"Polymers for applications"

The long way from an idea and work in the academic lab towards a product

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Research idea / objective

$n + 1 \text{ steps}$

Application
Technology readiness level (TRL)*

TRL 1 – Basic principles observed
TRL 2 – Technology concept formulated
TRL 3 – Experimental proof of concept
TRL 4 – Technology validated in lab
TRL 5 – Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 6 – Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 7 – System prototype demonstration in operational environment
TRL 8 – System complete and qualified
TRL 9 – Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)

The problem of *infected* burn wounds

- Difficult diagnosis:
  Inflammation and infection show similar symptoms

- Rapid result required

Pathogenic bacteria:
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa* etc.
Infection-signaling functional wound dressings

Responsive indicator dressing: triggered signaling only if pathogenic bacteria are present.

In a theranostic approach one could additionally counteract bacterial infection (signaling & therapy)
Infection-signaling polymeric nanocapsules

✓ **Light-on** due to de-quenching of dye that was encapsulated.

alternatively:

✓ **Light-off** due to dye release and precipitation.


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Most strains of *staphylococcus aureus* produce pronounced levels of the enzyme *hyaluronidase*.
Synthesis

• HYA-\(b\)-PLA by click chemistry

Infection-signaling polymeric nanocapsules

HYA$_{13}$-b-PLA$_{138}$

incubation with proteinase K

\[
\text{max. fluorescence intensity / a.u.}
\]

\[
\text{incubation time / h}
\]

Light-on due to de-quenching.

✓ Cytotoxicity (standardized tests with cell lines)

Endotoxin tests, sterilization

FDA approved materials??

Upscaling???

IP protection

➢ Good manufacturing practice (GMP)

➢ Regulatory affairs: Classification of biomedical devices and approval
Poly(ε-caprolactone) block copolymers

- Many strains of *staphylococcus aureus* produce pronounced levels of the enzyme *lipase*.

\[
\text{MeO}\underbrace{\text{H}}_{114} + n \text{cyclohexane} \xrightarrow{\text{Tin(II)octoate}} \underbrace{\text{H}}_{114}
\]
PEG$_{114}$-b-PCL$_{578}$

PEG$_{114}$-b-PCL$_{542}$ with Nile Red

AFM: cross-section

Dynamic Light Scattering

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Light-off effect for signalling

$\lambda_{ex} = 510 \text{ nm}$

➢ **Light-off due to dye release and precipitation!**

$PEG_{114-b-PCL_{240}}$ vesicles
Degradation of PEG-\(b\)-PCL with \textit{Nile red light-off} assay in supernatant of \textit{staphylococcus aureus}

\begin{itemize}
  \item [\textbf{Rapid response in supernatant of staph. aureus}]
  \item \textbf{PEG}_{114}\textit{-b-PCL}_{354} \quad d_h = 100 \text{ nm}
\end{itemize}

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Design

Amphiphilic block copolymers as enzyme-responsive nanocarriers

Poly(lactic acid)

Poly(e-caprolactone) (PCL)

proteinase

lipase

FDA approved materials etc.
Technological implementation?
Intact vesicles can be spray-coated.
Immobilization via electrostatic interactions

Negatively charged vesicles, $d_h = 120$ nm
Prototype of roll-to-roll system

Printer Epson R2880 with cartridges filled of nanoparticles GR-PLA.

Non-woven polymers

Diffuse Coplanar Surface Barrier Discharge Plasma

PEG-\textit{b}-PLA

Fluorescence

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Validation with enzyme on coated non-woven fabrics (roll-to-roll)

White Light

before incubation

180 minutes

UV
Bacterial enzyme-responsive hydrogels

- Selective enzymatic cleavage & release of reporter dye (chromogenic or fluorogenic substrate).
- Dye changes absorption or emission characteristics

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Detection of *E. Coli* enzyme with hydrogel-immobilized chromogenic substrate

Mir Morteza Sadat Ebrahimi, Benedikt Steinhoff and Holger Schönherr *European Polymer Journal* 2015, 72, 180–189.

Detection of E. Coli – Limit of detection (LOD)

\[ \lambda_{\text{exc}}: 365 \text{ nm} \]

\[ \beta\text{-glucuronidase} \]

\[ \text{LOD for [GUS]}_0 \text{ (nM)} \]

\[ \sim 500 \text{ pM} \]

Mir Morteza Sadat Ebrahimi, Yvonne Voss and Holger Schönherr ACS Applied Materials and Interfaces 2015, 7, 20190–20199.

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Selective detection of bacterial enzymes
(discrimination of panels of pathogenic bacteria)

Zhiyuan Jia, Mareike Müller, Tony Le Gall, Martijn Riool, Max Müller, Sebastian A. J. Zaat, Tristan Montier, and Holger Schönerr, Bioactive Materials. 2021, 6, 4286 - 4300.

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Highly applicable sensing and detection
Wound dressing with reporter function

Functional polymer

Bacterial enzymes,
virulence factors etc.

Sensory function activated

Photographs: FoKoS

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Summary & Conclusion

✓ Successful demonstration of novel polymeric sensor materials for detecting bacterial infections.

✓ Beyond TRL5 specialized external partners are required.

✓ Translation remains very challenging.
New approaches to holistic training and education are required, e.g. to break the traditional boundaries of disciplines.
New approaches to holistic training and education are required, e.g. to break the traditional boundaries of disciplines. STIMULUS is a European Training Network working on reducing healthcare-associated infections. We train early-stage researchers (Ph.D. students) for a career in biomaterials by researching smart wound dressings that can detect and treat bacterial infections without opening the wound.

To accomplish this, STIMULUS combines the expertise of organic, macromolecular, physical and materials chemists, materials scientists, electronic engineers, biotechnologists, medical doctors (clinicians), (micro)biologists, government policy experts, and representatives from both SMEs and large enterprises. Our consortium bridges from academia and medical research institutes to policymakers and industry.

Our researchers get individualized and joint training in all these disciplines and relevant sectors along the value chain, giving them a unique and genuinely interdisciplinary and multi-sectoral training experience.  

https://www.stimulus-etn.eu/
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