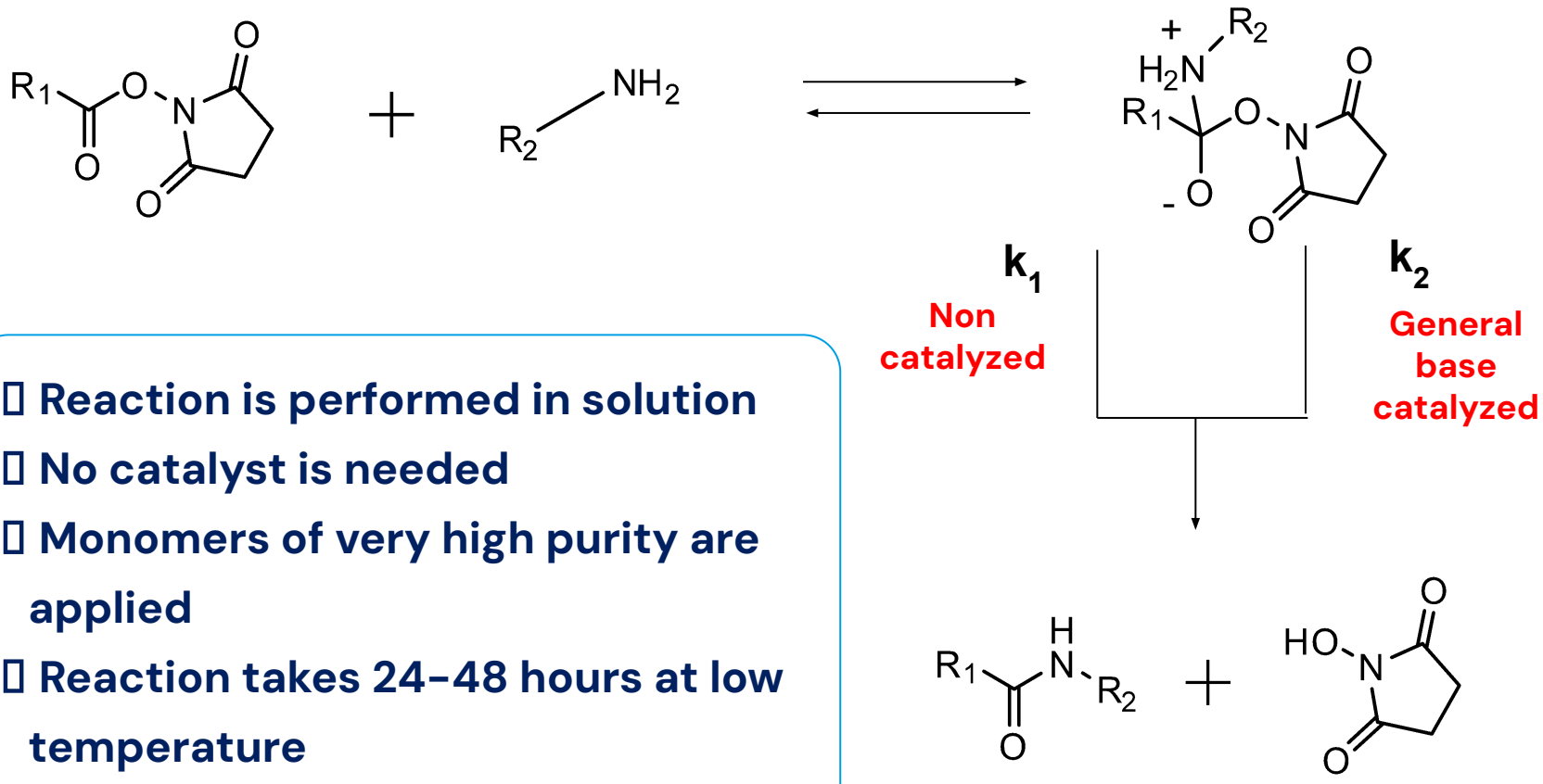
Ester and amide bonds combining biodegradability with improved material properties



Building blocks providing for optimal elastomeric and adhesion-to-metal properties

L-amino acids contributing to biocompatibility of the polymer and its biodegradation products

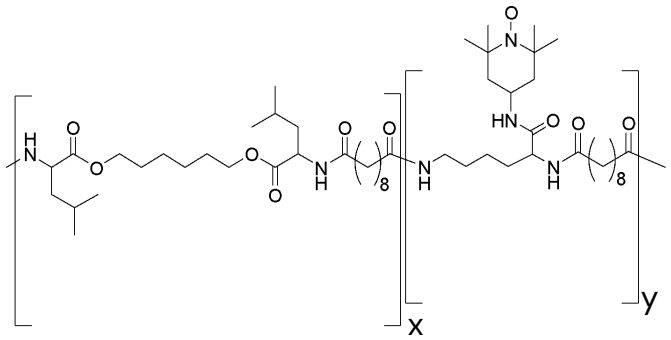
PEA condensation process



- Reaction is performed in solution
- No catalyst is needed
- Monomers of very high purity are applied
- Reaction takes 24-48 hours at low temperature
- No side reactions are observed
- Polymer purification is required

G. W. Cline, S. B. Hanna., J. Org. Chem. 1988, 53, 3583

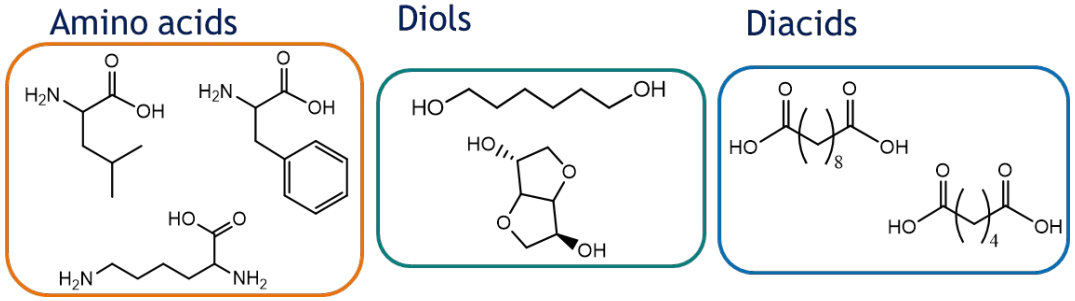
Programmable for material properties

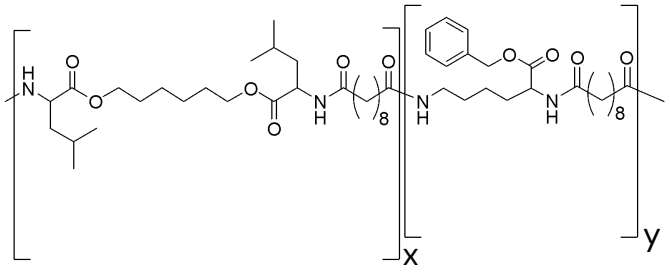


Nitroxide radical 4-amino TEMPO conjugated onto PEA

Functionalized TheraPEA™

TheraPEA™ building blocks

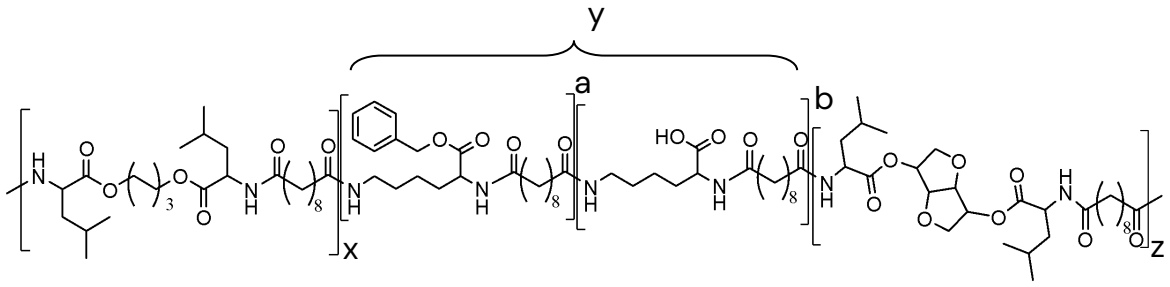




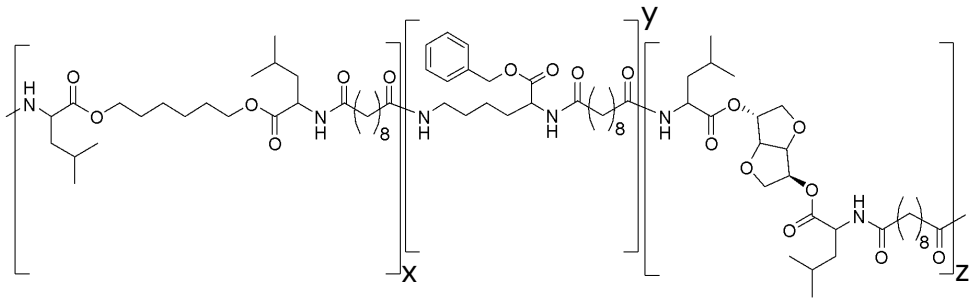
PEA I Ac Bz; Leu and Lys comprising elastomer biocompatible with good adhesion on metal

Enzymatically degradable TheraPEA™

Hydrolytically degradable TheraPEA™



PEA III X polymers; Hydrolytically degradable elastomers with tunable hydrophilicity and barrier properties



PEA III Ac Bz; Elastomer with improved mechanical and drug release properties.

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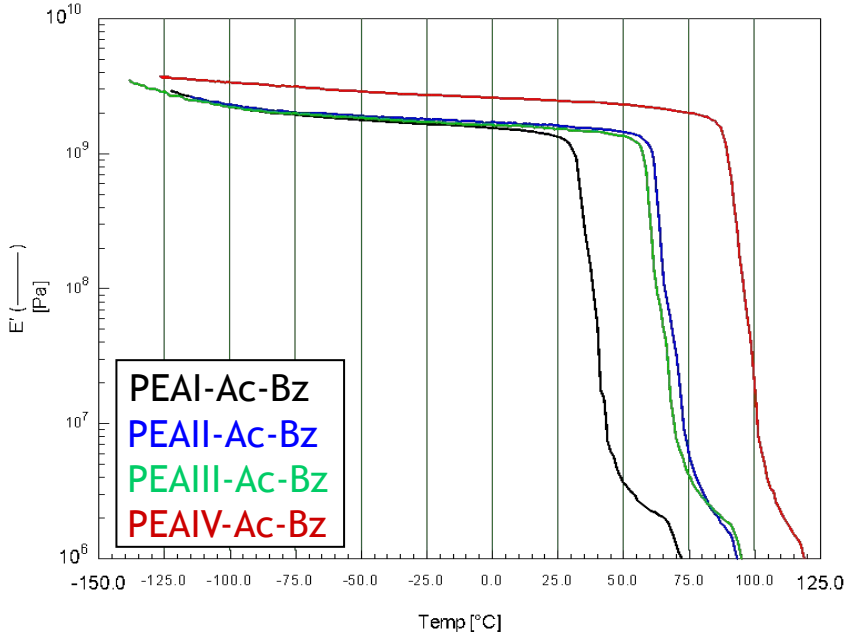
TheraPEA Material Properties and Physical Network

PEAs are amorphous, random copolymers
•
Mn 45 -75 kDa

Elastomers of MW between the entanglements 3-5 kDa

Dynamic Mechanical Thermal Analysis (DMTA)

TheraPEA™ technology demonstrates high mechanical coating integrity, a particularly relevant consideration when direct stenting. Hydrocarbon spacers provide optimal thermal and mechanical properties while low-yield strains coupled with high-break strains provide drug carrier integrity and resiliency when direct stenting and treating complex lesions[1]



TheraPEA solubility

Solvent	solubility
methanol	+
ethanol	+
isopropanol	+
tert-butanol	+
DCM	+
chloroform	+
acetone	-
THF	+
ethyl acetate	-
DMF	+
DMSO	+
water/buffer	-

[1]Verheye S., EXPERT REVIEW OF MEDICAL DEVICES, 2017, VOL. 14, NO. 9, 669–683

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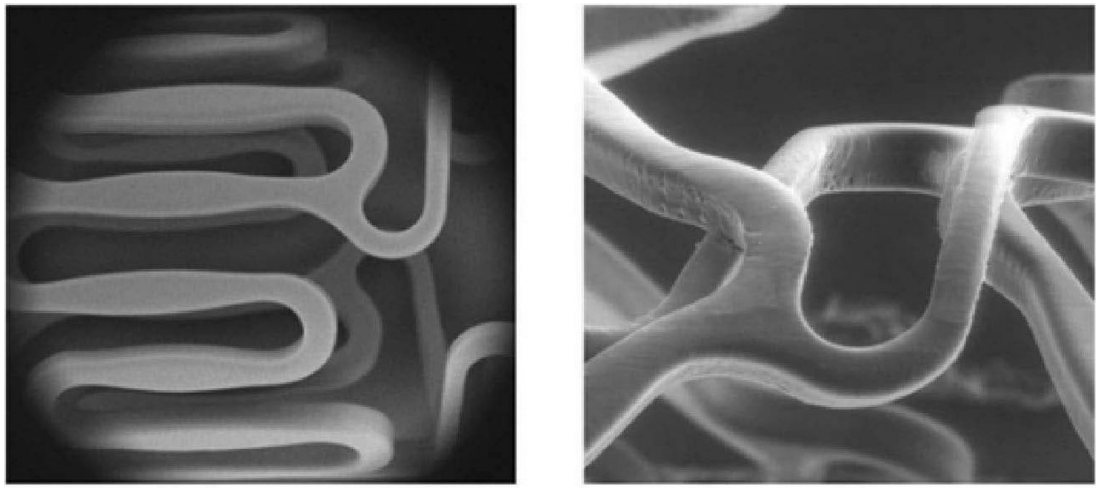
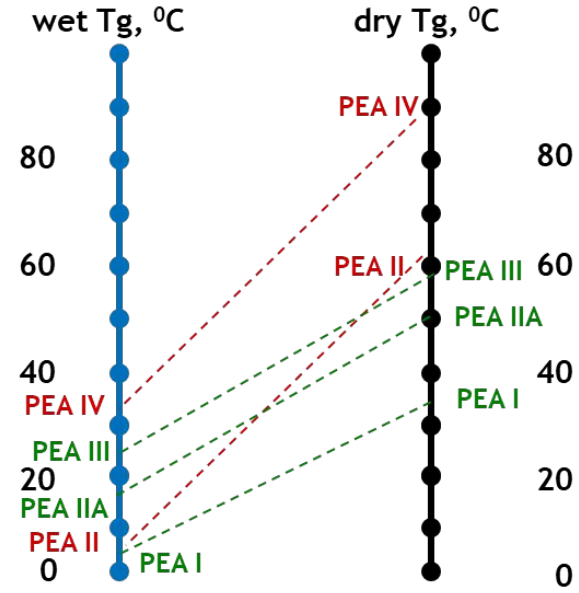
TheraPEA Material Properties and Physical Network





SEM images of TheraPEA™ drug coating. Elastomeric properties of the drug coating provide the mechanical integrity of the coating. These images represent views of an entire stent strut (left) and close-up of the overlapped area of 2 stents (right) with coating after 10 million cycles[1]

PEAs are hydrophilic and amorphous elastomers

•

Easily plasticized by water

[1]Verheye S., EXPERT REVIEW OF MEDICAL DEVICES, 2017, VOL. 14, NO. 9, 669–683

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Unique biodegradation

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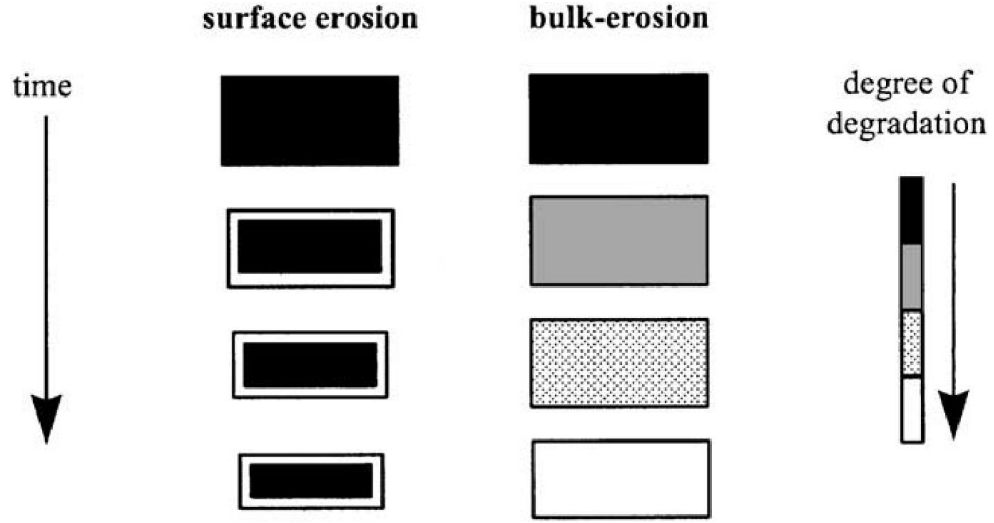
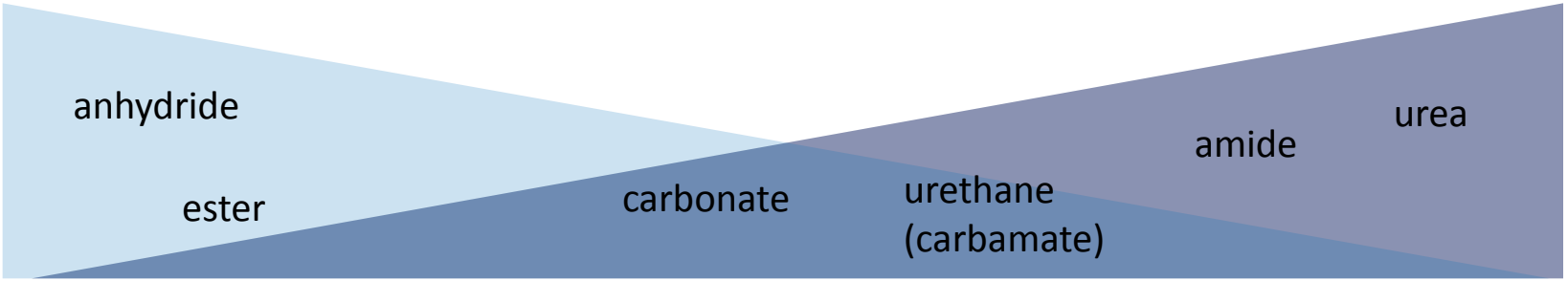
Biodegradation of TheraPEA Biomaterials

First generation TheraPEA polymers degrade via enzyme-mediated, surface erosion mechanism





Mallepally, R. Journal of applied polymer science, Vol. 112 (2008) 1873–1881
Pang, X., Chu, C., Biomaterials 31 (2010) 3745–3754
von Burkersroda, F., et al. Biomaterials 23 (2002) 4221–4231

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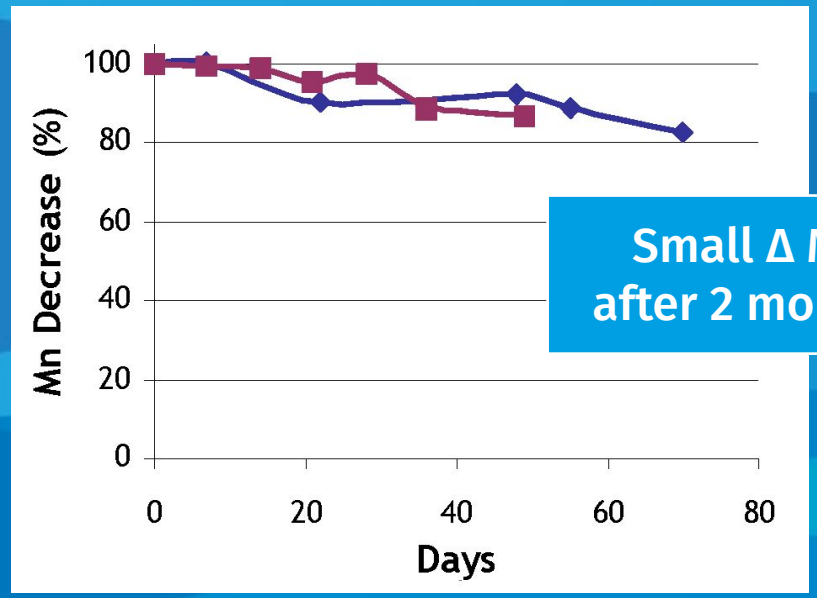
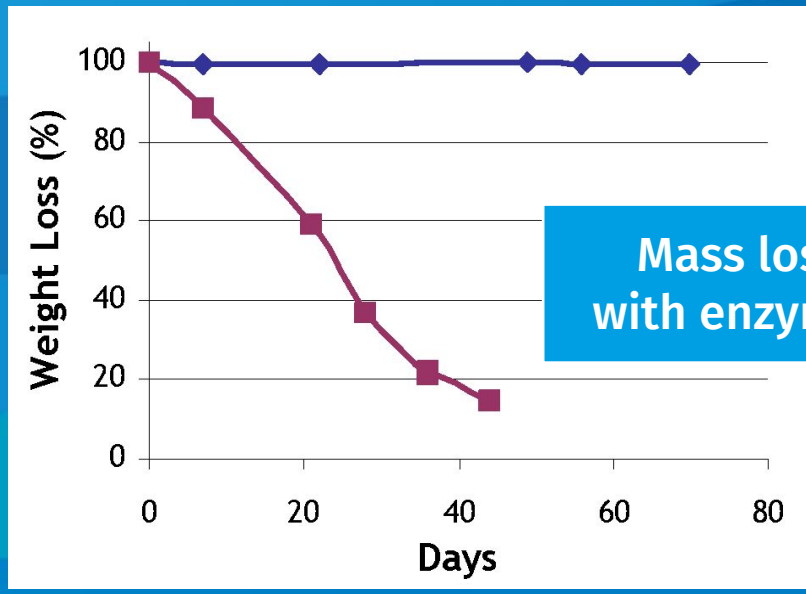
TheraPEA™ Degradation Features

Hydrolytic vs. Enzymatic



Small Δ Mn after 2 months



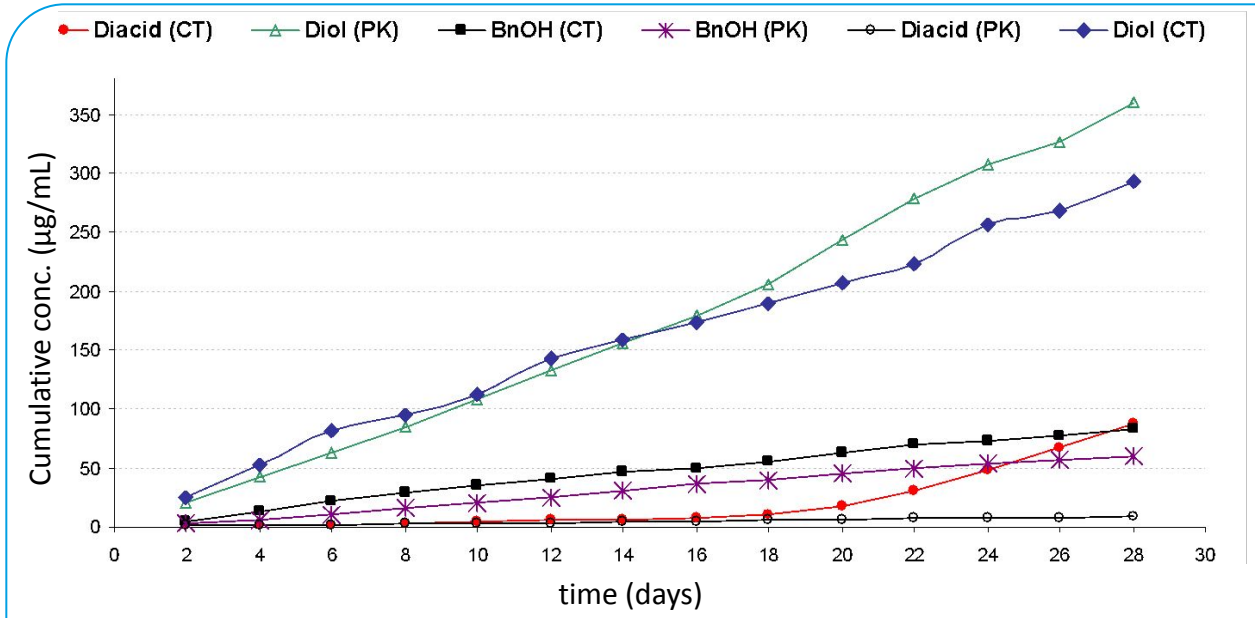
Mass loss with enzymes

PEA incubated in PBS at 37 °C — w/ Chymotrypsin

- Hydrolytically stable TheraPEA™ polymers
- Enzyme-mediated polymer degradation
- Preserved material properties at advanced stages of in-vitro degradation

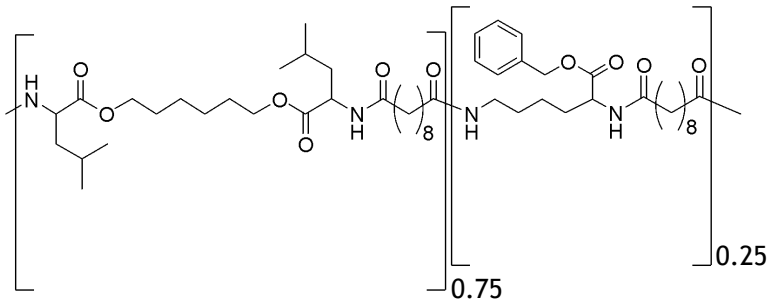
03TR279 In vitro degradation of polyester amides, internal report, data on file

Monitoring enzyme mediated degradation



- Insight in degradation mechanism and polymerization process
- Surface erosion was observed for proteinase-K and α-chymotrypsin mediated degradation

Main degradation products were identified for α-chymotrypsin and proteinase-K degradation of PEA-I-Ac-Bz



Ghaffar, A. et al., Biomacromolecules 12 (2011) 3243-3251

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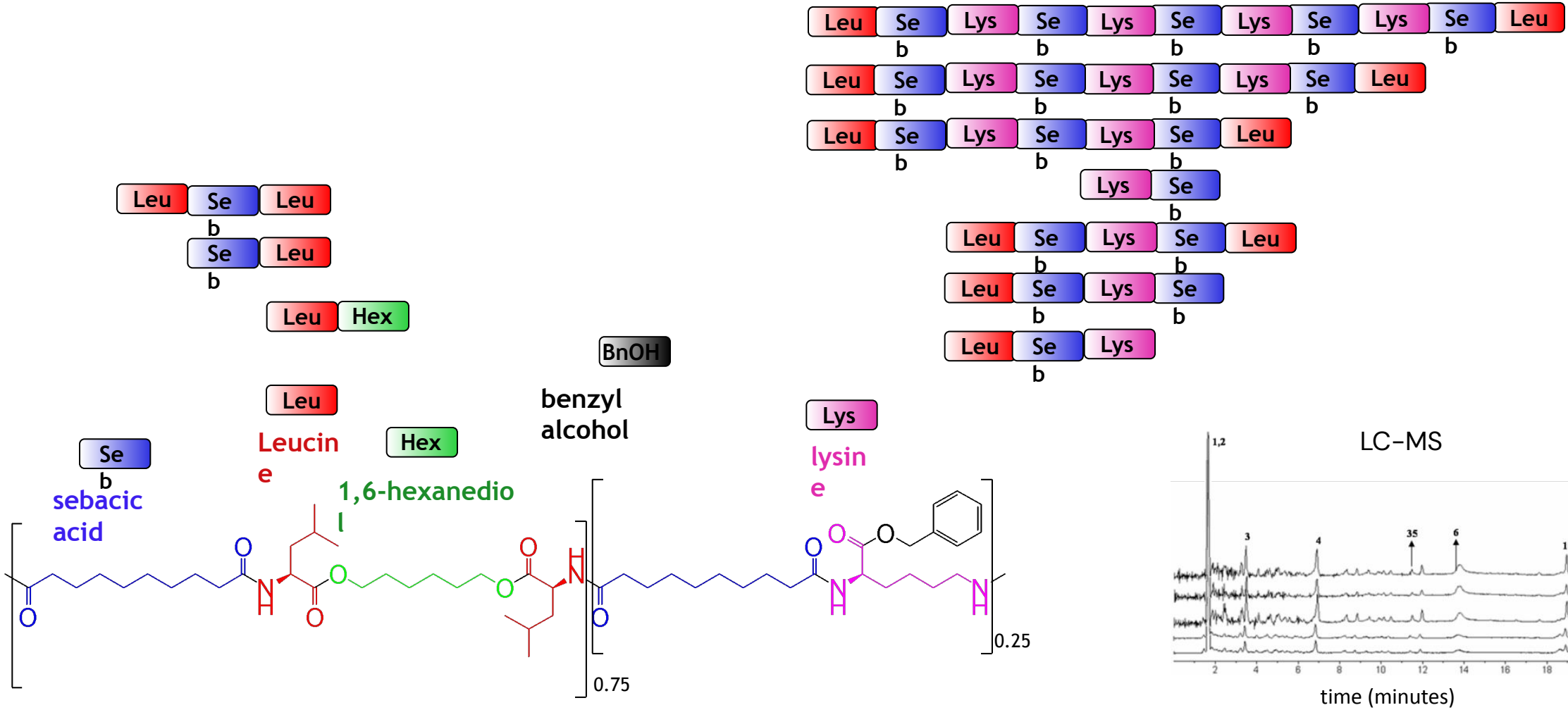
Monitoring enzyme mediated degradation

Degradation product identification



Ghaffar, A. et al., Biomacromolecules 12 (2011) 3243–3251

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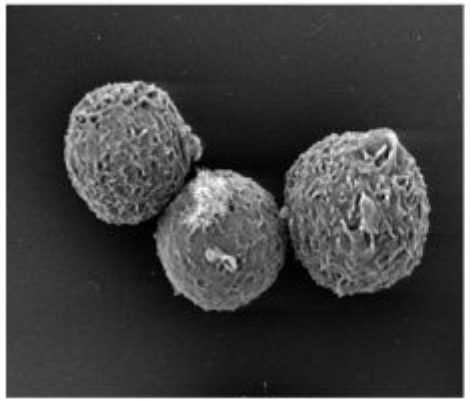
Biodegradation mechanism

Cell-mediated degradation

- Promyelocytic cells isolated from a 37-year-old leukemia patient in the 70's
- Most used cell-line to study neutrophil behavior

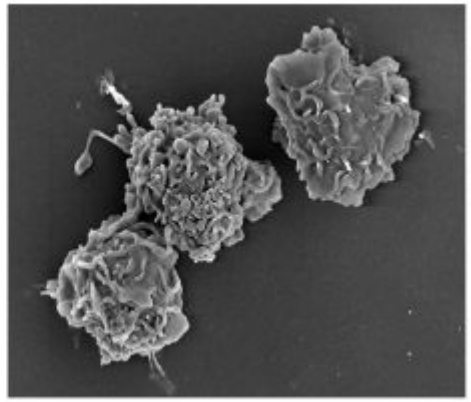
HL-60



Differentiation

- **1.25% DMSO 5-7 days**
- 100mM DMF for 5 days
- 0.1 µM ATRA 5 days
- ATRA, vitamin D3 and G-CSF 3 days

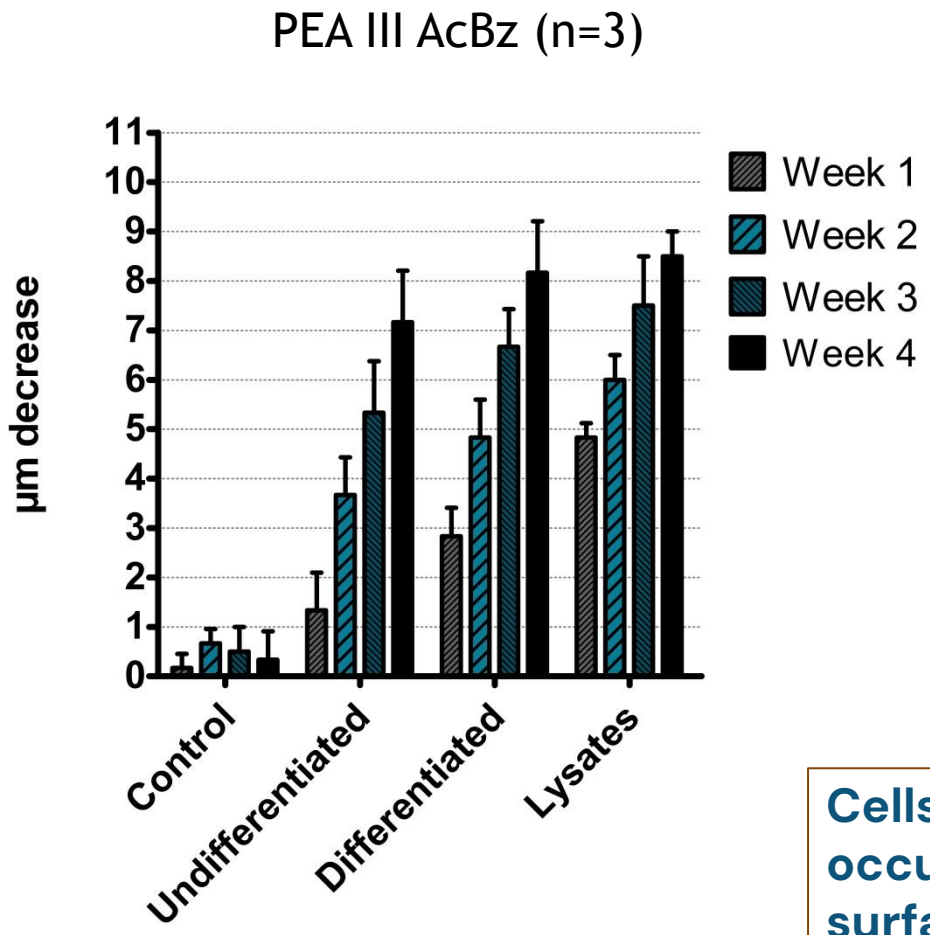
Neutrophil-like cells

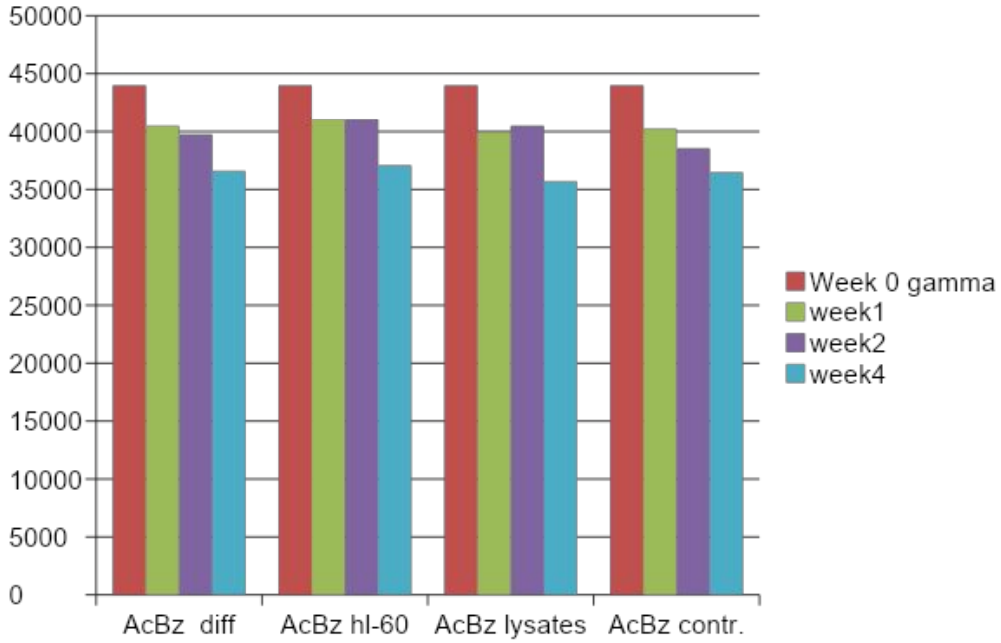


O3TRO92 PEA III Ac Bz cell mediated degradation, internal report, data on file

Biodegradation mechanism

Specimen thickness vs polymer molecular weight





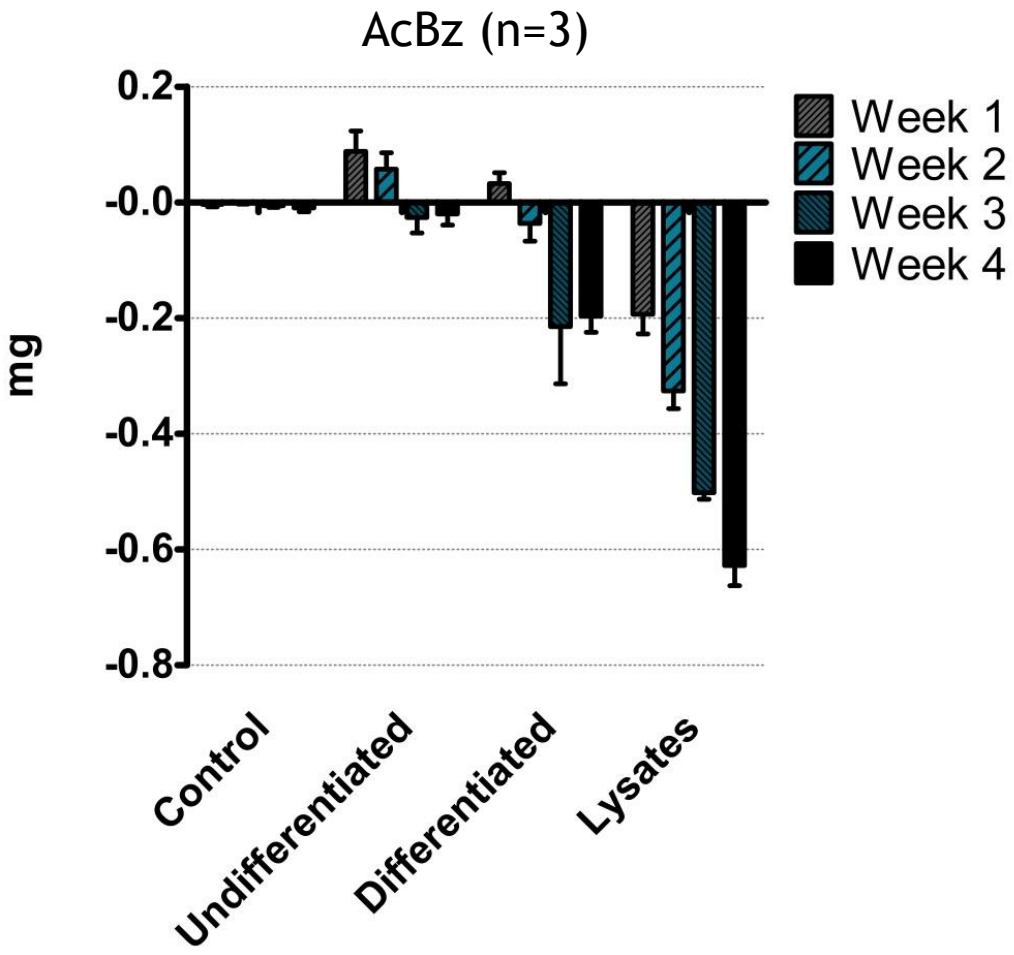
Cells mediated degradation occurs at the polymer surface

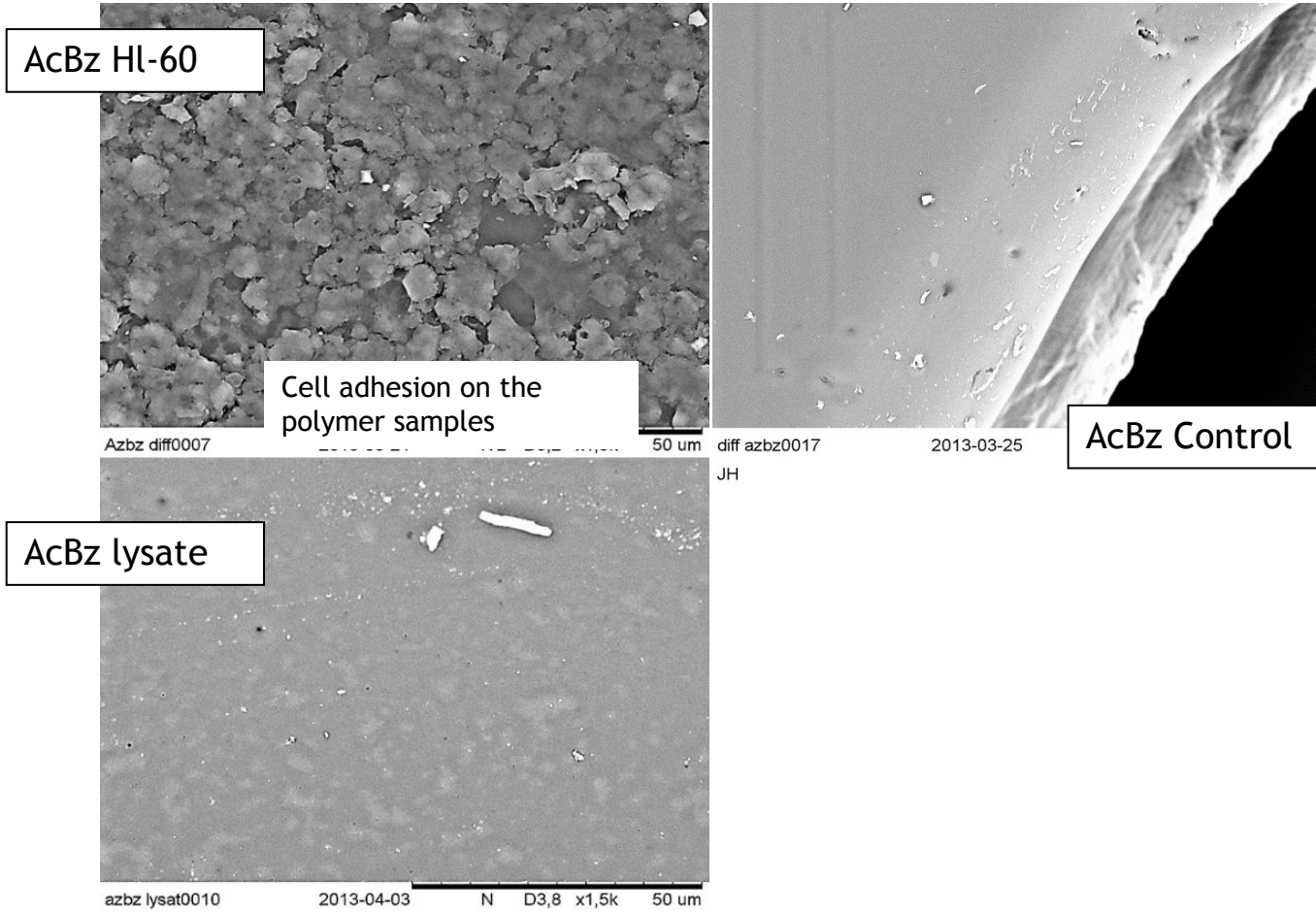
No impact on the MW!

O3TRO92 PEA III Ac Bz cell mediated degradation, internal report, data on file

Biodegradation mechanism

Cell-mediated bio-degradation – weight loss





Conclusive weight loss results are observed only in the lysate treated samples.

O3TRO92 PEA III Ac Bz cell mediated degradation, internal report, data on file

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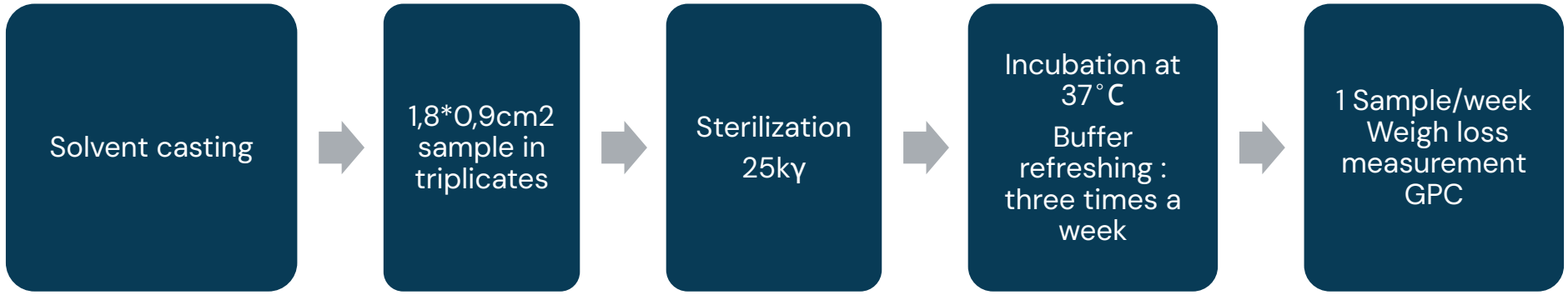
Biodegradation mechanism

Which proteases degrade TheraPEA?



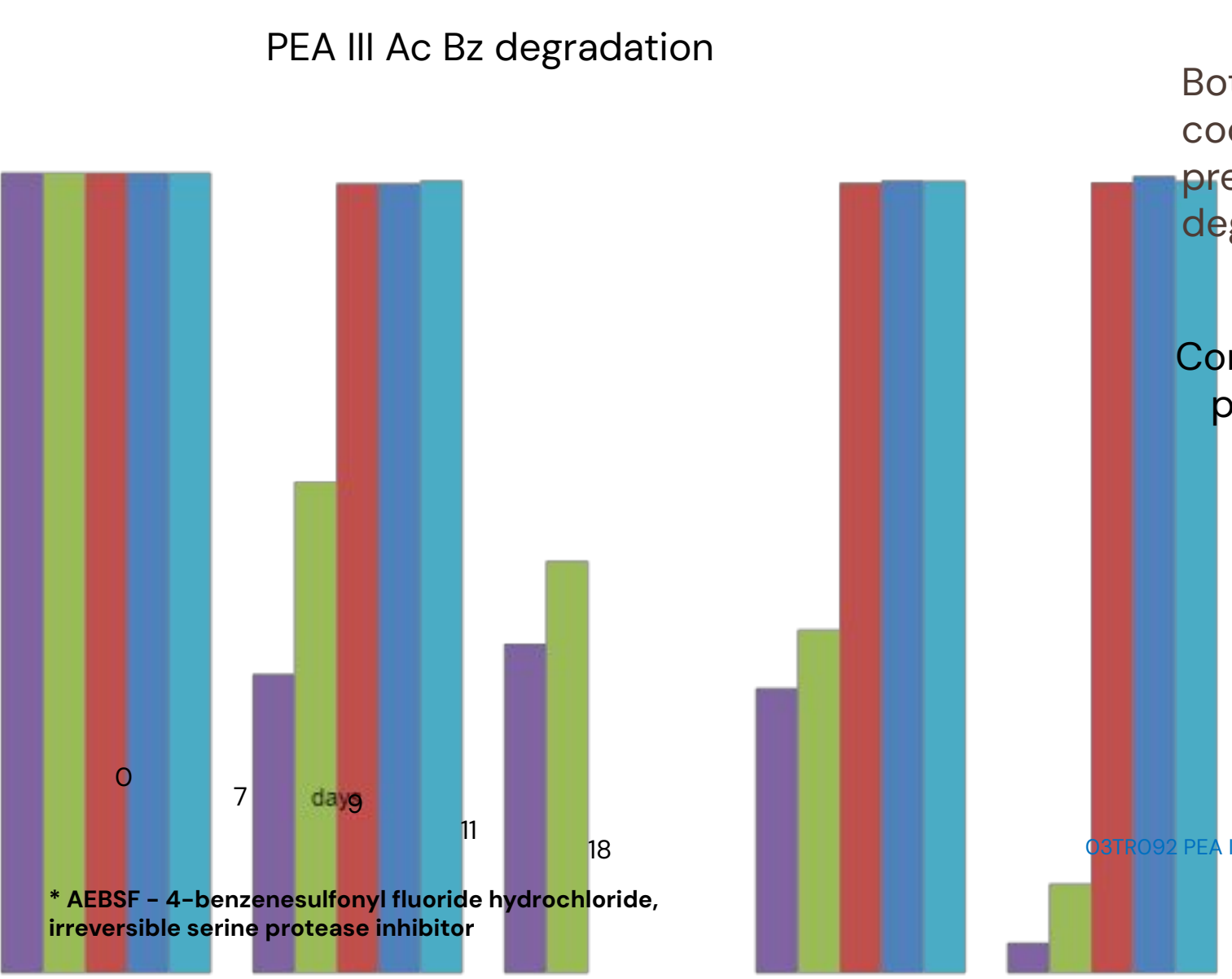
5 buffers :

- RPMI 1640 medium
- Lysates + cocktail proteases inhibitor + 1-10 Phenanthroline
- Lysates
- Lysates + 1-10 Phenanthroline
- Lysates + 4-(2-Aminoethyl)benzenesulfonyl fluoride hydrochloride (AEBSF)

03TRO92 PEA III Ac Bz cell mediated degradation, internal report, data on file

Serine Proteases – Major Role in Polymer Degradation

PEA III Ac Bz degradation



Both protease inhibitor cocktail and the AEBSF* prevented the polymer degradation

Conclusion: serine proteases play the major role in the polymer degradation

03TRO92 PEA III Ac Bz cell mediated degradation, internal report, data on file

*** AEBSF – 4-benzenesulfonyl fluoride hydrochloride, irreversible serine protease inhibitor**

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Biocompatibility and fit for intravascular applications

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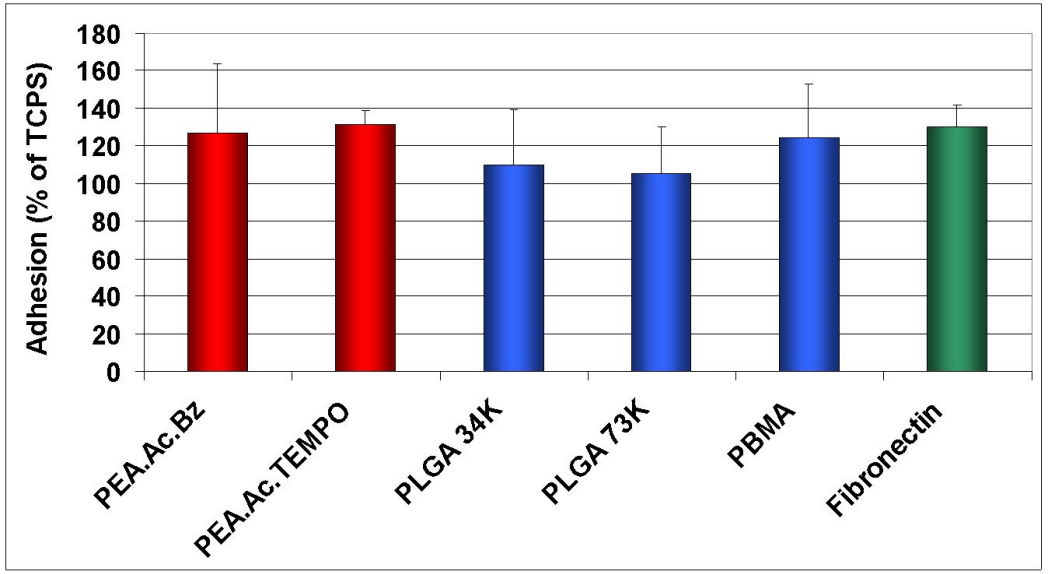
Anti-inflammatory activation of monocytes

Examining the blood and tissue culture responses



Human monocytes were seeded into wells containing polymers cast on coverslips at 1.6 x 105/cm2. Cells were incubated for 24 hours, and adhesion was measured by quantifying cellular ATP levels.

Monocyte adhesion to leucine and lysine containing PEAs showed equivalent to PLGA, PBMA and fibronectin-coated tissue culture polystyrene. PEA surfaces supported adhesion and differentiation of human monocytes in a similar rate than other biomaterials, however, PEA specimens do not appear to induce a hyper-activated state as judged by morphology and differentiation/fusion rates[1]

[1]DeFife et al., Journal of Biomaterials Science 20 (2009) 1495–1511

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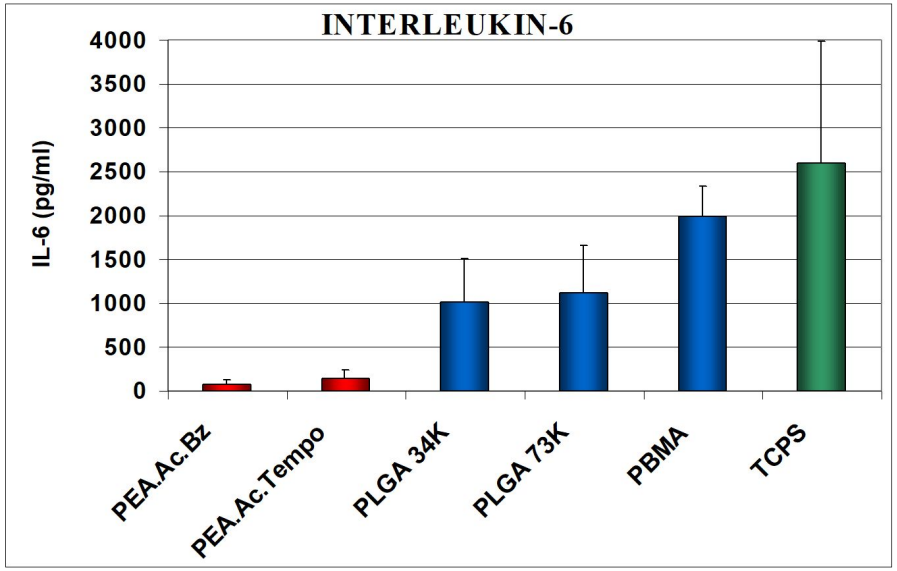
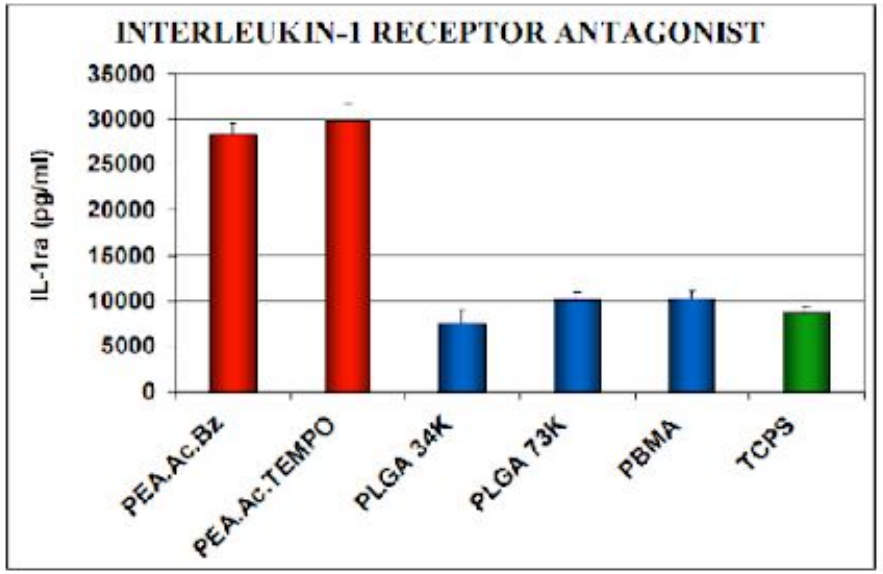
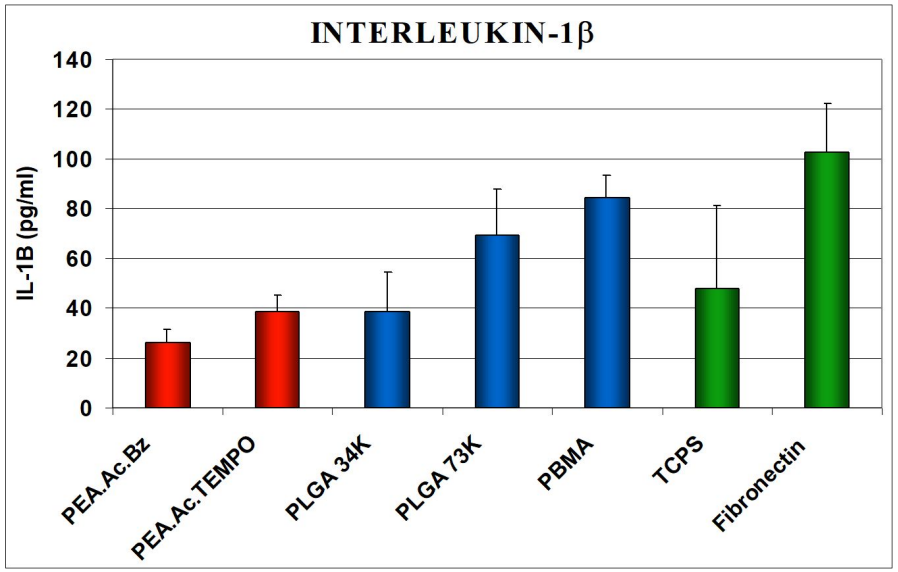
Anti-inflammatory activation of monocytes

PEAs induced adherent monocytes to secrete a significant amount of this anti-inflammatory mediator





Interleukin-1 receptor antagonist is a naturally occurring inhibitor of IL-1β that competitively binds the receptors for IL-1 and block pro-inflammatory signaling[1,2]



The pro-inflammatory cytokine secretion was lower than from monocytes on PLGA or PBMA specimens (Fig. A and Fig. B). Conversely, secretion of the anti-inflammatory mediator, interleukin-1 receptor antagonist, was significantly higher from monocytes on PEAs compared to other biomaterials (Figure C)[1,2]

[1]DeFife et al., Journal of Biomaterials Science 20 (2009) 1495–1511
[2]Verheye S., EXPERT REVIEW OF MEDICAL DEVICES, 2017, VOL. 14, NO. 9, 669–683

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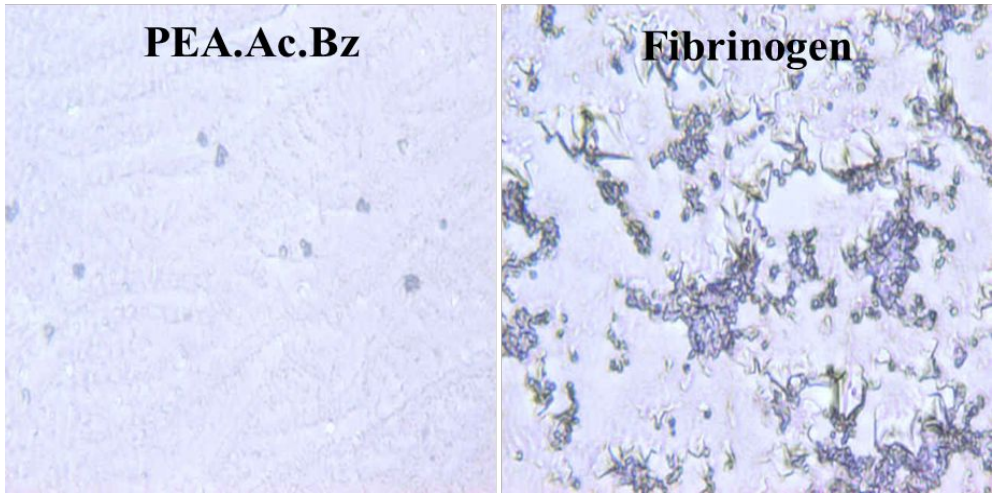
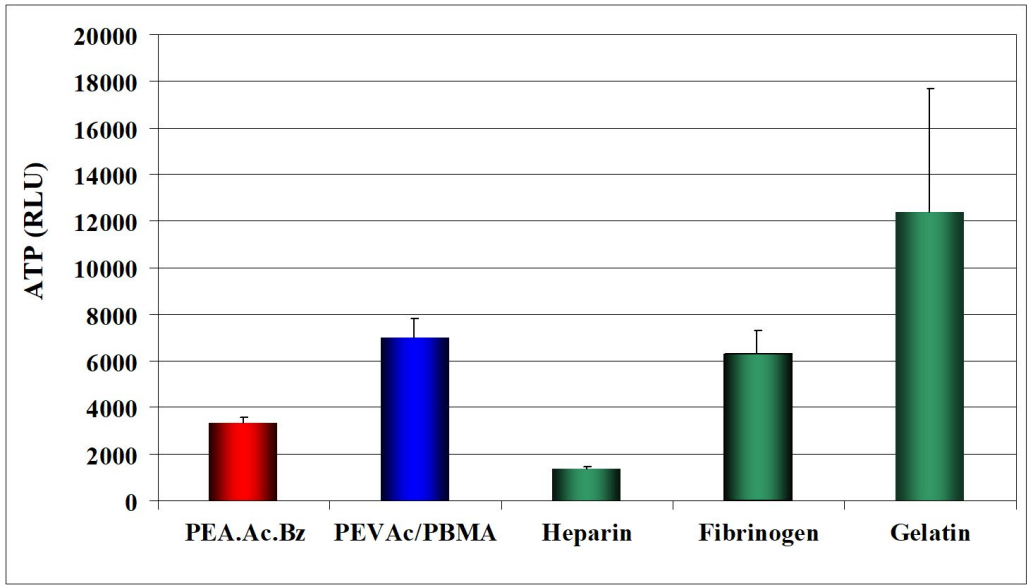
Platelet Adhesion, Aggregation and Activation

Markers of polymer hemocompatibility





Platelet aggregation, was examined exposing human platelets to PEA and a fibrinogen-coated surface for 30 minutes. Platelets did not readily adhere to or aggregate on PEA specimens[1]

Human platelets were incubated with polymer-coated or protein-coated wells for 30 minutes at 37°C, and ATP release was measured by luminescence assay. The low platelet activation on PEA surface suggests high hemocompatibility[1]

[1]DeFife et al., Journal of Biomaterials Science 20 (2009) 1495–1511

Pre-clinical and Clinical research examples

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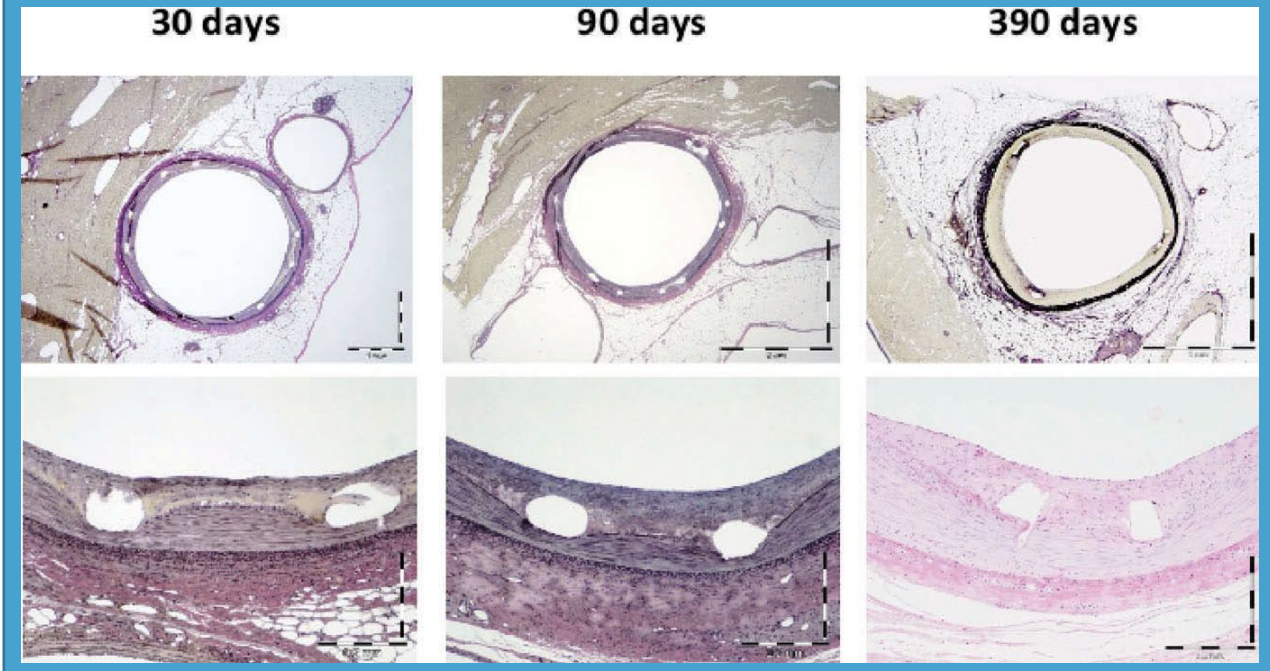
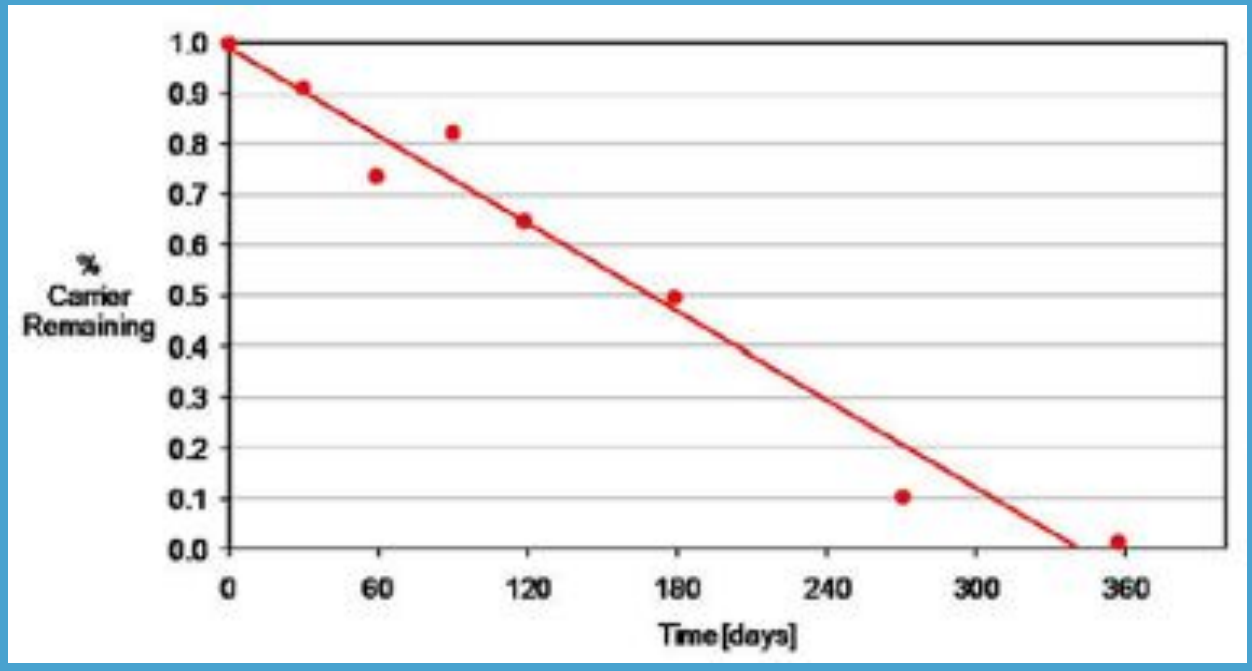
Healing and Biodegradation in preclinical model





Preclinical histology demonstrating complete endothelial coverage at 30 days, minimal fibrin deposition and robust healing at 90 days, and sustained healing with no catch-up through 390 days[2]

Controlled, multiple months in-vivo biodegradation of the TheraPEA coating in porcine preclinical model

[2]Verheye S., EXPERT REVIEW OF MEDICAL DEVICES, 2017, VOL. 14, NO. 9, 669–683

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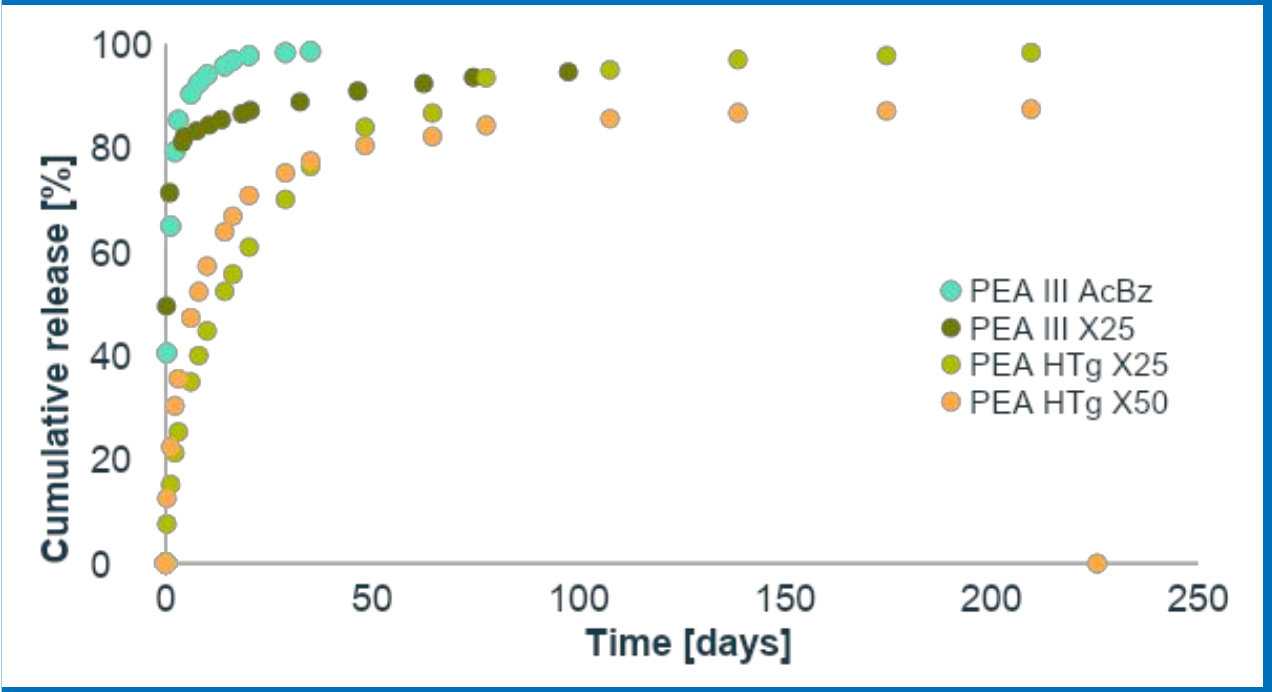
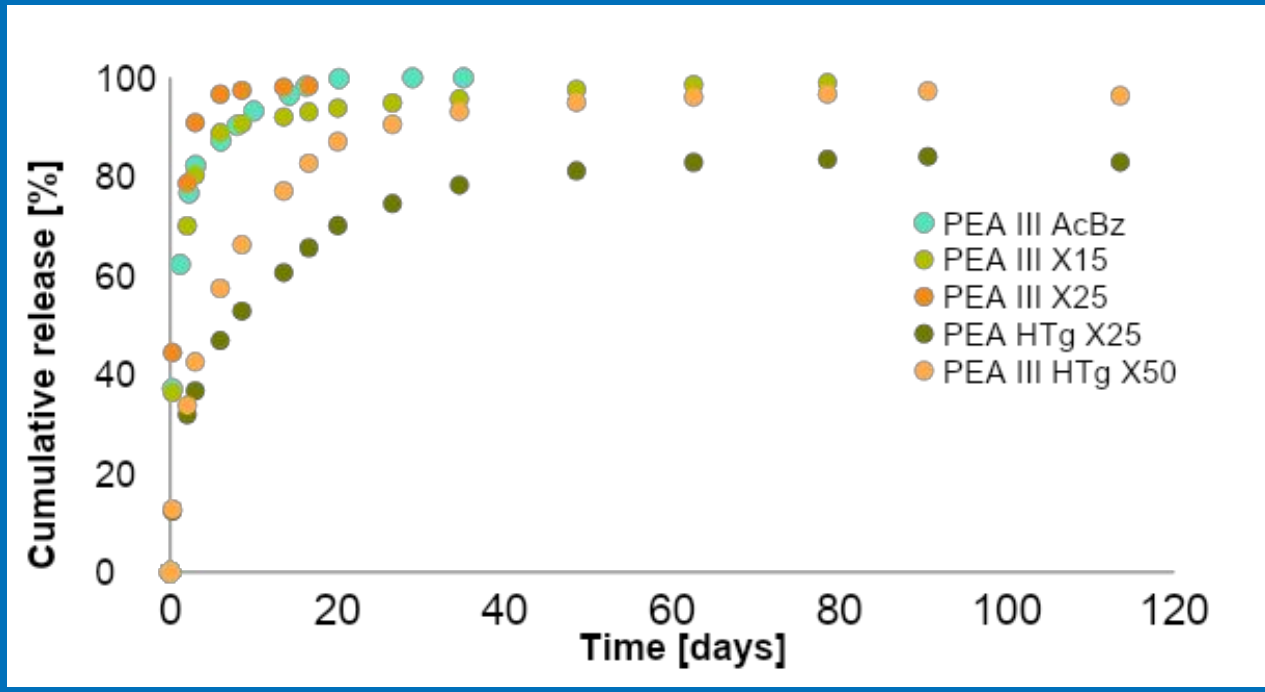
TheraPEA™ Facilitates Controlled Release of “Limus” API

Demonstrated release in highly tunable PEA based Microparticle formulations

High Load (40% w/w) Formulation



Medium Load (20% w/w) Formulation



Both low and high loading levels show >1 month release of API; release can be further tuned per application requirements.

3TR360 Formulation of Rapamycin into PEA microparticles of controlled size below 10 µm, Internal report, data on file

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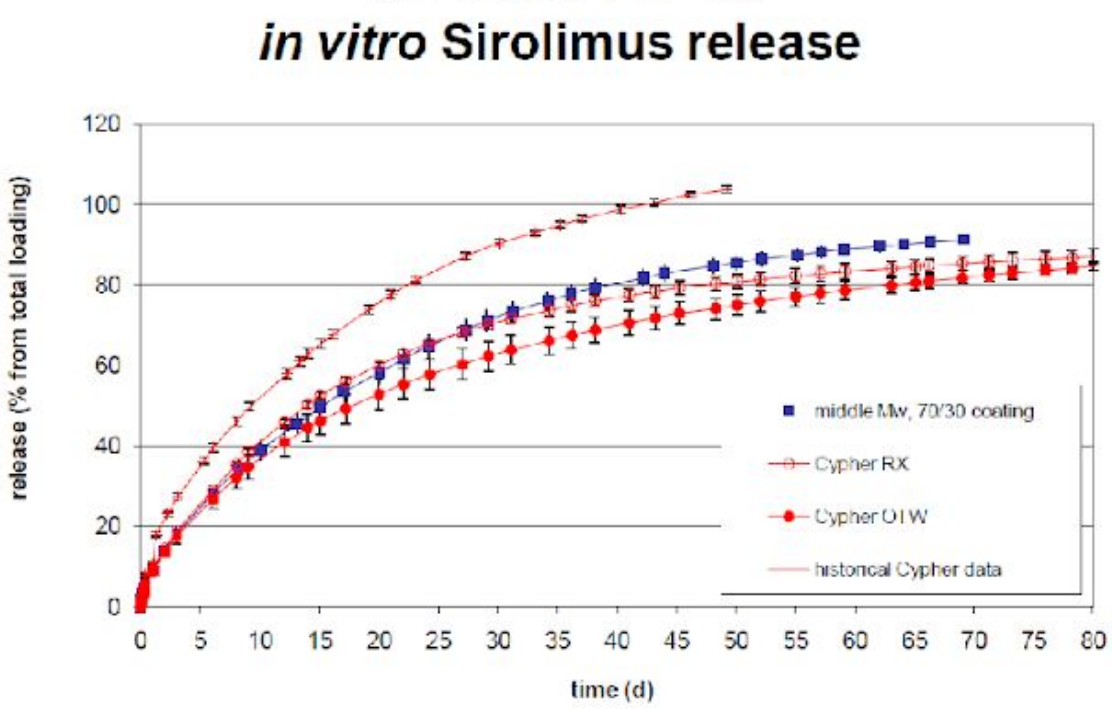
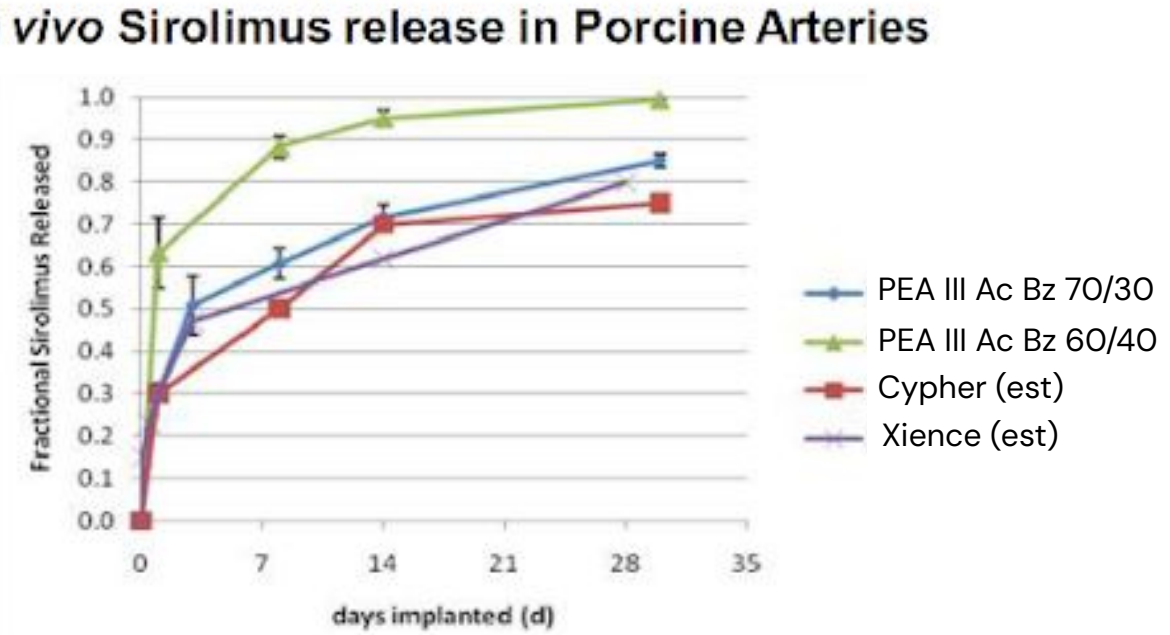
TheraPEA™ Facilitates Controlled Release of "Limus" API

Demonstrated release in highly tunable PEA based Microparticle formulations

TheraPEA-coated DES



Sirolimus release from TheraPEA coating closely follow the benchmark release (Cypher stent: biostable 3–layer coating of PEVA and PBMA)[3]



Pre-clinical research showed that sirolimus elution in-vivo follows classic unidirectional concentration-dependent diffusion kinetics, with approximately 80% of sirolimus released within 30 days and complete drug elution achieved in 60 days[2,3]

[2]Verheye S., EXPERT REVIEW OF MEDICAL DEVICES, 2017, VOL. 14, NO. 9, 669–683

[3]Granada J. F., Presented at EuroPCR, Paris, 2011

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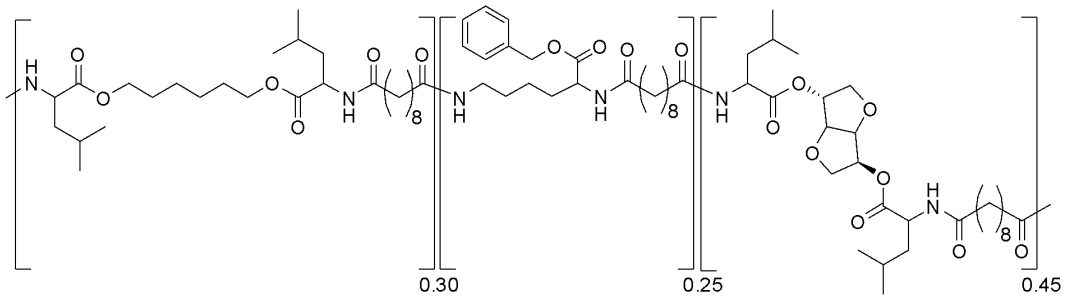
Robust performance in the clinical studies

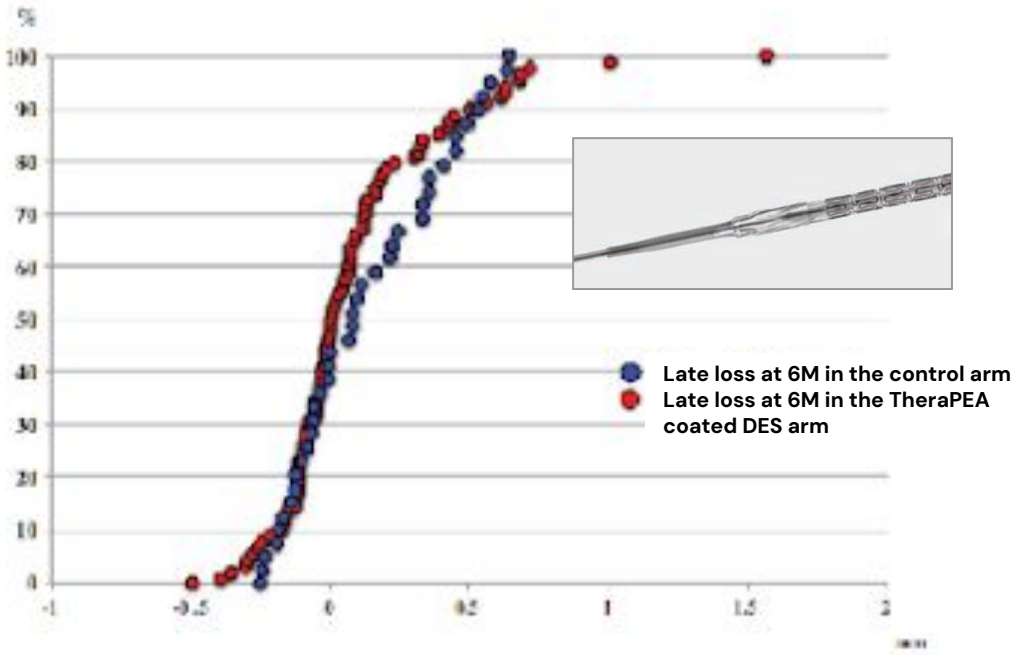


DIRECT II study highlights

At 6-month follow up the neointimal hyperplasia area was 0.89 ± 0.33 mm^2 and neointimal hyperplasia volume obstruction was 11.3%. The strut coverage averaged 94.2 ± 9.0%.

At one year, target vessel failure (TVF) was at 6.5 % (vs 9.8% in the control arm) with no thrombosis and no cardiac dead in either of the groups.

All results observed at one year were sustained through 2 years[2]



DIRECT II clinical study: *Cumulative frequency curves of angiographic late loss (in stent) at six months in the TheraPEA coated (0.09 ± 0.31), and control groups (0.13 ± 0.27), in patients with six-month angiographic follow-up, P value 0.430*

[2]Verheye S., EXPERT REVIEW OF MEDICAL DEVICES, 2017, VOL. 14, NO. 9, 669–683

Conclusions

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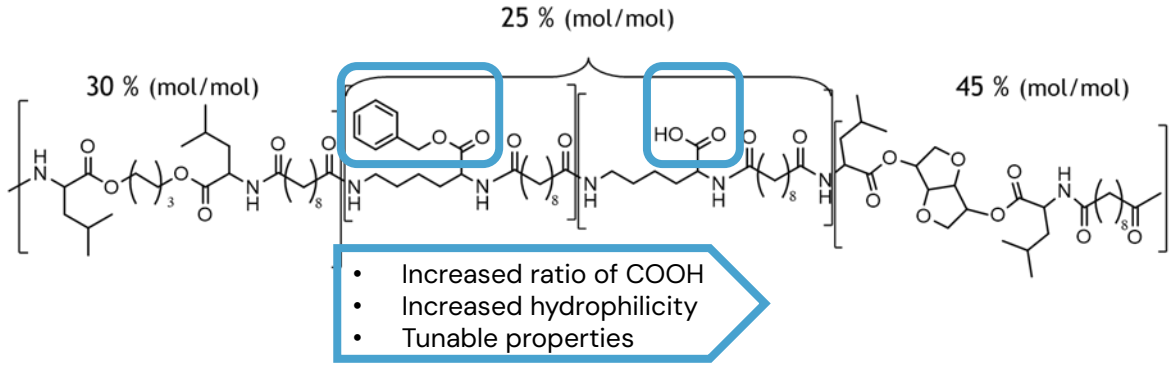
Enabling features of the TheraPEA™ platform

- **Random copolymer** – Product of catalyst-free polycondensation process at low temperature[2]
- **Material Properties** – amorphous elastomers, Mn 40 – 70 kDa, Tg 55 – 65 ^{0}C[2]
- **Bio-degradation** – Unique degradation mechanism controlled by the polymer's features[1]
- **Shelf-life stability** – GLP data support five years shelf-life[2]
- **Solubility** – Unique solubility in low hydrocarbon alcohols opening new opportunities for processing and co-processing with other biomaterials[2]

Enabling Features of TheraPEA™



- Tunable hydrophilicity
- Unique degradation mechanism (non-acidic degradation with zero order kinetics)[1]
- Controlled water-uptake properties ("slow-hydrogel like" behavior)[1]
- Protein inspired polymer structure provides a "buffering effect" during biodegradation[1]

[1] Presented at CRS 2022, Montreal
[2] MF PEA III Ac Bz, MF PEA III X25

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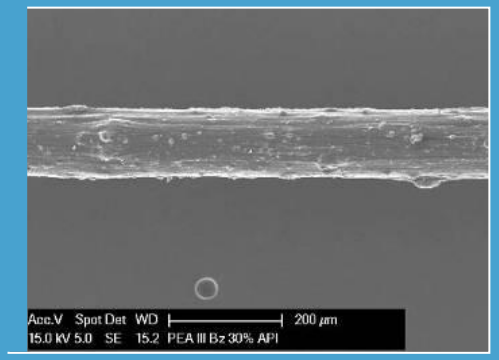
Our Versatility in Processing Forms

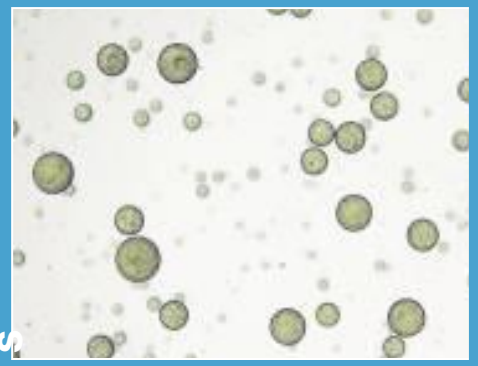
Ability to process TheraPEA™ into a variety of injectable and implantable forms

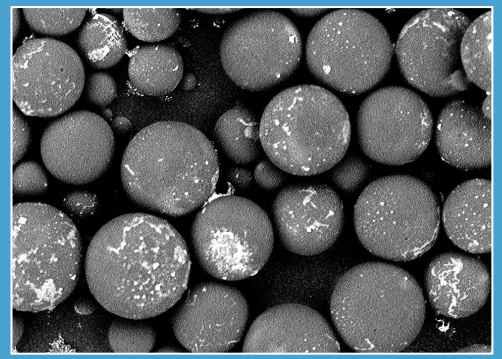
Fibers



- Enables possibility of low temperature melt processing
- Microfiber diameter: 100µm – mm
- API loading 10 – 50 wt%
- Melt – Extrusion, Spinning (g) and Injection molding (mg)
- Solution - Film casting and cutting

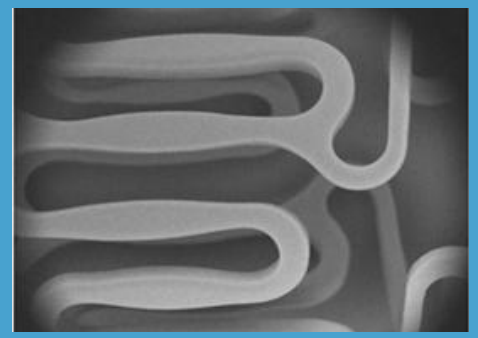
Microparticles

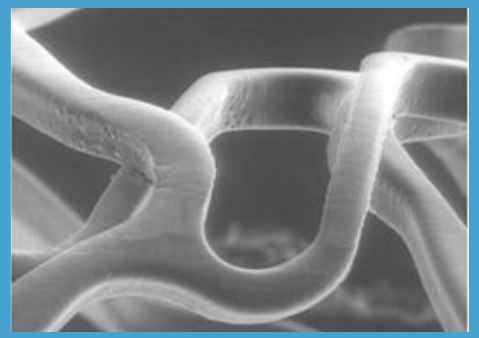




- Typical diameter can range from 10 – 100µm
- API loading >10 wt%
- Numerous: emulsification, spraying, etc.

Coatings and Films





- Compatibility with number of substrates
- Excellent adhesion to metals
- Numerous options available
- Excellent melt processability
- Unique solubility properties

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Why partner with DSM Biomedical?

TheraPEA™ biodegradable polyester amide

Differentiated technology to enable innovative sustained and controlled release therapies for the patient

Bridging the gap between biomaterials technology and drug delivery solution

Solving our world's healthcare needs through sustainable science, together with our partners

A partner you can depend on

Extensive in-house expertise, including analytical competencies and melt and solution-based processing techniques, to accelerate formulation development efforts in our dedicated high potency laboratory.

How Can DSM Biomedical Elevate Your Next Sustained Drug Delivery Project?

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