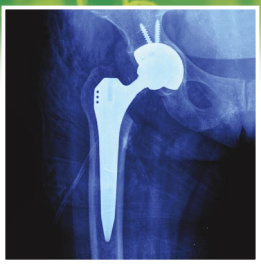
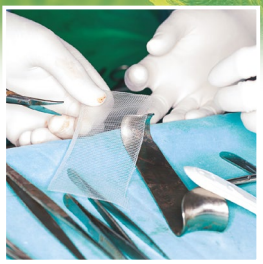
HyMedPoly

Drug-Free Antibacterial Hybrid Biopolymers for Medical Applications

A H2020 Marie Skłodowska-Curie Innovative Training Network





hymedpoly.eu

INTRO

HyMedPoly is a 4 year programme developing new anti-bacterial therapies based on polymers and inorganic materials for biomedical applications, supported by the EU Marie Skłodowska-Curie Action.

We are a partnership of four universities, working with a medical partner and three companies focused on materials, training a cohort of fifteen Early Stage Researchers to develop and qualify material systems with antibacterial activity for medical applications, such as wound care, implants, regenerative medicine and bio film prevention. The ultimate goal is to develop a new generation of professionals who will play a pivotal role in pushing forward new therapies based on drug-free antibacterial materials for the coming decades.

Research has focused in five areas:

INORGANIC MATERIALS ... ceramics and glasses
SYNTHETIC POLYMERS ... polyurethanes and polyesters
NATURAL POLYMERS ... polyhydroxyalkanoates
PRODUCT DEVELOPMENT
CLINICAL IMPACT ASSESSMENT

After initial emphasis on new material systems, the researchers have looked to incorporate their materials into products for hospitals and personal healthcare such as wound dressings, sutures, scaffolds, coatings, vascular grafts and nerve conduits. Additionally, a bacterial colonized 3D human skin equivalent has been developed to bio-evaluate novel antimicrobial materials. This booklet provides insight into these innovations. We are currently looking to build collaborations to bring our ideas into products and would welcome hearing your thoughts.

E-mail us on applications@hymedpoly.eu to open the discussions or share your thoughts.

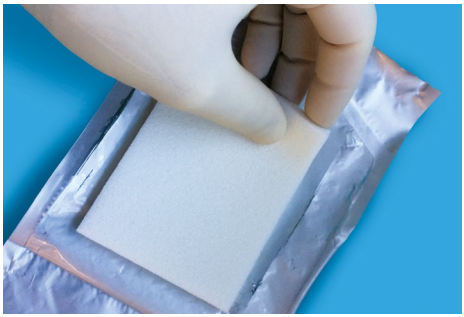
HyMedPoly is a four year project and has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 643050.

CHALLENGE

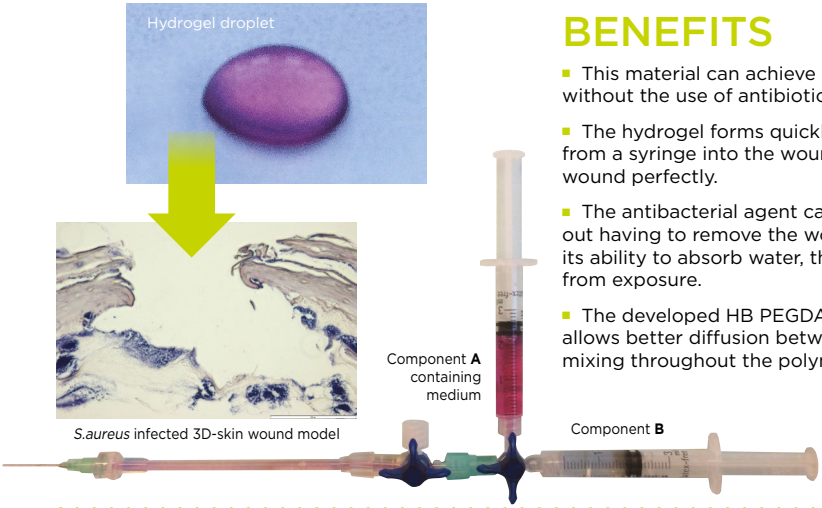
A drug free antibacterial wound dressing made from natural remedies

APPROACH

- Analyse the mechanism behind ancient remedies like the use of honey and improve them.
- One of the properties that gives honey an antibacterial effect is the production of Reactive Oxygen Species (ROS) by glucose oxidase and glucose.
- The HB PEGDA/HA-SH hydrogel has antibacterial activity without loading antibiotic drugs. The antibacterial ROS can be regenerated by replenishing the glucose supply into the hydrogel.
- The next stage is to continue chemical and biological tests and find a method to economically produce HA-SH and HB PEGDA.



Preparing a PVA hydrogel wound dressing for second and third grade burns and serious dermis and subcutaneous wounds



S.aureus infected 3D-skin wound model

BENEFITS

- This material can achieve antibacterial activity without the use of antibiotics.
- The hydrogel forms quickly and can be extruded from a syringe into the wound surface to cover the wound perfectly.
- The antibacterial agent can be replenished without having to remove the wound dressing by using its ability to absorb water, thus preventing infection from exposure.
- The developed HB PEGDA/HA-SH hydrogel allows better diffusion between glucose and GO by mixing throughout the polymer matrix.

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ESR 01 and ESR 14

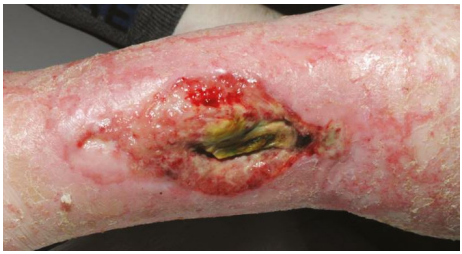
CHALLENGE

Drug-resistant bacteria, both in planktonic and sessile forms, are the root cause of life threatening infections. The sheer inability of therapeutics to reach the location of invasion of pathogenic bacteria in deep tissue layers, or even in interstices of cells in tissue in the case of chronic wounds, leads to persistent infection

APPROACH

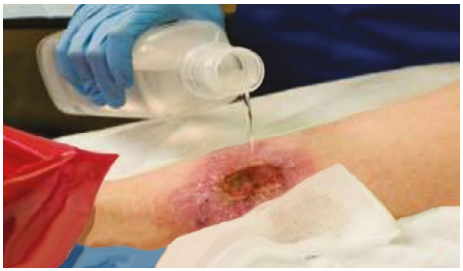
To tackle this problem, we developed biomimetic amphiphilic (cubosomes) patchy colloidal particles.

These colloidal particles were developed to induce disruption of the bacterial cell membrane and inhibition of the cell wall synthesis. Consequently there is a higher chance of overcoming the effect of induction of resistance by the bacteria.

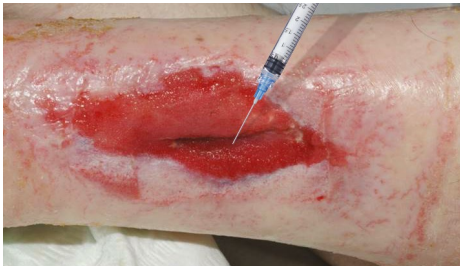


Infected

Possible routes of administration...



Topical



Intradermal application

BENEFITS

- Bactericidal against *Staphylococcus aureus*, MRSA, *Enterococcus faecium*, VRE and *Pseudomonas aeruginosa* which may often cause serious infections that may be fatal in worst case scenarios. This material can achieve antibacterial activity without the use of antibiotics.
- Fast bactericidal action, biofilm prevention and disruption of pre-established biofilms of Gram-positive bacteria.
- Higher selectivity towards bacterial cells over keratinocytes, fibroblasts, monocytes and macrophages.
- Easy to handle product to be applied directly on infected wounds.

ESR 02
and
ESR 15

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A novel antibiotic-free antibacterial and resorbable coating for surgical sutures based on therapeutic ions

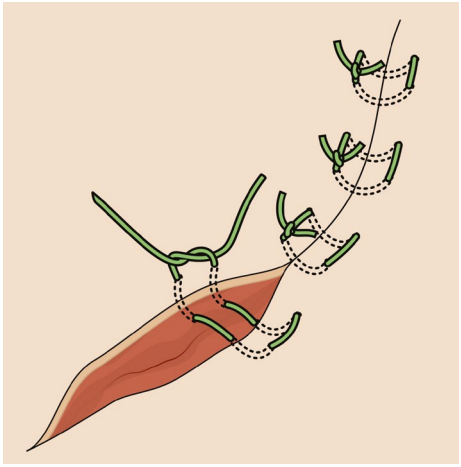
CHALLENGE

APPROACH

The current gold standard for antibacterial coatings on sutures is triclosan. However, triclosan use is too widespread, its real efficacy has been questioned and there are concerns regarding its environmental and human toxicity and triggering of resistance.

Our coating offers a versatile, bioresorbable and antibiotic-free alternative to current coated sutures. The composition of the coating can be adapted to deliver ions that, together with antibacterial activity, can provide other beneficial properties (e.g. angiogenesis regulation).

The current stage of development is aiming to optimise the proof of concept in order to obtain reproducible coatings on long portions of thread.



The next planned steps are:

- The systematic optimisation of the process by means of a Design-of-Experiment (DOE) approach.
- The benchmarking of our technology against the current main competitor in terms of degradative, mechanical and antibacterial properties.

BENEFITS

- Our novel sutures, compared to standard sutures, reduce the risk of infections around the wound site and offer a safer choice for patients and clinicians.
- Compared to the current triclosan state-of-the-art, therapeutic ions release:
  - Offers safety for the patient.
  - Is more environmentally friendly.
  - Reduces the risk of the development of antibacterial resistance.
  - Provides a beneficial stimulation of tissue regeneration while fighting bacteria.

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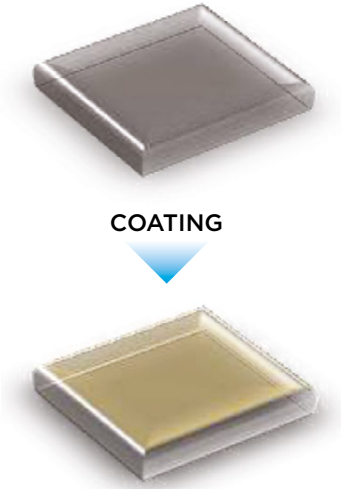
ESR 03
Bioresorbable Antibacterial Polyesters

CHALLENGE

Encapsulation and controlled release of essential oils using a bioresorbable polyester/bio-based polymer carrier for antimicrobial coatings on medical devices, such as implants, sutures or wound dressings

APPROACH

- A delivery system of blends of Polycaprolactone (PCL) and a bio-based polymer to encapsulate and control release of natural antibacterial essential oils.
- The ingredients of a polymeric matrix can be modified to optimise the properties.
- Two systems of PCL–Zein and PCL/–PGS were successfully produced to deliver cinnamon bark oil with excellent antibacterial activity.
- Advanced cytotoxicity analysis and optimisation of the dip-coating process are in progress.



BENEFITS

- The use of natural essential oils (EO) (e.g. cinnamon bark oil) overcomes the drug resistance. The naturally-sourced materials combine biocompatibility and environmentally friendly properties with low cost and ease of preparation.
- New polymeric combinations were developed to employ EOs in new bioapplications. The EO/polyester carriers deliver EO with antibacterial activity but with reduced risk of cytotoxicity associated with pure EO through controlling release.

ESR 04
Biodegradable & Bioresorbable Polyesters

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Development of novel antibacterial Polyhydroxyalkanoate based scaffolds for bone defect regeneration

CHALLENGE

APPROACH

How is the challenge being addressed?

Production of Polyhydroxyalkanoates (PHAs) and their fabrication into inherently active antibacterial PHA based scaffolds by 3D printing.

Why was this approach taken?

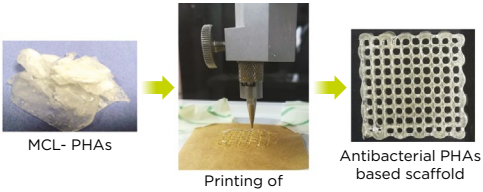
PHAs are biodegradable and biocompatible polyesters are obtained from renewable resources. The use of inherently active antibacterial material will result in long term efficacy without the use of antibiotics.

What is the state of the development?

Antibacterial PHAs have been produced and characterised. The production of the scaffold is under optimisation.

What are the next steps?

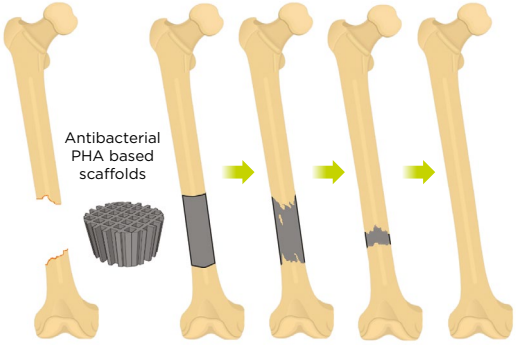
Incorporation of the antibacterial activity in the scaffolds. Evaluation of biocompatibility and antibacterial activity of the structures obtained.



MCL- PHAs

Printing of MCL- PHAs

Antibacterial PHAs based scaffold



BENEFITS

The antibacterial properties are achieved by the use of inherently active antibacterial Polyhydroxyalkanoates, providing long term efficacy without the use of antibiotics. Polyhydroxyalkanoates are biocompatible and degrade by surface erosion, allowing a controlled degradation important for bone application.

What differentiates it from the state-of-the-art?

This will avoid the drawbacks associated with the use of autografts (e.g. limited viability) using tissue engineering constructs. Compared to synthetic polymers, Polyhydroxyalkanoates are obtained from renewable resources and show less acidic degradation products, lowering the risk of an inflammatory response.

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ESR 05
Novel
Antibacterial
Natural Polymers

CHALLENGE

Develop a drug-free antibacterial wound dressing without triggering antibiotic resistance

APPROACH

How is the challenge being addressed?

Introduction of antibacterial groups by permanent surface modification without the incorporation of drugs.

Why was this approach taken?

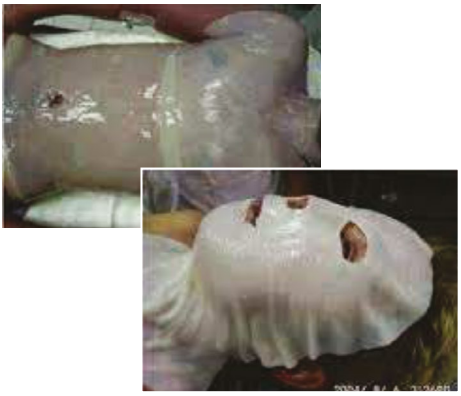
Introduction of antibacterial groups by surface modification of bacterial cellulose results in a wound dressing with inherent antibacterial activity for long-term efficiency.

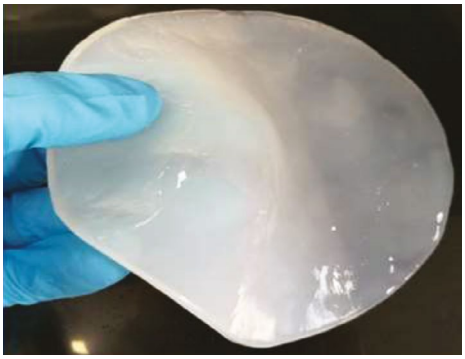
What is the state of the development?

Different modification pathways have been investigated and the antibacterial activity and preliminary biocompatibility of the materials has been evaluated.

What are the next steps?

Complete biocompatibility towards keratinocytes.





BENEFITS

The use of a hydrogel as a wound dressing for dry wounds can ensure additional hydration, enhancing the healing rate, helping the debridement of necrotic tissue and reducing the pain related to the change of the dressing. The use of a drug-free wound dressing does not trigger bacterial resistance, and can protect the wound from contamination.

What differentiates it from the state-of-the-art?

Bacterial cellulose-based wound dressings are available on the market thanks to their great biocompatibility, good mechanical properties and hydrogel-like structure. However, there is no report of an inherently antibacterial wound dressing based on bacterial cellulose.

ESR 06
Hydrogel Based Hybrid Antibacterial Polymers

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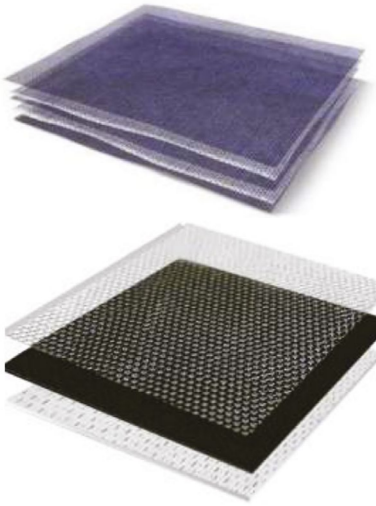
CHALLENGE

Development of a novel approach to antibacterial wound dressings which address the challenge of antibiotic resistance

APPROACH



How is the challenge being addressed?

Combination of a controlled release of antibacterial bioactive glass with a biocompatible polyetherurethane-based delivery system.

Why was this approach taken?

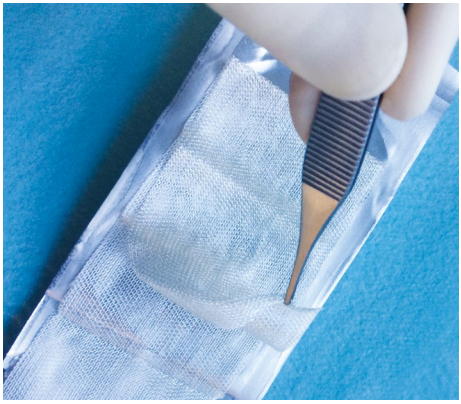
The structure and properties of both the bioactive glass (BG) and polyetherurethane can be modified to control the final properties.

What is the state of the development?

Antibacterial polymer/Ag BG composites have been obtained, however further modification is required with the polymer to achieve better cell viability.

What are the next steps?

After achieving good biocompatibility, prototypes are made to work.



BENEFITS

Antibiotics are not needed to achieve antibacterial activity. By adding functional groups to the polymer its cell viability can be enhanced. This material system enables a platform of technology that can be applied to different products.

What differentiates it from the state-of-the-art?

They can be used as films in composite wound dressings or the polymer/Ag BG solution can be used to coat a cotton gauze or non-adherent silicon foam. Different from commercial Ag dressings, the Ag BG is also good for cells due to its silicon, calcium and phosphorus ions.

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ESR 07
Bioactive
Silica Glass

CHALLENGE

Development of novel antibacterial and cyto hydroxyapatite compatible coatings on metallic implants for bone tissue regeneration applications

APPROACH

How is the challenge being addressed?

Controlled release of metal ions from substituted hydroxyapatite (HA) in combination with Chitosan polymer in composite coatings would be effective.

Why was this approach taken?

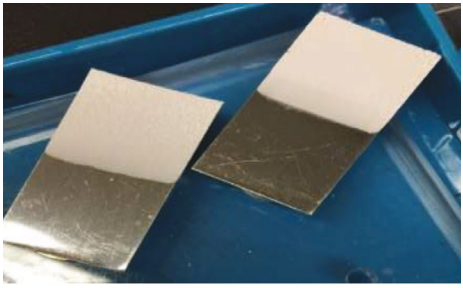
To effectively use the combined properties of hydroxyapatite, doped metal ions and polymers in the final product.

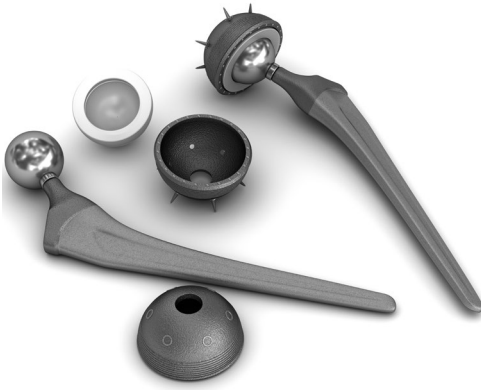
What is the state of the development?

Novel antibacterial substituted HA/chitosan composite coatings via electrophoretic deposition have been developed.

What are the next steps?

Further cell studies of composite coatings using specific cell lines. Coatings of substituted HA via plasma spray sintering.





BENEFITS

These coatings are proposed to significantly promote osseointegration between bone and various orthopaedic implants whilst providing intrinsic significant antibacterial properties without loss of cell viability. From a business aspect, this process uses low cost equipment which is easy to set up and is able to coat complex shapes and patterns.

What differentiates it from the state-of-the-art?

Use of multi-ion substituted HA in combination with biocompatible chitosan using a very simple coating technique, makes it different from the state-of-the-art. Fabrication of multilayer coatings via electrophoretic depostion for multifunctional properties, using doped HAs in combination with a suitable polymer.

ESR 08
Substituted Hydroxyapatite

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CHALLENGE

A growing problem of bacteria resistance to antibiotics could be solved by a new generation of drug-free biomaterials with release of antimicrobial ions

APPROACH

How is the challenge being addressed?

Soluble Phosphate based glasses (PBG) allow for controlled release of antibacterial ions.

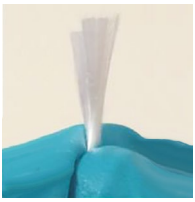
What is the state of the development?

Soluble glasses have been manufactured and their biological properties have been tested showing antibacterial behaviour and cytocompatibility.

What are the next steps?

Choosing the polymer to design a PBG composite.

SINTERED GLASS



GLASS FIBRES

MELT-QUENCHED GLASS

COMPOSITES

BENEFITS

PBG with antibacterial ions are relatively easy to produce, contain ions naturally occurring in the human body and are soluble, which makes them interesting materials for temporary implants. They are known to be suitable for a wide range of tissues such as nerve tissue, muscle tissue, skin and bone tissue.

Why is it better and what differentiates it from the state-of-the-art?

Bioactive glasses (silica-based) are well known and used in bone regeneration. However poor solubility of bioactive glasses and unknown silica metabolism may be a serious disadvantage. PBG are suitable for soft tissue applications, this expands their application and, due to high rates of dissolution, they are an ideal material for temporary implants without risk of reoperation following treatment. Additionally Gallium and Cerium are less toxic than other common antimicrobial ions eg. Ag or Cu.

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ESR 09
Bioactive Phosphate Glass

CHALLENGE

Development of a new family of antibacterial and conductive PHAs and their use in the generation of nerve conduits for peripheral nerve regeneration

APPROACH

How is the challenge being addressed?

Introduction of antibacterial and conductive agents within polyhydroxyalkanoates (PHA) matrices, followed by formation of tubes.

Why was this approach taken?

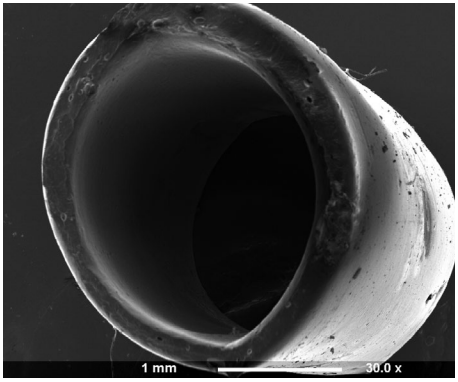
Introduction of antibacterial and conductive properties within a biocompatible and biodegradable polymer will extend its use in a huge range of applications. We have focused on nerve conduits as an example.

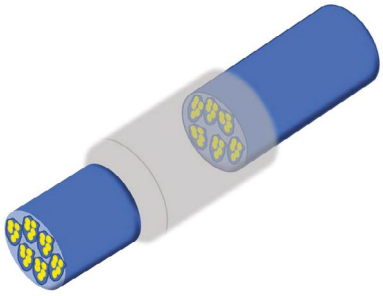
What is the state of the development?

These novel materials have already been produced and nerve conduit prototypes have been developed.

What are the next steps?

Complete biocompatibility towards nerve cells and exhaustive antibacterial assessment.





BENEFITS

Bacterial infection is a widespread problem in peripheral nerve injuries, hence a biocompatible, biodegradable material which is additionally antibacterial and conductive has a great attractiveness. The example of nerve conduits is taken in this case where active regeneration will additionally benefit from the antibacterial and conductive properties of the nerve conduits.

What differentiates it from the state-of-the-art?

There is no such natural material currently available in the market which has all the properties in the developed material, i.e. biocompatibility, biodegradability, antibacterial and conductive activity.

ESR 10
Novel Antibacterial Polymers

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CHALLENGE

Antibacterial anti-adhesion polyhydroxyalkanoates (PHAs) for biomedical applications

APPROACH

How is the challenge being addressed?

Combination of antibiofilm agents and Antimicrobial Peptides (AMPs) with biocompatible PHAs.

Why was this approach taken?

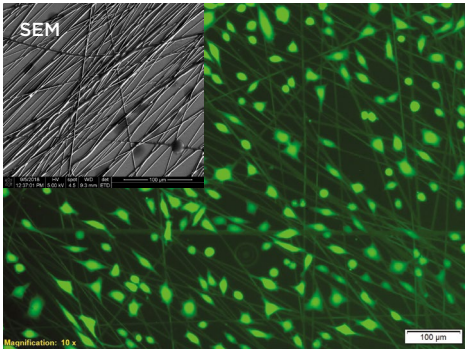
PHAs are highly biocompatible. Their combination with anti-biofilm agents will make an excellent material for a vast range of biomedical applications.

What is the state of the development?

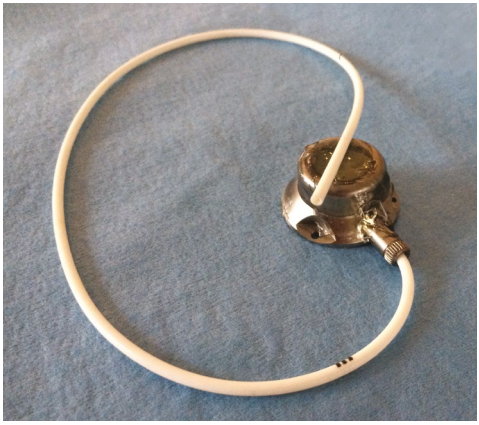
PHAs have been successfully combined with anti-biofilm agents, showing excellent antimicrobial activity and cytocompatibility.

What are the next steps?

Detailed characterisation of the materials applying to various medical device demonstrators.



Viable fibroblasts attached to the surface-modified PHA-PEG fibres



BENEFITS

The PHAs are highly biocompatible and biodegradable, hence extremely attractive for biomedical applications. The additional anti-biofilm properties will enhance their biomedical attractiveness.

What differentiates it from the state-of-the-art?

Our new generation of specifically modified biomaterials will shorten the time of tissue integration and simultaneously prevent any bacterial adhesion and biofilm formation, a requirement that many biomedical materials need but do not have.

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ESR 11
Antibacterial Materials for Tissue Engineering Scaffolds

CHALLENGE

Micro patterning of polymeric materials with predesigned surface structures is of great significance in a wide range of applications including tissue engineering.

Our ultimate aim is to develop methods to tailor the microscale topographies of scaffolds to influence cell responses which could benefit engineering of complex tissues.

Developing a novel idea to improve the cell behaviour in 3D printed tissue engineering implants.

APPROACH

How is the challenge being addressed?

Surface topography of scaffolds can be controlled and customised which has potential benefits in tailoring features for different cell types on 3D printed tissue engineering scaffolds. The challenge is being addressed through a novel approach to the design and fabrication of 3D printed scaffolds.

Why was this approach taken?

It is a novel idea which saves processing time and can be implemented affordably with scaffolds produced using currently available 3D printers.

What is the state of the development?

A range of scaffolds have been produced with a variety of topographies.

What are the next steps?

In vitro studies to assess cell growth on the scaffolds and investigate cell behaviours in response to surface topography.

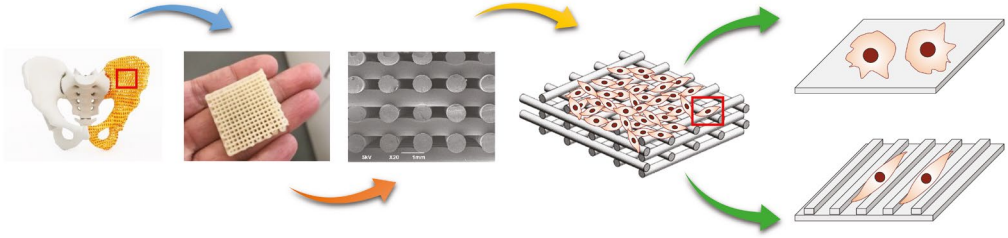
BENEFITS

The need for biomaterials and scaffolds required for different applications is growing fast. Therefore, any improvement in this area is of interest. Design and fabrication of scaffolds which facilitate the controlled growth of healthy functioning tissues is a key challenge for development in implant technologies and bioartificial organs.

What differentiates it from the state-of-the-art?

Our method:

- can tailor different surface features
- is affordable with current 3D printers.



ESR 12
Mechanics of Cell-Surface Interactions

University of Southampton

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Fused Deposition Modelling 3D printing is currently limited in the number of its applications due to the lack of knowledge on the properties of 3D printed structures, and the link between manufacturing and the mechanical response

CHALLENGE

APPROACH

How is the challenge being addressed?

We are developing techniques to use Fused Deposition Modelling (FDM) to produce functionally graded scaffolds.

Why was this approach taken?

FDM is accessible, cheap and easy to use. Extending its capability would allow this manufacturing process to be used for applications for which the current state-of-the-art is expensive or challenging. Mechanical characterisation enables performance optimisation.

What is the state of the development?

Samples with the desired properties have been 3D printed and mechanically tested to prove the efficacy of the approach.

What are the next steps?

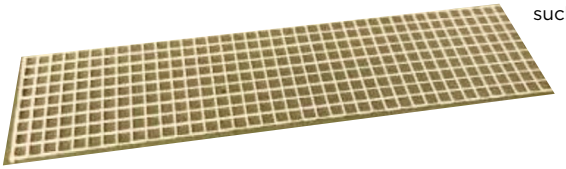
Manufacture functionally graded lattices (significant thickness compared to length), to perform mechanical tests.

BENEFITS

Manufacturing scaffolds using FDM would significantly reduce cost compared to the current production techniques, as well as increase the possibility to make a custom-made design. The proposed technology introduces functional gradation into FDM manufacturing, making it available for applications that could not otherwise make use of it. Hence, the same benefits that FDM delivers over other (additive) manufacturing techniques - such as the ease of operation and a wider accessibility - are delivered.

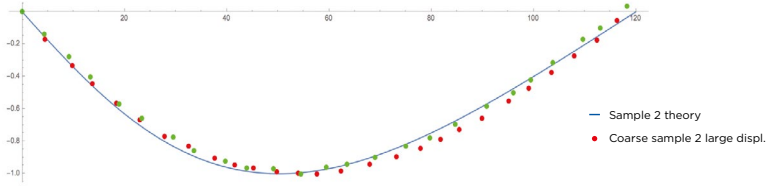
What differentiates it from the state-of-the-art?

The production of scaffolds with graded properties makes use of advanced materials and procedures requiring constant professional support, for example porogens or self-foaming followed by pyrolysis. This results in a very high price. Extending the capability of FDM could lead to scaffolds manufactured by the clinician from the imaging data of the patient. This would allow the price for such operations to drop considerably.



As an example, we show an apparently homogeneous sample that results in an asymmetric profile under bending conditions

This demonstrates the feasibility of the technique we propose for the production of functionally graded samples using FDM



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