Muster

für einen Abschlussbericht in der Einzelförderung: Programm Sachbeihilfe

ABSCHLUSSBERICHT

1 Allgemeine Angaben

DFG-Geschäftszeichen: MA 8575/3-1

Projektnummer: 467116484

2 Titel des Projekts: Hybrid-Aerogele als biomemetische 3D-Gerüststrukturen für regenerative Knochenkrebstherapie

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Name(n) der Kooperationspartnerinnen und –partner: Professorin Dr. Nicola Hüsing; Professor Dr. João F. Mano

Berichtszeitraum (gesamte Förderdauer): 01.01.2022-31.12.2024

3 Zusammenfassung / Summary

The treatment of malignant bone tumors and the restoration of bone damage following tumor resection remain significant clinical challenges. Addressing tumor-induced bone damage typically requires the implantation of biomimetic porous 3D materials with dual functionality: the local treatment of residual tumor cells and the subsequent restoration of bone tissue. There is an urgent need to develop dual-functional scaffold materials that fulfill the stringent requirements for both biological and tumor-therapeutic efficacy.
Aerogels have emerged as promising biomaterials for targeted bone tissue regeneration due to their exceptional physical and microstructural properties, particularly their extensive porosity, pore interconnectivity, and high internal surface area.
The primary objective of this project is to develop novel multi-functional 3D-printed composite aerogels as scaffold materials for bone tumor management. These aerogels are designed using surface-modified silk fibroin (SF) combined with functional nanoparticles to achieve dual functionality: high photothermal conversion for tumor ablation and osteogenic properties for bone regeneration. The design leverages surface modification, self-assembly, and advanced 3D printing techniques. The unique self-assembly properties of surface-modified SF in solution, coupled with its hybridization with anisotropic nanomaterials (*e.g.*, electrospun silica nanofibers, photothermally active nanoparticles/ agents such 2D nanosheets), enable the production of range of multifunctional composite aerogel scaffolds with interconnected and hierarchical porosity and biodegradability. Furthermore, the most promising materials undergo evaluation for their *in vitro* therapeutic efficacy and bone regeneration capabilities. By integrating 3D printing with innovative material concepts (e.g., composite aerogels), this project aims to address the critical clinical challenges of bone healing.

4 Wissenschaftlicher Arbeits- und Ergebnisbericht

Every year, 2-3 million people worldwide are diagnosed with **osteosarcoma**, a highly malignant primary bone tumor in adolescent under age of 20[1]. Approximately 15% of newly diagnosed osteosarcoma patients present with metastatic disease, most commonly in the lungs, which leads to a 5-year survival rate of around 20%[2,3]. The traditional clinical treatments for osteosarcoma include surgical resection followed by radiotherapy/ chemotherapy of the resected area[3,4]. In most cases, surgical resection does not completely remove the tumor, leading to postoperative recurrences and metastases. In addition, osteosarcoma and subsequent critical bone loss cause a range of serious health[5] and psychological problems for patients[6], which calls for novel treatment procedures with higher therapeutic index and treatment efficiencies.

Currently, autologous grafts are a clinically admissible method of bone tissue reconstruction after osteosarcoma treatment with successful outcomes. Despite their benefits, autograft bone is associated with some risks, such as impaired normal body functions, limited availability, complex harvesting procedures, and donor site morbidity[7]. Another critical challenge is the difficulty in shaping and fixing the rigid autograft tightly into the irregular bone defect for sufficient osteointegration[8].

Therefore, considering the clinical limitations in both tumor therapy and bone regeneration, development of novel approaches based on bioactive **theragenerative materials**[3,9,10,11]

(combining therapy and regeneration) facilitated with minimally invasive delivery/implantation features is an urgent clinical need for bone tumor management.

Our primary focus during this DFG project has been creating **theragenerative** biomaterials designed for applications in both bone tissue engineering (BTE) and bone cancer therapy. However, employing pristine aerogels created through sol-gel processes (inorganic) or self-assembly techniques (biopolymers) in combination with $scCO_2$ drying as a three-dimensional (3D) biomaterial or scaffold for facilitating bone healing presents a notable challenge[16]. This challenge arises from the fact that aerogels possess 1) a mesoporous nanostructure in their pristine state characterized by pore sizes ranging from 2 to 50 nanometers. 2) Furthermore, their mechanical strength is inherently limited, which hampers their effectiveness in supporting the colonization of cells in both *in vitro* and *in vivo* contexts, as well as impeding their delivery or implantation to bone defect during *in vivo* settings. Therefore, the key research questions in this DFG project focus on addressing the current structural limitations of pristine aerogels to design potent scaffolds in the context of bone tissue engineering (BTE) and optimizing aerogel properties by incorporating functional nanoparticles with specific therapeutic and bioactivity to achieve multifunctionality for both bone regeneration and localized tumor treatment for final aerogel.

To achieve this goal, in this granted DFG project **(MA 8575/3-1),** we firstly adopted a series of novel synthesis and processing techniques to synergistically improve the **pore size regime, mechanical properties**, and **bioactivity** in aerogels. We employed **SF biopolymer** as a fundamental component of our bio-inspired aerogels. SF is an abundant fibrous protein that can be extracted from *b. Mori* silkworm cocoons as one of the SF sources[22]. Its intriguing properties, which include high mechanical strength and resilience, biocompatibility, and biodegradability combined with facile surface modification and processability, render it an attractive material for fabricating various functional materials for diverse applications, mainly in tissue engineering[23, 24, 25].

We have developed a series of 3D biomimetic hybrid aerogel-based scaffolds with multiscale porosity and improved bioactivity (**Fig. 1 I-III**). For scaffold **I**[12] (*cf.* **Fig. 1 I (a-d)**), we fabricated a versatile hybrid silica-SF hydrogel by fine-tuning the synthesis and freeze-casting conditions. These aerogel hybrids possess a unique hierarchically organized porous structure featuring nano and micron-size pores, honeycomb-like micromorphology, and bone-like microstructural anisotropy with excellent mechanical compressive behavior (80% strain). *In vitro* experiments confirmed the biocompatibility and osteoconductivity of these aerogels, promoting cell attachment, proliferation, and alkaline phosphatase (ALP) activity. In an *in vivo* rat femoral bone defect model, the aerogel implants facilitated substantial new bone formation within only 25 days, without adverse effects on blood biochemical parameters.

In scaffold **II**[13] (*cf.* **Fig. 1 II (a-e)**), we used micro-extrusion 3D printing to create interconnected pores in the range of 100-1000 µm. To boost cell response and antibacterial properties, we conjugated thiol-ended antimicrobial peptide CM-RGD into SF prior to self-assembly. The Silica-SF-CM-RGD hydrogel ink was 3D printed, forming a scaffold with hierarchically organized porosity and multiple advantages. The covalently attached antibacterial peptide effectively showed antibacterial properties toward Gram-positive and Gram-negative bacteria. The nanostructured silica network in the 3D-printed composites also improved mechanical

strength and scaffold osteoconductivity. This project has been conducted through collaboration of **Prof. Bent Brachvogel** who supported cell biology aspect of designed aerogel.

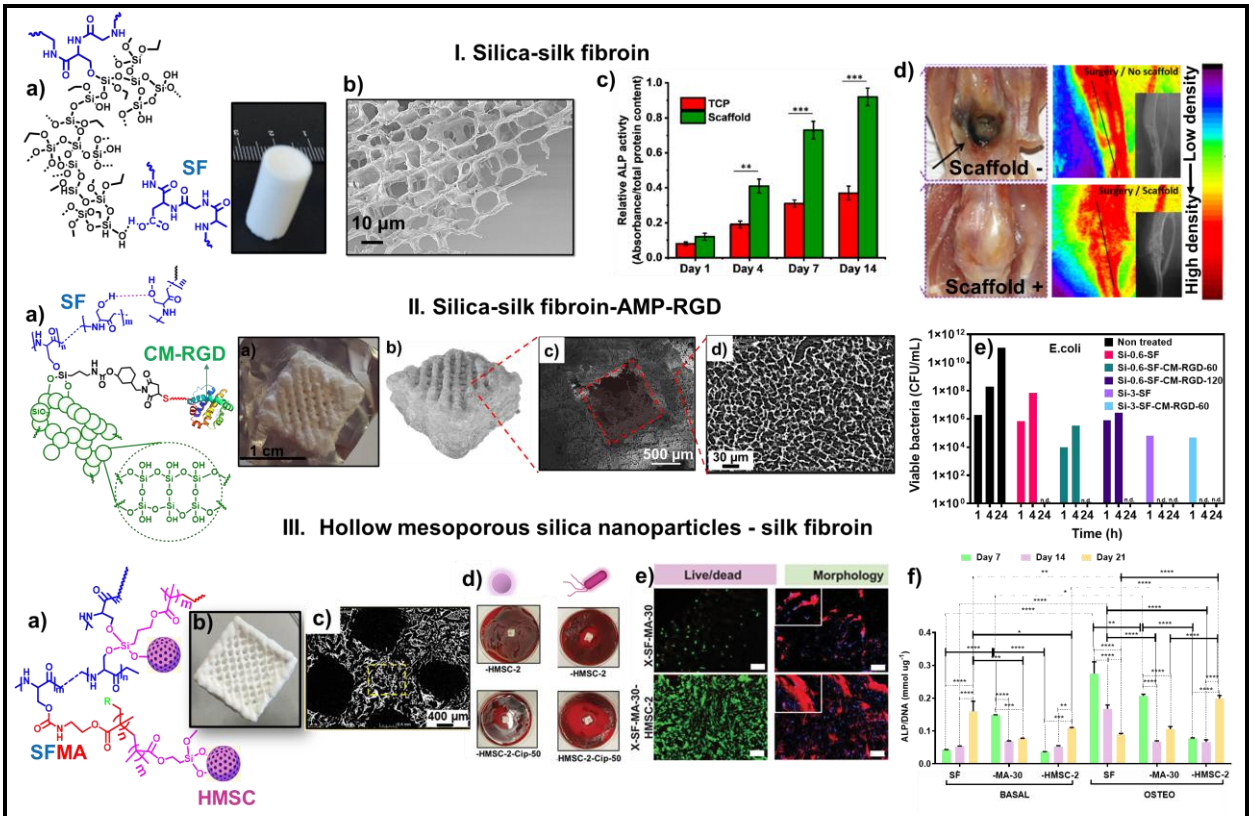

Figure 1. Three different 3D scaffolds were developed in Dr. Maleki's group. I. (a-d) Dual porous anisotropic silica-SF aerogel hybrids scaffold with an interpenetrating network structure, ALP activity of MG-63 cell seeded on the scaffold and *in vivo* bone formation after 25 days of implantation in the defect site of the tibia of the rat[12]. The red area in the radiographic images indicated high bone density, whereas the green color demonstrates the defect area without bone formation. II (a-e) 3D printed Silica-SF-RGD-AMP aerogel scaffold with hierarchical porosities and anti-bacterial activities[13]. III (a-f) Anti-bacterial and osteoconductive hybrid scaffolds based on silk fibroin – ciprofloxacin loaded hollow mesoporous silica capsules (HMSC) with hierarchical porosities and enhanced hMSC colonization and proliferation and osteoblastic gene expression/ differentiation[14].

In scaffold **III**[14] (*cf.* **Fig. 1 III (a-d)**), we developed 3D printed aerogel scaffolds with excellent shape fidelity and antibacterial properties. This involved incorporating ciprofloxacin-loaded hollow mesoporous silica capsules (HMSC-MA) as a nano-drug carrier into SF methacrylate (SF-MA) biopolymer. We prepared a uniform gel ink and used 3D printing, photo-crosslinking, and directional freeze casting to create highly porous scaffolds with interconnected hierarchical pores. These aerogels were strong and showed a sustained release of the ciprofloxacin to kill the bacteria effectively. Incorporating HMSC into scaffold improved human mesenchymal stem cell (hMSC) growth, osteoblastic differentiation, and mineralization. This highlights the potential of our printed aerogel hybrid as bone implants with osteogenic properties (*cf.* **Fig. 1 III (e-f)**). This project was a collaborative effort in which Prof. **Sanjay Mathur (Uni. Cologne)** provided the HMSC nanoparticles for the designed aerogel and Prof. **Joao Mano** (Uni Aveiro, Portugal) supported the cell biology part of the project most importantly the osteogenic differentiation of stem cell into osteoblastic cell line seeded on the scaffold. Dr. Marc Herb (CECAD research center, UniKilink Koeln) supported the antibacterial assays on the aerogels.

To demonstrate the potential for simultaneous bone regeneration and osteosarcoma therapy, we developed dual-functional 3D printed aerogel scaffolds.

My group has recently engineered a series of biomimetic composite aerogels by incorporating Ti_3C_2 (MXene) nanosheets[15] (*cf.* **Fig. 2a**), methacrylate-modified Bi_2S_3 nanobelts[16] (*cf.* **Fig. 2b**) and bioactive glass nanofibers (BGF, $70SiO_2$, $25CaO$, $5P_2O_5$)[17] (*cf.* **Fig. 2c**) inside the self-assembled SF hydrogels with a strong NIR absorption property. After rheological optimization, the composite gels were 3D printed and photocrosslinked. The hybrid 3D scaffold with dual crosslinked structure underwent freeze-casting and supercritical drying to obtain composite aerogels with hierarchical porosity and mechanical stability. While obtained scaffolds could accelerate *in vitro* growth and proliferation of human Mesenchymal Stem Cell (hMSCs), they also demonstrated a strong photothermal conversion upon remote irradiation with a NIR laser with a wavelength of 808 nm. The generated heat in the scaffold was optimized by controlling the NIR laser power density and the mass fraction of the incorporated inorganic nanofillers into the aerogel scaffolds.

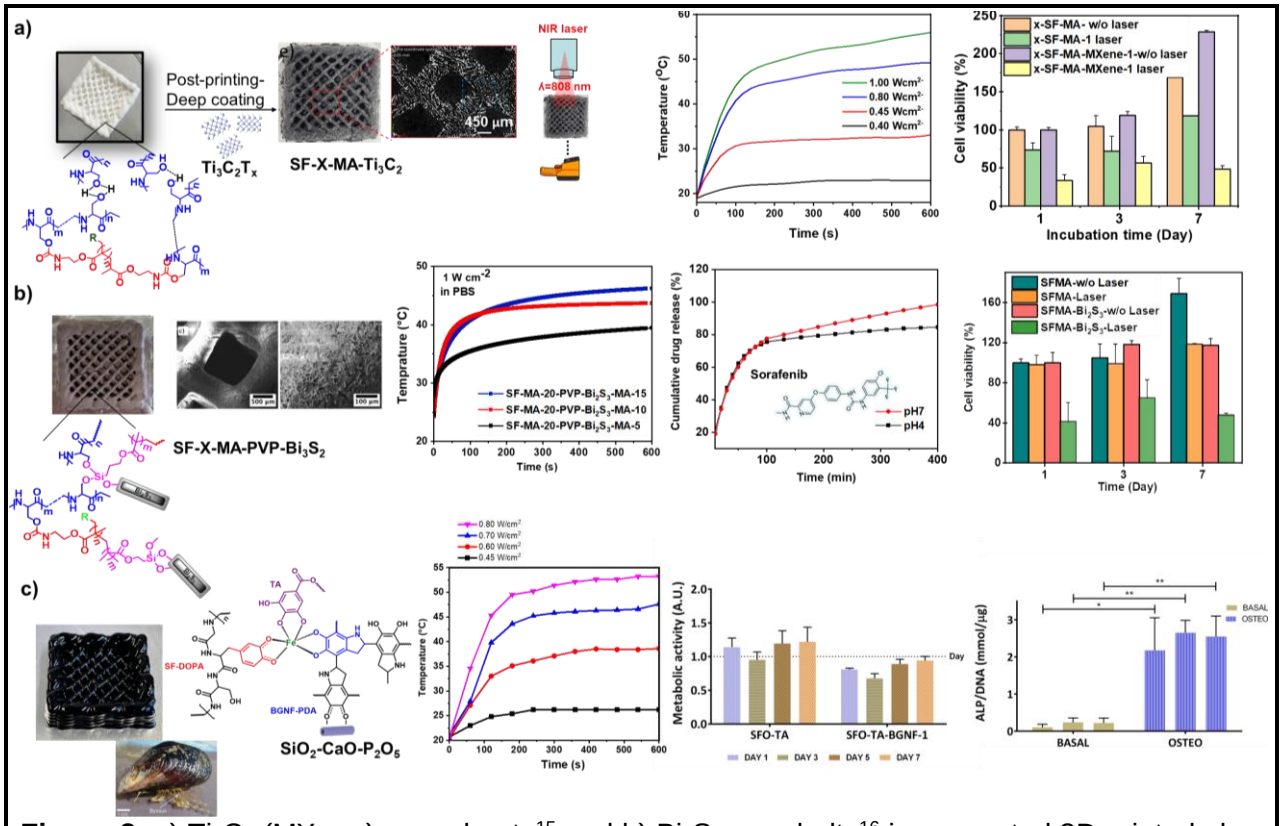

Figure 2. a) Ti_3C_2 (MXene) nanosheets[15] and b) Bi_2S_3 nanobelts[16] incorporated 3D printed photocrosslinked SF-based composite aerogels with strong NIR photon absorptions. The released heat was exploited to accelerate the rate of cumulative release of an anti-cancer drug (sorafenib) and significantly ablate the MG63 cancer cells *in vitro*. c) Design process of self-healing BGF-SF-DOPA-TA composite aerogels through mussel-inspired chemistry and 3D printing. The aerogels have significant photothermal conversion for osteosarcoma ablation and demonstrated biocompatibility and osteogenic functions (enhanced ALP enzyme activity)[17].

At an optimized concentration of MXene and Bi_2S_3, the equilibrium temperature of the scaffolds was raised to 45-50 °C within 10 minutes, providing an opportunity to trigger the release

of the anti-cancer drug (sorafenib) and simultaneous *in vitro* photothermal ablation of osteosarcoma. The MXene incorporated theragenerative aerogels were conducted as a result of our collaborative effort with **Prof. Bent Brachvogel**, where Bent group supported us with all cell biology part of this project. Bi_2S_3 nanobelt incorporated aerogel were designed in my group and all the cell biology experiment in terms of osteosarcoma ablation and bone regeneration were conducted in the group **Prof. Silvia Fare** Polytechnic University of Milan as a results of shared master student.

We also developed a self-assembled, self-healable 3D printed composite aerogels by incorporating polydopamine-modified electrospun BGNF into tyrosinase-mediated oxidized SF (SF-DOPA) using mussel-inspired chemistry (cf. Fig. 2c)[17]. The dynamic coordination bonding between SF-DOPA, tannic acid (TA), and BGNF with ferric ions results in controlled rheological properties, excellent shear thinning, self-healing capabilities, and 3D printability, creating scaffolds with multifaceted biological functions. Namely scaffolds exhibited photothermal conversion upon exposure to NIR light enabling photothermal anti-osteosarcoma and antibacterial treatment. Additionally, the in vitro osteogenic performance of the scaffold has been recently confirmed, demonstrating their excellent capability for mediating the differentiation of hMSC into osteoblast cell lines confirmed by gene expression relevant to the bone ECM proteins and mineral deposition on the scaffold [17].

During the course of this DFG project, we also published a collaborative review article on **Advanced Fabrication and Biomedical Applications of Aerogels** in collabaoration with the esteemed group of Prof. Ali Khademhosseini from the Terasaki Institute, USA. Prof. Khademhosseini is a world-leading expert in tissue engineering and organ printing, and this collaboration further enhanced our knowledge on Aerogels during the course of the project highlights the interdisciplinary and cutting-edge nature of our work[18].

Another biomimetic aerogel developed during the DFG project was a composite aerogel inspired by the mild silicification process observed in diatoms. Diatoms employ polyamine-rich proteins as catalysts to facilitate the mild silicification or polycondensation of silicic acid in their cell walls, resulting in silica structures with hierarchical, interconnected porosities. Inspired by this natural mechanism, we designed a polyethylene-imine-modified silk-silica composite aerogel that demonstrates high mechanical flexibility without compromising its outstanding physical properties[19].

As part of **our ongoing research,** we have developed H_2 and heat-releasing hybrid micro(aero)gels through self-assembly and hybridization of bisphosphonate (BP)-modified methacrylated SF (SF-MA) and black bioactive glass (BBG). These microgels exhibit a controlled, on-demand, and sustained release of molecular H_2 along with heat, providing a synergistic approach for the eradication of osteosarcoma within bone defects. Preliminary results have confirmed that the combination of H_2 and heat enhances ROS levels in osteosarcoma cells. However, further in-depth studies are necessary to fully elucidate the underlying mechanisms of this therapeutic interaction (unpublished work).

During this project, I also supervised a visiting PhD student, Dr. Akbar Vaseghi from Tarbiat University in Iran, who worked on propolis-loaded 3D-printed aerogels in my lab. Throughout his PhD, he encapsulated propolis (PS), a polyphenolic resinous natural compound derived from beehives known for its antibacterial, anti-inflammatory, and anti-cancer properties[20,21] within chitosan (CH) nanoparticles (PS-CH). The PS-CH nanoparticles were chemically anchored to an oxidized silk fibroin biopolymer-silica sol, resulting in a composite gel. This gel was synthesized through a combination of in situ sol-gel chemistry and self-assembly, followed by 3D printing and supercritical drying to produce anti-infective and regenerative aero-

gels. A systematic investigation was conducted on the extraction of propolis, its encapsulation within chitosan nanoparticles, and its release profile at both the nanoparticle and aerogel structural levels. Subsequently, in collaboration with **Dr. Marc Herb,** a comprehensive antibacterial assessment was performed against both Gram-negative and Gram-positive bacteria using microdilution and bacterial ring tests. These studies confirmed the potent anti-infective properties of the aerogel scaffolds[22].

In addition, this project enabled me to expand my collaboration with Fibrothelium GmbH, a company based in Aachen specializing in silk-based solutions and medical products derived from silk proteins. This collaboration provided me with valuable insights into the industrial and commercialization aspects of our silk-based 3D aerogels and hybrid gel components, tailored to realistic scales and industrial needs.

While the scope of this project did not focus on aerogels, it centered on developing injectable, self-healing, and adhesive hydrogels based on silk proteins for minimally invasive bone tumor management and bone regeneration—aligning closely with the objectives of this granted DFG project. We worked in alignment with the company's core interests, designing injectable gels using two key silk proteins: sericin and fibroin.

By employing surface modifications through catechol moieties—either via enzyme-based oxidation of tyrosine amino acids on the silk fibroin chain or by incorporating catechol-containing compounds like dopamine—we developed adhesive and injectable hydrogels inspired by the attachment mechanisms of mussel-foot proteins, mediated by the amino acid l-3,4-dihydroxyphenylalanine (DOPA). The resulting hydrogels demonstrated significant potential for regeneration and adhesive capabilities (submitted work).

Beside this research work about injectable hydrogel, recently we also published a comprehensive review articles compiling the research existed in literature in the realm of designing **2D nanomaterials incorporated hydrogels for bone regeneration and bone cancer therapy**[10].

Besides our primary focus on theragenerative aerogels, the synergy observed within the material properties prompted us to explore additional application areas. I concentrated on designing self-healable, stretchable, and electrically conductive hybrid hydrogels and aerogels by incorporating MXene 2D nanosheets into self-assembled gels formed from a combination of oxidized silk fibroin and tannic acid. These materials were developed as potent strain sensors for subtle human body monitoring[23,24].

This investigation opened up further opportunities for my group to explore the broader applications of our designed materials, particularly in the development of hydrogels for continuous health care monitoring.

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Veröffentlichte Projektergebnisse

4.1 Publikationen mit wissenschaftlicher Qualitätssicherung

Published Research and Review Papers Resulted from the DFG Project:

(1) Ng, P.; Pinho, A. R.; Gomes, M. C.; Demidov, Y.; Krakor, E.; Grume, D.; Herb, M.; Lê, K.; Mano, J.; Mathur, S.; **Maleki*, H**. Fabrication of Antibacterial, Osteo-Inductor 3D Printed Aerogel-Based Scaffolds by Incorporation of Drug Laden Hollow Mesoporous Silica Micr Oparticles into the Self-Assembled Silk Fibroin Biopolymer. *Macromol. Biosci.* **2022**, *22* (4), 2100442. https://doi.org/10.1002/mabi.202100442.

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-Other collaborative research articles:

(12) Al-Hamamre, Z.; Alnaief, M.; Daameh, S.; Yamin, J.; Sandouqa, A.; Alhammouri, R.; **Maleki, H.;** Altarawneh, I. Sustainable Biodiesel Production Using Lignin-Derived Sulfonated Carbon Aerogels Catalyst. *Int. J. Sustain. Energy* **2024**, *43* (1), 2400657. https://doi.org/10.1080/14786451.2024.2400657.

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(14) Ehsan Tabesh, Daniela Grumme, Marc Herb, Pouya Rezai, **Maleki*, H.** Siu Ning Leung a Fabrication of MXene integrated superabsorbent polymers composites hydrogels for bacterial enrichment, *Separation and Purification Technology*, 368, **2025,** 133022. https://doi.org/10.1016/j.seppur.2025.133022

4.2 Weitere Publikationen und öffentlich gemachte Ergebnisse

Invited Talks:

2025 Healing from Within: Biomimetic Hybrid Aerogels as Extracellular Matrix for Bone Repair, **Centers for Biochemistry and Physiology, DFG research Unite FOR2722 Seminar Series, University Clinic Cologne.**

2024 Biomimetic Aerogels, Faculty of processing and system engineering, Institute of Chemistry, **Otto Von Guericke University of Magdeburg, Magdeburg, Germany, 13.05.2024.**

2024 Advanced Biomimetic Hybrid Aerogels: From Theragenerative Materials for Osteosarcoma Management to Soft Electronics and Energy Applications, **Department of Chemistry of the University of Ulm, Germany, 08.02.2024**

2024 Aerogel Theragenerative, 17th Scandinavian Society for Biomaterials Annual Meeting (ScSB2024), Helsingør, **Technical University of Denmark (DTU), Denmark, 23.04.2024-26.04.2024.**

2023 Functional Hybrid Bio-inspired Aerogels: Towards Theragenerative Biomaterials for Bone Regeneration, ***Keynote lecture***, **Indo-German workshop** on "Design and manufacturing of biomaterials and implants for dental and craniomaxillofacial reconstruction and regeneration", **Institute of Biomaterials, University of Erlangen-Nuremberg, Germany, 02.13-15, 2023.**

2023 Functional Hybrid Bio-inspired Aerogels: Towards Theragenerative Biomaterials for Bone Regeneration, ***Keynote lecture,*** **Indo-German Workshop** on ''Biofabrication: Emerging Biomaterials, Machines & Digital Tools'' **(IGBMDT-02.2023), Sastra University - Ruhr University of Bochum, Thanjavur, India.**

2022 From Protein Building Blocks to Functional Bio-inspired Aerogels Faculty of Mathematic and natural science, ***Invited talk,*** **Department of Chemistry and Biology, Bergische Universität Wuppertal, Germany.**

2022 From Protein Building Blocks to Functional Bio-inspired Aerogels, Faculty of Mathematic and natural science, ***Invited talk,*** **Department of Chemistry, University of Cologne, Germany.**

2022 Scaffold-mediated bone tissue engineering and bone cancer therapy, ***Keynote lecture*** 5th Workshop in Advanced Nano- and Micro-Structured Materials for Medical Applications, International School of Nanomedicine- Erice Ettore Majorana Foundation and Centre for Scientific Culture Bionanomedicine Center- **University Milano-Bicocca, Italy.**

2022 Functional Hybrid Bio-inspired Aerogels: Towards Theragenerative Biomaterials for Bone Regeneration, ***Invited talk,*** **Faculty of Medicine, RWTH Aachen University, Germany.**

2022 Functional Hybrid Bio-inspired Aerogels: Towards Theragenerative Biomaterials for Bone Regeneration, ***Invited talk, in Summer Edition for Seminar Series in* Center for Molecular Medicine Cologne (CMMC), University Hospital Cologne, Germany.**

2022 3D and 4D printing of Aerogels, ***Invited trainer* Cost Action Workshop on 3D printing of gels and aerogels, Faculty of Pharmacy, Universidade de Santiago de Compostela - Santiago de Compostela, Spain.**

2022 Environmental and Biomedical Applications of Aerogels, ***Invited Lecturer, Aerogels Consortium Matchmaking Meeting,* FCT NOVA University NOVA, Campus de Caparica, Lisbon, Portugal.**

2022 Bio-inspired Assembly of Peptide-Ceramic Aerogel Composites for Bone Healing Applications, ***Invited Talk*, Brandenburgische Technische Universität Cottbus-Senftenberg, Department of Chemistry, Germany.**

4.3 Patente (angemeldete und erteilte)

NA

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