Innovative RNA transfection kit based on hybrid polymer–lipid nanoparticles

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# Abstracts
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require elasticity to function. What bestows this elasticity is the protein elastin, which in turn is assembled from the structural protein building-block tropoelastin. We have found that tropoelastin can promote the repair many types of damaged tissues; and identified collaboratively that tropoelastin can allow stem cells to delay senescence, while retaining phenotype and function. Despite these critical abilities, and even though the tropoelastin gene is essential, paradoxically the production of tropoelastin drops precipitously with age.

This presentation will present advances in our mechanistic understanding in the use of tropoelastin to deliver organized elastin in vascular walls during replacement-repair in vivo, promote heart muscle survival and recovery in an in vivo model of ischemic injury, its ability to compress the inflammatory sequence displayed by macrophages, and their commercialization.

Collaboratively, we are seeing responses by mesenchymal stromal cells that extend to expression differences accompanied by delayed senescence that fundamentally reflect the role of the elastic extracellular matrix. In vivo and model studies will be presented that show the value of using tropoelastin to modify cell performance in these cases, in order to help heal surgical wounds, repair arteries and modulate immunity while delivering synthetic tissue-materials for building 3D constructs.

This bench-to-bedside commercialization has been facilitated by 174 granted international patents in 23 distinct families, comprising protein production, mutants, tropoelastin stability, elastin production, tissue regeneration, sealants for soft tissue, bone repair, injectables, triggered elastogenesis, scaled production of elastic materials, enhanced repair of wounds. Venture capital funding and 3 completed clinical trials led to Elastagen's acquisition by Allergan, an AbbVie company, in one of the largest national transactions.

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### 44. Bioengineered collagen-coated scaffolds for advanced tendon regeneration

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Tendons are dense connective tissues mainly composed of collagen I fibers, providing mechanical strength and stability to joints. However, their limited self-healing capacity, due to poor vascularity and cellularity, makes tendon ruptures a major clinical challenge. Surgical repair often leads to fibrotic tissue formation, compromising mechanical function. To overcome this, we propose a combined tissue engineering and drug delivery strategy aimed at mitigating post-surgical tendon fibrosis.

Our strategy exploits a 3D electrospun scaffold with tendon-like microarchitecture, cellularized with human tenocytes (hTCs), and loaded with Rolipram as antifibrotic agent to actively avoid the tendon fibrosis after surgical repair. In our study, we used PLA to produce aligned microfibers that closely mimic the natural arrangement of collagen fibers in native tendons, also promoting a native-like hTCs spatial arrangement. We provided microfibers with a type I collagen coating to modulate the drug delivery kinetics, and to induce a self-assembling of microfibers into fascicle-like substructures. These substructures were preserved in 3D scaffolds fabricated with a custom-made bundle-making device, which assembles microfibers into a helicoidal quaternary structure.

Collagen coating significantly increased the Young's modulus of both drug-free (from 102.93 to 140.09 MPa) and drug-loaded (from 103.3 to 144.23 MPa) scaffolds, while Rolipram loading did not affect mechanical performance. Moreover, the coating modulated Rolipram release. Specifically, we didn't notice any burst release neither from uncoated (PLA/Rol) nor from coated (PLA/Rol/Coll) scaffolds within first 2h. Excitingly, we obtained compelling result also from biological characterization of our tendon-like scaffolds. Histomorphological analysis performed via hematoxylin/eosin staining revealed hTCs in both inner and outer scaffold regions. This effect was enhanced in collagen-coated scaffolds that showed a more intense staining.

Overall our study shows encouraging results, demonstrating the potential high-impact that our methodology may have in the surgical repair of tendon ruptures, by inducing the regeneration of non-fibrotic tendons.

### 45. Multifunctional five-layer collagen laminates for integrated infection control and bone regeneration in contaminated fracture models - SEMIT

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Open bone fractures, particularly those involving severe tissue damage and microbial contamination, pose major clinical challenges due to the dual need for infection control and bone regeneration. Conventional treatments, such as systemic antibiotics and bone grafting, often fail to achieve localized therapeutic concentrations or complete tissue healing.[1] To address these limitations, we developed a multifunctional, five-layer collagen laminate that combines structural support with the spatially organized delivery of bioactive molecules for antibacterial action, osteogenesis, and angiogenesis.

The laminates, composed of commercially available collagen sheets, were fabricated using a photochemical crosslinking method with rose bengal and green light, allowing rapid and biocompatible bonding of individual collagen layers. Each layer incorporated a specific therapeutic agent: vancomycin for localized infection control, bone morphogenetic protein-2 (BMP-2) for osteoinduction, and stromal cell-derived factor-1α (SDF-1α) for cell recruitment and vascularization. Material characterization included mechanical testing and drug release profiling. An in vitro osteomyelitis model was established to evaluate antibacterial, osteogenic, and pro-angiogenic properties.

The laminates exhibited strong mechanical integrity and layer-specific bioactive release. Vancomycin showed an initial burst, while BMP-2 and SDF-1α displayed sustained release, enabling temporal separation of antimicrobial and regenerative effects. In the in vitro osteomyelitis model, the laminates inhibited Staphylococcus aureus, promoted osteoblast differentiation, and enhanced endothelial cell migration, demonstrating synergistic regenerative potential.

This study introduces a multifunctional, five-layer collagen laminate that integrates antimicrobial defense, osteoinduction, and vascular recruitment to address the complex requirements of bone healing in contaminated or high-risk fractures. Its tunable, spatially organized therapeutic delivery offers a promising strategy for regenerative orthopedic and trauma applications.

[1] M. J. Flores et al., J. Clin. Med. 2022, 11, 7461 DOI: 10.3390/jcm11247461

### 46. Innovative RNA transfection kit based on hybrid polymer–lipid nanoparticles

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MicroRNAs (miRNAs) play crucial roles in several biological processes and therapeutic strategies based on their delivery appear extremely promising for tissue regeneration [1]. However, current delivery systems remain suboptimal: viral vectors are limited by safety issues and high costs, while commercial transfection agents exhibit poor stability, low loading efficiency, and uncontrolled

release kinetics [2]. To overcome these challenges, novel hybrid polymer-lipid nanoparticles (H-NPs) were designed as innovative transfection agent for miRNAs delivery.

H-NPs were prepared using a patented nanoprecipitation method with a lipoplex core capable of encapsulating miRNAs and a polymeric shell to enhance stability [3]. H-NPs showed nanometric size, negative Z-potential, excellent miRNA encapsulation efficiency (99%), and good colloidal stability. Controlled miRNA release was observed for up to 9 days, compared with complete release within 72 h for commercial agent Lipofectamine RNAiMAX. As a proof of concept, two strategies were explored to promote cardiac regeneration following myocardial infarction: direct reprogramming of adult human cardiac fibroblasts (AHCFs) into induced cardiomyocytes using miRcombo (miR-1, 133, 208, 499) [4], and stimulation of cardiomyocyte proliferation in H9c2 cells with miR-199 [1]. AHCFs transfected with H-NPs had superior cell viability (100% vs. 70%) compared to RNAiMAX, while in H9c2 viability was comparable (100%). Both cell types efficiently internalized H-NPs. Transfection with miR-1-loaded H-NPs induced significant downregulation of TWF-1 after 48 h, while miRcombo/H-NPs increased cardiac troponin T expression in AHCFs at gene and protein levels after 15 days, indicating successful reprogramming. In H9c2, miR-199/H-NPs enhanced Ki67-positive cell counts after 72 h, confirming proliferative activity. Furthermore, H-NPs maintained physicochemical and biological properties after freeze-drying with trehalose and 14 days of storage.

These results highlight H-NPs versatility and potential for broader therapeutic and industrial applications, overcoming key limitations of existing transfection systems.

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2. Lee et al., J. Control. Release, 2019
3. Nicoletti, Paoletti et al. AHM, 2025
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### 47. Comparative evaluation of mesoporous silica and polyplex-based nanocarriers for controlled RNAi release against post-traumatic stress disorder (PTSD)

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The development of nanocarrier systems capable of efficiently delivering RNA interference (RNAi) molecules, including small interfering RNA (siRNA) and microRNA (miRNA), represents a promising frontier in precision therapeutics. This study aimed to develop more effective therapies for post-traumatic stress disorder (PTSD) through the integration of nanotechnology with next-generation therapeutics. Specifically, we engineered two complementary nanoparticle systems: (i) amino mesoporous silica nanoparticles (SN) (size ~20 nm), and (ii) chitosan/poly(lactic-co-glycolic acid) (Ch/PLGA) polyplexes nanoparticles (PN) (size ~200 nm). Each nanocarrier was developed according to the physicochemical nature of the RNA cargo and the intended release kinetics, combining structural stability with biocompatibility. Indeed, silica nanoparticles were employed for RNAi surface loading, whereas Ch/PLGA polyplexes were produced via emulsion–solvent evaporation and electrostatic complexation for RNAi internal encapsulation. The RNAi agents included siRNA-PPP6C-mus-827, targeting the PPP6C gene involved in neuronal potassium channel modulation (Kv3.2), and miRNA-hsa-511-5p, a regulator of a PTSD-associated transcriptional gene (FKBP5), and also in the expression of inflammatory cytokines. Both systems were further modified using a Layer-by-Layer (LbL) assembly, testing different numbers of polyelectrolyte bilayers (pectin as polyanion and chitosan as polycation) to tune surface charge for enhancing their cell uptake, and RNAi retention and release behavior. Dynamic light scattering confirmed nanoscalesize distribution (SN/PN 20-90/200-300 nm), and tunable zeta potential (SN/PN +40/+25 mV) for polyplex-based nanoparticles, while fluorescence-based assays quantified encapsulation efficiency (SN/PN 95/97%). CryoSEM revealed well-defined morphologies and uniform surface coatings. RNAi release kinetics in PBS (37°C) demonstrated controlled and sustained release, strongly influenced by the number of LbL layers. In vitro cytocompatibility assays in SH-SY5Y neuroblastoma cells confirmed excellent biocompatibility and uptake demonstrated by flow-cytometry. qPCR has confirmed the successful modulation of FKBP5 expression, indicating that an in vitro PTSD model has been effectively established.

### 48. Cell-Dense tissue bioprinting

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Cell-dense tissues are essential in tissue engineering because they closely replicate the structural and functional characteristics of native organs. High cell density promotes extensive cell-cell and cell-matrix interactions, drives extracellular matrix production, and supports tissue-specific differentiation and maturation. These properties are crucial for achieving physiologically relevant mechanical strengths, metabolic activities, and long-term functions. However, current bioprinting approaches often fail to reproduce such dense yet sophisticated cellular architectures. Technical constraints in bioink formulation and printing methods typically result in constructs with insufficient cell content. This lack of cellular richness restricts the maturation and functional integration of bioprinted tissues. In this presentation, I will discuss our recent progress in developing technologies to fabricate functional, cell-dense engineered tissues. These approaches are likely to offer new opportunities in drug discovery, therapeutic screening, and regenerative medicine.

### 49. Miniature engineered heart tissues from human iPSC-cardiomyocytes on a hypoxia-on-chip platform

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Ischemic heart disease (IHD) is the leading cause of death worldwide. It results from reduced myocardial blood flow, causing oxygen deprivation and scar tissue formation. While reperfusion therapy and antiarrhythmic drugs are standard treatments, reperfusion may aggravate tissue injury. Promising results from animal studies have not translated to clinical success, highlighting the need for human-based models. Induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) offer a patient-specific platform for in vitro cardiac research. Our aim is to develop a more physiologically relevant model to study cardiac responses to hypoxia and support therapeutic development.

Here we present a novel 3D hypoxia-on-a-chip platform integrating miniature engineered heart tissues (mini-EHTs) with a system enabling precise oxygen control. The base of the platform is an OxyGenie mini-incubator (BioGenium Microsystems, Finland) combined with field stimulation electrodes and a custom EHT-insert. This setup enables electrical stimulation and real-time functional analysis of cardiac tissue under hypoxic conditions.

Mini-EHTs formed from iPSC-CMs begin spontaneously beating within the first week, with the beating rate stabilizing by week two. Fixed samples collected at weeks 2–4 show progressive cardiomyocyte alignment, indicating tissue development. Contractile force is quantified by measuring deflection of the EHT insert's flexible poles.