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Stem Cell

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Stem Cell and Entanglement Research Literatures

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Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
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Key words: stem cell; technology; life; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Agrawal, R. K., et al. (2020). "Effect of ultrasonic shot peening duration on microstructure, corrosion behavior and cell response of cp-Ti." Ultrasonics **104**: 106110.

Surface mechanical attrition treatment (SMAT) of metallic biomaterials has gained significant importance due to its ability to develop nano structure in the surface region. In the present study, the microstructural changes and corrosion behavior of the commercially pure titanium (cp-Ti), following different durations of ultrasonic shot peening (USSP) has been investigated. cp-Ti was shot peened for different durations from 0 to 120 s and the treated samples were examined for microstructural changes in the surface region, cell viability and corrosion behavior. Cell viability was considerably increased after USSP for 60-120 s, exhibiting maximum for the 90 s of USSP. The passivation tendency was also improved with peening duration up to 90 s, however, it declined for longer duration of USSP. The beneficial effects of USSP may be attributed to nano structuring in the surface region and development of higher positive potentials at the USSP treated surface. Transmission Electron Microscope (TEM) examination of the USSPed surface revealed dislocation entanglement and substructure. Also, higher surface volta potential was observed over the USSPed sample exhibiting better cell proliferation. The present work is corollary to previous work of the group and mainly discusses the role of USSP duration, as a process parameter, on the cell viability and corrosion resistance of cp-Ti.

Andjelic, S., et al. (2016). "Anterior lens epithelial cells attachment to the basal lamina." Acta Ophthalmol **94**(3): e183-188.

PURPOSE: To study the structure of the anterior lens epithelial cells (aLECs) and the contacts of the aLECs with the basal lamina (BL) in order to understand their role in the lens epithelium's function. METHODS: The aLCs (BL and associated aLECs) were obtained from routine uneventful cataract surgery, prepared for and studied by scanning electron microscopy (SEM), transmission electron microscopy (TEM) and confocal microscopy. RESULTS: SEM shows that the basal surface of the aLECs (~10-15 mum) is with aLECs foldings (~1-3 mum) and extensions (~0.5-3 mum) attached to the BL. Confocal microscopy images of the basal sections of the aLECs after membrane staining also suggest that the basal part of aLECs has foldings (~1-3 mum). TEM shows in the

aLECs basal parts, towards BL, the structures that look like entanglement (~1-4 mum). In cases where there is a swelling of the cytoplasm and offset of the aLECs from the BL, individual extensions (~0.5-2 mum) that extend to the BL are visible by TEM. CONCLUSIONS: We provide detail evidence about the structural organization of the aLECs, in particular about their basal side which is in contact with the BL. This is supported by the complementary use of three techniques, SEM, TEM and confocal microscopy, each of them showing the same morphological features, the extensions and the entanglements of the aLECs cytoplasmic membrane at the border with the BL. The basal surface of the aLECs is increased. It suggests the functional importance of the contact between aLECs and BL.

Asheghali, D., et al. (2020). "Enhanced neuronal differentiation of neural stem cells with mechanically enhanced touch-spun nanofibrous scaffolds." Nanomedicine **24**: 102152.

We studied NE-4C neural cells differentiation on 2D polycaprolactone (PCL) nanofibrous scaffolds with systematically varied mechanical characteristics of nanofibers while retaining an unchanged fiber alignment, diameter, and chemical composition. Our experiments demonstrated that the nanofibers with enhanced mechanical properties are beneficial for the preferential development of neuronal cells vs. glial cells. Electrospun (ES) and touch-spun (TS) nanofibers were fabricated with Young's modulus in the range of 10 MPa to 230 MPa and a fraction of crystallinity from 30% to 80%. The TS fibers undergo a greater drawing ratio and thus approach a greater polymer chain stretching and alignment that resulted in an increased crystallinity. The TS scaffolds demonstrated improved stability in the aqueous cell culture environment, resisting misalignment and entanglement after a period of 2 weeks of swelling followed by 14 days of neural differentiation. The results confirmed that the neurites on the TS fibers have a preferred orientation even after swelling.

Barger, M. A. and B. B. Nickol (1998). "Structure of Leptorhynchoides thecatus and Pomphorhynchus bulbocolli (Acanthocephala) eggs in habitat partitioning and transmission." J Parasitol **84**(3): 534-537.

The role of egg structure in transmission and habitat use of Leptorhynchoides thecatus and Pomphorhynchus bulbocolli (Acanthocephala) was investigated. During storage in tap water at 4 C, the outer membrane of L. thecatus eggs was lost, releasing ribbonlike filaments of the fibrillar coat. After similar storage, the outer membrane and fibrillar coat of P. bulbocolli eggs remained intact. Eggs of L. thecatus entangled in algae, whereas those of P. bulbocolli settled to the substratum. Leptorhynchoides thecatus infections in amphipod intermediate hosts were significantly more prevalent and dense when eggs were allowed to entangle than when they were not. Prevalence and relative density of P. bulbocolli infections in amphipods were not significantly different between trials in which entanglement was possible and those in which it was not. These results indicate that although the same species of amphipod, Hyalella azteca, is the intermediate host for both acanthocephalan species, mechanisms of transmission differ. Differences in fibrillar coats result in segregation of the environment in a manner that affects transmission and occurrence in intermediate hosts.

Benler, S. and E. V. Koonin (2022). "Recruitment of Mobile Genetic Elements for Diverse Cellular Functions in Prokaryotes." Front Mol Biosci **9**: 821197.

Prokaryotic genomes are replete with mobile genetic elements (MGE) that span a continuum of replication autonomy. On numerous occasions during microbial evolution, diverse MGE lose their autonomy altogether but, rather than being quickly purged from the host genome, assume a new function that benefits the host, rendering the immobilized MGE subject to purifying selection, and resulting in its vertical inheritance. This mini-review highlights the diversity of the repurposed (exapted) MGE as well as the plethora of cellular functions that they perform. The principal contribution of the exaptation of MGE and their components is to the prokaryotic functional systems involved in biological conflicts, and in particular, defense against viruses and other MGE. This evolutionary entanglement between MGE and defense systems appears to stem both from mechanistic similarities and from similar evolutionary predicaments whereby both MGEs and defense systems tend to incur fitness costs to the hosts and thereby evolve mechanisms for survival including horizontal mobility, causing host addiction, and exaptation for functions beneficial to the host. The examples discussed demonstrate that the identity of an MGE, overall mobility and relationship with the host cell (mutualistic, symbiotic, commensal, or parasitic) are all factors that affect exaptation.

Brown, A. and H. Geiger (2018). "Chromosome integrity checkpoints in stem and progenitor cells: transitions upon differentiation, pathogenesis, and aging." Cell Mol Life Sci **75**(20): 3771-3779.

Loss of chromosome integrity is a major contributor to cancer. Checkpoints within the cell division cycle that facilitate the accuracy and outcome of chromosome segregation are thus critical pathways for preserving chromosome integrity and preventing

chromosomal instability. The spindle assembly checkpoint, the decatenation checkpoint and the post-mitotic tetraploidy checkpoint ensure the appropriate establishment of the spindle apparatus, block mitotic entry upon entanglement of chromosomes or prevent further progression of post-mitotic cells that display massive spindle defects. Most of our knowledge on these mechanisms originates from studies conducted in yeast, cancer cell lines and differentiated cells. Considering that in many instances cancer derives from transformed stem and progenitor cells, our knowledge on these checkpoints in these cells just started to emerge. With this review, we provide a general overview of the current knowledge of these checkpoints in embryonic as well as in adult stem and progenitor cells with a focus on the hematopoietic system and outline common mis-regulations of their function associated with cancer and leukemia. Most cancers are aging-associated diseases. We will thus also discuss changes in the function and outcome of these checkpoints upon aging of stem and progenitor cells.

Caljon, G., et al. (2016). "The Dermis as a Delivery Site of Trypanosoma brucei for Tsetse Flies." PLoS Pathog **12**(7): e1005744.

Tsetse flies are the sole vectors of Trypanosoma brucei parasites that cause sleeping sickness. Our knowledge on the early interface between the infective metacyclic forms and the mammalian host skin is currently highly limited. Glossina morsitans flies infected with fluorescently tagged T. brucei parasites were used in this study to initiate natural infections in mice. Metacyclic trypanosomes were found to be highly infectious through the intradermal route in sharp contrast with blood stream form trypanosomes. Parasite emigration from the dermal inoculation site resulted in detectable parasite levels in the draining lymph nodes within 18 hours and in the peripheral blood within 42 h. A subset of parasites remained and actively proliferated in the dermis. By initiating mixed infections with differentially labeled parasites, dermal parasites were unequivocally shown to arise from the initial inoculum and not from a re-invasion from the blood circulation. Scanning electron microscopy demonstrated intricate interactions of these skin-residing parasites with adipocytes in the connective tissue, entanglement by reticular fibers of the periadipocytic baskets and embedment between collagen bundles. Experimental transmission experiments combined with molecular parasite detection in blood fed flies provided evidence that dermal trypanosomes can be acquired from the inoculation site immediately after the initial transmission. High resolution thermographic imaging also revealed that intradermal parasite expansion induces elevated skin surface temperatures. Collectively, the dermis represents a delivery site of the highly infective metacyclic trypanosomes from which the host is systemically colonized and where a proliferative subpopulation remains that is physically constrained by intricate interactions with adipocytes and collagen fibrous structures.

Chansoria, P., et al. (2021). "Characterizing the Effects of Synergistic Thermal and Photo-Cross-Linking during Biofabrication on the Structural and Functional Properties of Gelatin Methacryloyl (GelMA) Hydrogels." ACS Biomater Sci Eng **7**(11): 5175-5188.

Gelatin methacryloyl (GelMA) hydrogels have emerged as promising and versatile biomaterial matrices with applications spanning drug delivery, disease modeling, and tissue engineering and regenerative medicine. GelMA exhibits reversible thermal cross-linking at temperatures below 37 degrees C due to the entanglement of constitutive polymeric chains, and subsequent ultraviolet (UV) photo-cross-linking can covalently bind neighboring chains to create irreversibly cross-linked hydrogels. However, how these cross-linking modalities interact and can be modulated during biofabrication to control the structural and functional characteristics of this versatile biomaterial is not well explored yet. Accordingly, this work characterizes the effects of synergistic thermal and photo-cross-linking as a function of GelMA solution temperature and UV photo-cross-linking duration during biofabrication on the hydrogels' stiffness, microstructure, proteolytic degradation, and responses of NIH 3T3 and human adipose-derived stem cells (hASC). Smaller pore size, lower degradation rate, and increased stiffness are reported in hydrogels processed at lower temperature or prolonged UV exposure. In hydrogels with low stiffness, the cells were found to shear the matrix and cluster into microspheroids, while poor cell attachment was noted in high stiffness hydrogels. In hydrogels with moderate stiffness, ones processed at lower temperature demonstrated better shape fidelity and cell proliferation over time. Analysis of gene expression of hASC encapsulated within the hydrogels showed that, while the GelMA matrix assisted in maintenance of stem cell phenotype (CD44), a higher matrix stiffness resulted in higher pro-inflammatory marker (ICAM1) and markers for cell-matrix interaction (ITGA1 and ITGA10). Analysis of constructs with ultrasonically patterned hASC showed that hydrogels processed at higher temperature possessed lower structural fidelity but resulted in more cell elongation and greater anisotropy over time. These findings demonstrate the significant impact of GelMA material formulation and processing conditions on the structural and functional properties of the hydrogels. The understanding of these material-

process-structure-function interactions is critical toward optimizing the functional properties of GelMA hydrogels for different targeted applications.

Chimene, D., et al. (2020). "Nanoengineered Osteoinductive Bioink for 3D Bioprinting Bone Tissue." ACS Appl Mater Interfaces **12**(14): 15976-15988.

Bioprinting is an emerging additive manufacturing approach to the fabrication of patient-specific, implantable three-dimensional (3D) constructs for regenerative medicine. However, developing cell-compatible bioinks with high printability, structural stability, biodegradability, and bioactive characteristics is still a primary challenge for translating 3D bioprinting technology to preclinical and clinal models. To overcome this challenge, we developed a nanoengineered ionic covalent entanglement (NICE) bioink formulation for 3D bone bioprinting. The NICE bioinks allow precise control over printability, mechanical properties, and degradation characteristics, enabling custom 3D fabrication of mechanically resilient, cellularized structures. We demonstrate cell-induced remodeling of 3D bioprinted scaffolds over 60 days, demonstrating deposition of nascent extracellular matrix proteins. Interestingly, the bioprinted constructs induce endochondral differentiation of encapsulated human mesenchymal stem cells (hMSCs) in the absence of osteoinducing agent. Using next-generation transcriptome sequencing (RNA-seq) technology, we establish the role of nanosilicates, a bioactive component of NICE bioink, to stimulate endochondral differentiation at the transcriptome level. Overall, the osteoinductive bioink has the ability to induce formation of osteo-related mineralized extracellular matrix by encapsulated hMSCs in growth factor-free conditions. Furthermore, we demonstrate the ability of NICE bioink to fabricate patient-specific, implantable 3D scaffolds for repair of craniomaxillofacial bone defects. We envision development of this NICE bioink technology toward a realistic clinical process for 3D bioprinting patient-specific bone tissue for regenerative medicine.

Cope, L. A. (2016). "Morphological Variations in the Canine (Canis familiaris) Right Ventricle Trabecula Septomarginalis Dextra and a Proposed Classification Scheme." Anat Histol Embryol **45**(6): 437-442.

The trabecula septomarginalis dextra is a structure routinely mentioned in veterinary anatomy. While there are several studies on the morphology of this structure in select animal species, there are some characteristics that are not adequately described. The purpose of this study was to describe and classify this trabecula in the domestic dog using the number of branches that insert onto the ventricular free wall. In the 39 examined hearts, 17.95% were single stranded (type I) and 2.56% were y-shaped (IA). Then, 28.21% were web-like with 3 to 4 points of insertion (IB) and 51.28% were web-like with 5 or more points of insertion (IC). While the purpose of this study was to describe the morphology of this trabecula, it also showed there is variability in this structure within the same species. This undocumented variability could present a problem to researchers who use dogs as an animal model when testing catheters for invasive cardiac monitoring or cardiac stem cell therapy. Also a web-like trabecula could create problems during pacemaker lead placement for the treatment of symptomatic bradycardia because of the potential for catheter entanglement in these branches.

Godbe, J. M., et al. (2021). "Hydrogen Bonding Stiffens Peptide Amphiphile Supramolecular Filaments by Aza-Glycine Residues." Acta Biomater **135**: 87-99.

Peptide amphiphiles (PAs) are a class of molecules comprised of short amino acid sequences conjugated to hydrophobic moieties that may exhibit self-assembly in water into supramolecular structures. We investigate here how mechanical properties of hydrogels formed by PA supramolecular nanofibers are affected by hydrogen bond densities within their internal structure by substituting glycine for aza-glycine (azaG) residues. We found that increasing the number of PA molecules that contain azaG up to 5 mol% in PA supramolecular nanofibers increases their persistence length fivefold and decreases their diffusion coefficients as measured by fluorescence recovery after photobleaching. When these PAs are used to create hydrogels, their bulk storage modulus (G') was found to increase as azaG PA content in the supramolecular assemblies increases up to a value of 10 mol% and beyond this value a decrease was observed, likely due to diminished levels of nanofiber entanglement in the hydrogels as a direct result of increased supramolecular rigidity. Interestingly, we found that the bioactivity of the scaffolds toward dopaminergic neurons derived from induced pluripotent stem cells can be enhanced directly by persistence length independently of storage modulus. We hypothesize that this is due to interactions between the cells and the extracellular environment across different size scales: from filopodia adhering to individual nanofiber bundles to cell adhesion sites that interact with the hydrogel as a bulk substrate. Fine tuning of hydrogen bond density in self-assembling peptide biomaterials such as PAs provides an approach to control nanoscale stiffness as part of an overall strategy to optimize bioactivity in these supramolecular systems. supramolecular biomaterials. STATEMENT OF SIGNIFICANCE: Hydrogen bonding is an important driving force for the self-assembly of peptides in both biological and artificial

systems. Here, we increase the amount of hydrogen bonding within self-assembled peptide amphiphile (PA) nanofibers by substituting glycine for an aza-glycine (azaG). We show that increasing the molar concentration of azaG increases the internal order of individual nanofibers and increases their persistence length. We also show that these changes are sufficient to increase survival and tyrosine hydroxylase expression in induced pluripotent stem cell-derived dopaminergic neurons cultured in 3D gels made of these materials. Our strategy of tuning the number of hydrogen bonds in a supramolecular assembly provides mechanical customization for 3D cell culture and tissue engineering.

Guglielmetti, G., et al. (2020). ""War to the knife" against thromboinflammation to protect endothelial function of COVID-19 patients." Crit Care **24**(1): 365.

In this viewpoint, we summarize the relevance of thromboinflammation in COVID-19 and discuss potential mechanisms of endothelial injury as a key point for the development of lung and distant organ dysfunction, with a focus on direct viral infection and cytokine-mediated injury. Entanglement between inflammation and coagulation and resistance to heparin provide a rationale to consider other therapeutic approaches in order to preserve endothelial function and limit microthrombosis, especially in severe forms. These strategies include nebulized heparin, N-acetylcysteine, plasma exchange and/or fresh frozen plasma, plasma derivatives to increase the level of endogenous anticoagulants (tissue factor pathway inhibitor, activated protein C, thrombomodulin, antithrombin), dipyridamole, complement blockers, different types of stem cells, and extracellular vesicles. An integrated therapy including these drugs has the potential to improve outcomes in COVID-19.

Hameroff, S. R. (2004). "A new theory of the origin of cancer: quantum coherent entanglement, centrioles, mitosis, and differentiation." Biosystems **77**(1-3): 119-136.

Malignant cells are characterized by abnormal segregation of chromosomes during mitosis ("aneuploidy"), generally considered a result of malignancy originating in genetic mutations. However, recent evidence supports a century-old concept that maldistribution of chromosomes (and resultant genomic instability) due to abnormalities in mitosis itself is the primary cause of malignancy rather than a mere byproduct. In normal mitosis chromosomes replicate into sister chromatids which are then precisely separated and transported into mirror-like sets by structural protein assemblies called mitotic spindles and centrioles, both composed of microtubules. The elegant yet poorly understood ballet-like movements and geometric organization occurring in mitosis have suggested guidance by some type of organizing field, however neither electromagnetic nor chemical gradient fields have been demonstrated or shown to be sufficient. It is proposed here that normal mirror-like mitosis is organized by quantum coherence and quantum entanglement among microtubule-based centrioles and mitotic spindles which ensure precise, complementary duplication of daughter cell genomes and recognition of daughter cell boundaries. Evidence and theory supporting organized quantum states in cytoplasm/nucleoplasm (and quantum optical properties of centrioles in particular) at physiological temperature are presented. Impairment of quantum coherence and/or entanglement among microtubule-based mitotic spindles and centrioles can result in abnormal distribution of chromosomes, abnormal differentiation and uncontrolled growth, and account for all aspects of malignancy. New approaches to cancer therapy and stem cell production are suggested via non-thermal laser-mediated effects aimed at quantum optical states of centrioles.

Katiyar, A., et al. (2022). "The Nucleus Bypasses Obstacles by Deforming Like a Drop with Surface Tension Mediated by Lamin A/C." Adv Sci (Weinh) **9**(23): e2201248.

Migrating cells must deform their stiff cell nucleus to move through pores and fibers in tissue. Lamin A/C is known to hinder cell migration by limiting nuclear deformation and passage through confining channels, but its role in nuclear deformation and passage through fibrous environments is less clear. Cell and nuclear migration through discrete, closely spaced, slender obstacles which mimic the mechanical properties of collagen fibers are studied. Nuclei bypass slender obstacles while preserving their overall morphology by deforming around them with deep local invaginations of little resisting force. The obstacles do not impede the nuclear trajectory and do not cause rupture of the nuclear envelope. Nuclei likewise deform around single collagen fibers in cells migrating in 3D collagen gels. In contrast to its limiting role in nuclear passage through confining channels, lamin A/C facilitates nuclear deformation and passage through fibrous environments; nuclei in lamin-null (Lmna(-/-)) cells lose their overall morphology and become entangled on the obstacles. Analogous to surface tension-mediated deformation of a liquid drop, lamin A/C imparts a surface tension on the nucleus that allows nuclear invaginations with little mechanical resistance, preventing nuclear entanglement and allowing nuclear passage through fibrous environments.

Lee, Y., et al. (2011). "Integrative analysis of transgenic alfalfa (Medicago sativa L.) suggests new

metabolic control mechanisms for monolignol biosynthesis." PLoS Comput Biol **7**(5): e1002047.

The entanglement of lignin polymers with cellulose and hemicellulose in plant cell walls is a major biological barrier to the economically viable production of biofuels from woody biomass. Recent efforts of reducing this recalcitrance with transgenic techniques have been showing promise for ameliorating or even obviating the need for costly pretreatments that are otherwise required to remove lignin from cellulose and hemicelluloses. At the same time, genetic manipulations of lignin biosynthetic enzymes have sometimes yielded unforeseen consequences on lignin composition, thus raising the question of whether the current understanding of the pathway is indeed correct. To address this question systemically, we developed and applied a novel modeling approach that, instead of analyzing the pathway within a single target context, permits a comprehensive, simultaneous investigation of different datasets in wild type and transgenic plants. Specifically, the proposed approach combines static flux-based analysis with a Monte Carlo simulation in which very many randomly chosen sets of parameter values are evaluated against kinetic models of lignin biosynthesis in different stem internodes of wild type and lignin-modified alfalfa plants. In addition to four new postulates that address the reversibility of some key reactions, the modeling effort led to two novel postulates regarding the control of the lignin biosynthetic pathway. The first posits functionally independent pathways toward the synthesis of different lignin monomers, while the second postulate proposes a novel feedforward regulatory mechanism. Subsequent laboratory experiments have identified the signaling molecule salicylic acid as a potential mediator of the postulated control mechanism. Overall, the results demonstrate that mathematical modeling can be a valuable complement to conventional transgenic approaches and that it can provide biological insights that are otherwise difficult to obtain.

Li, H., et al. (2021). "Recent advances in development of dendritic polymer-based nanomedicines for cancer diagnosis." Wiley Interdiscip Rev Nanomed Nanobiotechnol **13**(2): e1670.

Dendritic polymers have highly branched three-dimensional architectures, the fourth type apart from linear, cross-linked, and branched one. They possess not only a large number of terminal functional units and interior cavities, but also a low viscosity with weak or no entanglement. These features endow them with great potential in various biomedicine applications, including drug delivery, gene therapy, tissue engineering, immunoassay and bioimaging. Most review articles related to bio-related applications of dendritic polymers focus on their drug or gene delivery, while very few of them are devoted to their function as cancer diagnosis agents, which are essential for cancer treatment. In this review, we will provide comprehensive insights into various dendritic polymer-based cancer diagnosis agents. Their classification and preparation are presented for readers to have a precise understanding of dendritic polymers. On account of physical/chemical properties of dendritic polymers and biological properties of cancer, we will suggest a few design strategies for constructing dendritic polymer-based diagnosis agents, such as active or passive targeting strategies, imaging reporters-incorporating strategies, and/or internal stimuli-responsive degradable/enhanced imaging strategies. Their recent applications in in vitro diagnosis of cancer cells or exosomes and in vivo diagnosis of primary and metastasis tumor sites with the aid of single/multiple imaging modalities will be discussed in great detail. This article is categorized under: Therapeutic Approaches and Drug Discovery > Nanomedicine for Oncologic Disease Diagnostic Tools > in vivo Nanodiagnostics and Imaging Diagnostic Tools > in vitro Nanoparticle-Based Sensing.

Luca, A., et al. (2017). "Biomacromolecular-based ionic-covalent hydrogels for cell encapsulation: The atelocollagen - Oxidized polysaccharides couples." Carbohydr Polym **169**: 366-375.

Mixed crosslinked networks of ionic-covalent entanglement type were prepared starting from ternary mixtures of atelocollagen (aK; as fibrillary matrix generator), sodium hyaluronate (NaHyal; a microfibrillation assistant), and oxidized polysaccharides (OxPolys; as both cross-linkers and matrix fillers), and were tested as hydrogels for eukaryotic cell encapsulation. Either oxidized gellan (GellOx) or pullulan (PullOx) were used. An original procedure and optimal hydrogel recipes were developed to encapsulate fibroblasts and adipose-derived stem cells, while preserving their viability and proliferative ability during ex vivo temporarily storage. Physical-chemical, rheological, and biocompatibility properties of the prepared hydrogels were compared against the classic alginate hydrogel used for cell encapsulation. A larger range of material characteristics (from lax to stiff) and better laboratory maneuverability were demonstrated, which permit to design appropriate compositions for particular cell types. All hydrogels undergo fast liquefaction at temperatures between 42 and 50 degrees C, permitting the cell release after a short innocuous thermal shock.

Luo, Q., et al. (2022). "Dual stimuli-responsive dendronized prodrug derived from poly(oligo-(ethylene glycol) methacrylate)-based copolymers for enhanced

anti-cancer therapeutic effect." Acta Biomater **143**: 320-332.

In this study, we developed an enzyme- and pH-responsive dendronized poly(oligo-(ethylene glycol) methacrylate) (pOEGMA)-doxorubicin (DOX) polymeric prodrug, which combined the pOEGMA structure with a degradable peptide dendron. The introduction of the dendron in the prodrug hindered the entanglement of brush oligo-(ethylene glycol) (OEG) chains, allowed the prodrug to possess dual stimuli-responsiveness, and mediated self-assembly of the polymeric prodrug to form stable nanoparticles (NPs). Brush conformation of polyethylene glycol (PEG) side chains endowed the NPs with long-term circulation with a half-life of 16.0 h. The dual-responsive dendritic structure enhanced cellular uptake of NPs and facilitated drug release in response to overexpressed cathepsin B and an acidic pH in the tumor microenvironment, resulting in an enhanced therapeutic effect with a tumor inhibition rate of 72.9% for 4T1 tumor-bearing mice. The NPs were demonstrated to possess great hemocompatibility and biosafety. Therefore, this strategy could provide great insight for the design of poly(oligo-(ethylene glycol) methacrylate)-based copolymers as drug delivery carriers. STATEMENT OF SIGNIFICANCE: We propose a dual-stimuli-responsive dendronized strategy for improving the cancer therapeutic effect of the poly(oligo-(ethylene glycol) methacrylate) (pOEGMA)-based drug conjugates. The introduction of the functional dendron promotes self-assembly of the polymeric prodrug into nanoparticles, hindering the entanglement of brush oligo-(ethylene glycol) (OEG) chains in the conjugated drugs. The obtained poly OEGMA-GFLG-Dendron-NH-N=DOX nanoparticles maintains long circulation, while addresses the drug release issue due to the presence of high-density PEG. The drug delivery system exhibits a high therapeutic potentcy with negligible side effects.

Majidi, S. S., et al. (2018). "Wet electrospun alginate/gelatin hydrogel nanofibers for 3D cell culture." Int J Biol Macromol **118**(Pt B): 1648-1654.

Convergence of biological and biofabrication approaches is necessary to progress new biomaterials promoting three-dimensional (3D) cell growth and maturation towards tissue regeneration and integration. Here, we have developed a novel approach to fabricate 3D macroporous, alginate/gelatin hydrogel nanofibers (Alg/GelF-MA), which provide superior cell adhesion, motility, proliferation and maturation. The electrospinning process greatly depends on the ionic strength and viscoelastic behavior of the solution. The polyelectrolyte nature of alginate favors intramolecular bundles over intermolecular entanglement, which hinders its electrospinnability. Electrospinning of alginate was achieved by the aid of a supporting polymer, polyethylene oxide and a surfactant, Pluronic(R)F127. Furthermore, the Ca(2+)-mediated coagulation process of alginate was realized in situ during wet electrospinning, where the rapid physical crosslink-ability of alginate was applied in conjunction with the jet entrance into the wet electrospinning collector, a coagulation bath. Consequently, the rapid formation of Ca(2+)-alginate complex stabilized the nanofiber morphology. The low surface tension of the non-solvent ethanol used in the bath prevented fibers from dense packing, thus allowing the generation of 3D macroporous structure favoring cell motility. The subsequent UV-mediated chemical crosslinking further stabilized the gelatin content in the Alg/GelF-MA hydrogel nanofibers. It is demonstrated that the Alg/GelF-MA nanofibers with low cytotoxicity (below 10%) supported an over 8-fold proliferation of mesenchymal stem cells over 5weeks and supported the maturation of human iPSC-derived ventricular cardiomyocytes, which significantly outperform the cell encapsulated bulk GelF-MA hydrogel. The work provides an insight for rational design and development of 3D cell culture matrix for advancement of stem cell therapy and tissue regeneration.

Passet, B., et al. (2020). "The Prion-like protein Shadoo is involved in mouse embryonic and mammary development and differentiation." Sci Rep **10**(1): 6765.

Shadoo belongs to the prion protein family, an evolutionary conserved and extensively studied family due to the implication of PrP in Transmissible Spongiform Encephalopathies. However, the biological function of these genes remains poorly understood. While Sprn-knockdown experiments suggested an involvement of Shadoo during mouse embryonic development, Sprn-knockout experiments in 129Pas/C57BL/6J or 129Pas/FVB/NCr mice did not confirm it. In the present study, we analyzed the impact of Sprn gene invalidation in a pure FVB/NJ genetic background, using a zinc finger nuclease approach. The in-depth analysis of the derived knockout transgenic mice revealed a significant increase in embryonic lethality at early post-implantation stages, a growth retardation of young Sprn-knockout pups fed by wild type mice and a lactation defect of Sprn-knockout females. Histological and transcriptional analyses of knockout E7.5 embryos, E14.5 placentas and G7.5 mammary glands revealed specific roles of the Shadoo protein in mouse early embryogenesis, tissue development and differentiation with a potential antagonist action between PrP and Shadoo. This study thus highlights the entanglement between the proteins of the prion family.

Qin, M., et al. (2020). "Solvent-Controlled Topological Evolution from Nanospheres to Superhelices." Small **16**(47): e2004756.

Supramolecular assemblies with diverse morphologies are crucial in determining their biochemical or physical properties. However, the topological evolution and self-assembly intermediates as well as the mechanism remain elusive. Herein, a dynamic morphological evolution from solid nanospheres to superhelical nanofibers is revealed via self-assembly of a minimal l-tryptophan-based derivative (LPWM) with various mixed solvent combinations, including the formation of solid nanospheres, the fusion of nanospheres into pearling necklace, the disintegration of necklace into short nanofibers, the distortion of nanofibers into nanotwists, and the entanglement of nanotwists into superhelices. It is found that the breakage of intramolecular H-bonds and reconstruction of intermolecular H-bonds, as well as the variation of aromatic interactions and hydrophobic effects, are the key driving forces for topological transformation, especially the dimensional evolution. The nanospheres and nanofibers demonstrate discrepant behaviors towards mouse neural stem cell (NSC) differentiation that compared with negligible impact of nanospheres scaffold, the nanofibers scaffold is favorable for NSC differentiation into neurons. The remarkable dynamic regulation of assembly process, together with the NSC differentiation on twisted nanofibers are making this system an ideal model to interpret complex proteins fibrillation processes and investigate the structure-function relationship.

Schwan, S., et al. (2017). "Morphological Characterization of the Self-Assembly of Virus Movement Proteins into Nanotubes in the Absence of Virus Particles." Adv Biosyst **1**(12): e1700113.

One infection mechanism of plant viruses is the generation of nanotubes by viral movement proteins, allowing cell-to-cell virus particle transport. Previously, it was assumed that viral nanotubes extend directly from the host-cell plasma membrane. In virus-infected plants, these nanotubes reach an extraordinary diameter:length ratio (approximately 100 nm:microm or mm range). Here, viral nanotubes are produced in a transient protoplast system; the coding sequence for alfalfa mosaic virus movement protein is translationally fused to green fluorescent protein. The maximum extension of viral nanotubes into the culture medium is achieved 24-48 h posttransfection, with lengths in the micro- and millimeter ranges. Scanning electron microscopy and transmission electron microscopy show that strong inhomogeneous viral nanotubes are formed compared to particle-filled systems. The nanotubes have similar length, but fluctuating wall thickness and diameter and are susceptible to entanglement and recombination. Indirect methods demonstrate that movement proteins assemble independently at the top of the nanotube. These viral nanotubes grow distinctly from previously known natural particle-filled systems and are a unique biological tubular nanomaterial that has the potential for micro- or nanoapplications as a mechanically stable structural component.

Sears, C., et al. (2020). "Conditioning of 3D Printed Nanoengineered Ionic-Covalent Entanglement Scaffolds with iP-hMSCs Derived Matrix." Adv Healthc Mater **9**(15): e1901580.

Additive manufacturing is a promising method for producing customized 3D bioactive constructs for regenerative medicine. Here, 3D printed highly osteogenic scaffolds using nanoengineered ionic-covalent entanglement ink (NICE) for bone tissue engineering are reported. This NICE ink consists of ionic-covalent entanglement reinforced with Laponite, a 2D nanosilicate (nSi) clay, allowing for the printing of anatomic-sized constructs with high accuracy. The 3D printed structure is able to maintain high structural stability in physiological conditions without any significant swelling or deswelling. The presence of nSi imparts osteoinductive characteristics to the NICE scaffolds, which is further augmented by depositing pluripotent stem cell-derived extracellular matrix (ECM) on the scaffolds. This is achieved by stimulating human induced pluripotent stem cell-derived mesenchymal stem cells (iP-hMSCs) with 2-chloro-5-nitrobenzanilide, a PPARgamma inhibitor that enhances Wnt pathway, resulting in the deposition of an ECM characterized by high levels of collagens VI and XII found in anabolic bone. The osteoinductive characteristics of these bioconditioned NICE (bNICE) scaffolds is demonstrated through osteogenic differentiation of bone marrow derived human mesenchymal stem cells. A significant increase in the expression of osteogenic gene markers as well as mineralized ECM are observed on bioconditioned NICE (bNICE) scaffolds compared to bare scaffolds (NICE). The bioconditioned 3D printed scaffolds provide a unique strategy to design personalized bone grafts for in situ bone regeneration.

Succar, P., et al. (2016). "Priming Adipose-Derived Mesenchymal Stem Cells with Hyaluronan Alters Growth Kinetics and Increases Attachment to Articular Cartilage." Stem Cells Int **2016**: 9364213.

Background. Biological therapeutics such as adipose-derived mesenchymal stem cell (MSC) therapy are gaining acceptance for knee-osteoarthritis (OA) treatment. Reports of OA-patients show reductions in cartilage defects and regeneration of hyaline-like-cartilage with MSC-therapy. Suspending MSCs in

hyaluronan commonly occurs in animals and humans, usually without supporting data. Objective. To elucidate the effects of different concentrations of hyaluronan on MSC growth kinetics. Methods. Using a range of hyaluronan concentrations, we measured MSC adherence and proliferation on culture plastic surfaces and a novel cartilage-adhesion assay. We employed time-course and dispersion imaging to assess MSC binding to cartilage. Cytokine profiling was also conducted on the MSC-secretome. Results. Hyaluronan had dose-dependent effects on growth kinetics of MSCs at concentrations of entanglement point (1 mg/mL). At higher concentrations, viscosity effects outweighed benefits of additional hyaluronan. The cartilage-adhesion assay highlighted for the first time that hyaluronan-primed MSCs increased cell attachment to cartilage whilst the presence of hyaluronan did not. Our time-course suggested patients undergoing MSC-therapy for OA could benefit from joint-immobilisation for up to 8 hours. Hyaluronan also greatly affected dispersion of MSCs on cartilage. Conclusion. Our results should be considered in future trials with MSC-therapy using hyaluronan as a vehicle, for the treatment of OA.

Tutak, W., et al. (2013). "The support of bone marrow stromal cell differentiation by airbrushed nanofiber scaffolds." Biomaterials **34**(10): 2389-2398.

Nanofiber scaffolds are effective for tissue engineering since they emulate the fibrous nanostructure of native extracellular matrix (ECM). Although electrospinning has been the most common approach for fabricating nanofiber scaffolds, airbrushing approaches have also been advanced for making nanofibers. For airbrushing, compressed gas is used to blow polymer solution through a small nozzle which shears the polymer solution into fibers. Our goals were 1) to assess the versatility of airbrushing, 2) to compare the properties of airbrushed and electrospun nanofiber scaffolds and 3) to test the ability of airbrushed nanofibers to support stem cell differentiation. The results demonstrated that airbrushing could produce nanofibers from a wide range of polymers and onto a wide range of targets. Airbrushing was safer, 10-fold faster, 100-fold less expensive to set-up and able to deposit nanofibers onto a broader range of targets than electrospinning. Airbrushing yielded nanofibers that formed loosely packed bundles of aligned nanofibers, while electrospinning produced un-aligned, single nanofibers that were tightly packed and highly entangled. Airbrushed nanofiber mats had larger pores, higher porosity and lower modulus than electrospun mats, results that were likely caused by the differences in morphology (nanofiber packing and entanglement). Airbrushed nanofiber scaffolds fabricated from 4 different polymers were each able to support osteogenic differentiation of primary human bone marrow stromal cells (hBMSCs). Finally, the differences in airbrushed versus electrospun nanofiber morphology caused differences in hBMSC shape where cells had a smaller spread area and a smaller volume on airbrushed nanofiber scaffolds. These results highlight the advantages and disadvantages of airbrushing versus electrospinning nanofiber scaffolds and demonstrate that airbrushed nanofiber scaffolds can support stem cell differentiation.

Ventura, C. (2005). "CAM and cell fate targeting: molecular and energetic insights into cell growth and differentiation." Evid Based Complement Alternat Med **2**(3): 277-283.

Evidence-based medicine is switching from the analysis of single diseases at a time toward an integrated assessment of a diseased person. Complementary and alternative medicine (CAM) offers multiple holistic approaches, including osteopathy, homeopathy, chiropractic, acupuncture, herbal and energy medicine and meditation, all potentially impacting on major human diseases. It is now becoming evident that acupuncture can modify the expression of different endorphin genes and the expression of genes encoding for crucial transcription factors in cellular homeostasis. Extremely low frequency magnetic fields have been found to prime the commitment to a myocardial lineage in mouse embryonic stem cells, suggesting that magnetic energy may direct stem cell differentiation into specific cellular phenotypes without the aid of gene transfer technologies. This finding may pave the way to novel approaches in tissue engineering and regeneration. Different ginseng extracts have been shown to modulate growth and differentiation in pluripotent cells and to exert wound-healing and antitumor effects through opposing activities on the vascular system, prompting the hypothesis that ancient compounds may be the target for new logics in cell therapy. These observations and the subtle entanglement among different CAM systems suggest that CAM modalities may deeply affect both the signaling and transcriptional level of cellular homeostasis. Such a perception holds promises for a new era in CAM, prompting reproducible documentation of biological responses to CAM-related strategies and compounds. To this end, functional genomics and proteomics and the comprehension of the cell signaling networks may substantially contribute to the development of a molecular evidence-based CAM.

Walia, S., et al. (2021). "Designer DNA Hydrogels Stimulate 3D Cell Invasion by Enhanced Receptor

Expression and Membrane Endocytosis." ACS Biomater Sci Eng **7**(12): 5933-5942.

DNA has emerged as one of the smartest biopolymers to bridge the gap between chemical science and biology to design scaffolds like hydrogels by physical entanglement or chemical bonding with remarkable properties. We present here a completely new application of DNA-based hydrogels in terms of their capacity to stimulate membrane endocytosis, leading to enhanced cell spreading and invasion for cells in ex vivo 3D spheroids models. Multiscale simulation studies along with DLS data showed that the hydrogel formation was enhanced at lower temperature and it converts to liquid with increase in temperature. DNA hydrogels induced cell spreading as observed by the increase in cellular area by almost two-fold followed by an increase in the receptor expression, the endocytosis, and the 3D invasion potential of migrating cells. Our first results lay the foundation for upcoming diverse applications of hydrogels to probe and program various cellular and physiological processes that can have lasting applications in stem cell programming and regenerative therapeutics.

Xu, H., et al. (2019). "Injectable, Self-Healing, beta-Chitin-Based Hydrogels with Excellent Cytocompatibility, Antibacterial Activity, and Potential As Drug/Cell Carriers." ACS Appl Bio Mater **2**(1): 196-204.

Dynamic chemistry has been recently applied to design injectable hydrogels capable of self-healing. Among current strategies for preparing hydrogels that are suitable for cell encapsulation and culture, the fabrication of injectable, self-healing hydrogels is immensely superior. Here, novel beta-chitin-based, injectable, self-healing hydrogels were constructed through the self-assembly and entanglement of amphiphilic quaternized beta-chitin (QC) and hydrophilic oxidized dextran (OD) chains as well as the dynamic Schiff base linkages without extra additives under physiological conditions. The gelation time, viscoelastic behavior, mechanical properties, biodegradability, stimulus sensitivity, shear-thinning ability and self-healing properties of the QC/OD hydrogels were thoroughly characterized. Moreover, the QC/OD hydrogels could be applied for the controlled pH-sensitive release of doxorubicin hydrochloride. Because of the excellent cytocompatibility, the QC/OD hydrogels were further used as a promising platform for the three-dimensional encapsulation and culture of NIH-3T3 cells and mouse bone marrow-derived mesenchymal stem cells. Specifically, these novel beta-chitin-based hydrogels can be used as an antibacterial vehicle for the delivery of cells in the gel form and thus have potential for applications in regenerative medicine, drug/gene/cell delivery, and cell therapy.

Yang, Q., et al. (2022). "Alterations in 3D chromatin organization contribute to tumorigenesis of EGFR-amplified glioblastoma." Comput Struct Biotechnol J **20**: 1967-1978.

Background: EGFR amplification and/or mutation are found in more than half of the cases with glioblastoma. Yet, the role of chromatin interactions and its regulation of gene expression in EGFR-amplified glioblastoma remains unclear. Methods: In this study, we explored alterations in 3D chromatin organization of EGFR-amplified glioblastoma and its subsequent impact by performing a comparative analysis of Hi-C, RNA-seq, and whole-genome sequencing (WGS) on EGFR-amplified glioblastoma-derived A172 and normal astrocytes (HA1800 cell line). Results: A172 cells showed an elevated chromatin relaxation, and unexpected entanglement of chromosome regions. A genome-wide landscape of switched compartments and differentially expressed genes between HA1800 and A172 cell lines demonstrated that compartment activation reshaped chromatin accessibility and activated tumorigenesis-related genes. Topological associating domain (TAD) analysis revealed that altered TAD domains in A172 also contribute to oncogene activation and tumor repressor deactivation. Interestingly, glioblastoma-derived A172 cells showed a different chromatin loop contact propensity. Genes in tumorigenesis-associated signaling pathways were significantly enriched at the anchor loci of altered chromatin loops. Oncogene activation and tumor repressor deactivation were associated with chromatin loop alteration. Structure variations (SVs) had a dramatic impact on the chromatin conformation of EGFR-amplified glioblastoma-derived tumor cells. Moreover, our results revealed that 7p11.2 duplication activated EGFR expression in EGFR-amplified glioblastoma via neo-TAD formation and novel enhancer-promoter interaction emergence between LINC01446 and EGFR. Conclusions: The disordered 3D genomic map and multi-omics data of EGFR-amplified glioblastoma provide a resource for future interrogation of the relationship between chromatin interactions and transcriptome in tumorigenesis.

Yao, C., et al. (2021). "Rolling circle amplification (RCA)-based DNA hydrogel." Nat Protoc **16**(12): 5460-5483.

DNA hydrogels have unique properties, including sequence programmability, precise molecular recognition, stimuli-responsiveness, biocompatibility and biodegradability, that have enabled their use in diverse applications ranging from material science to

biomedicine. Here, we describe a rolling circle amplification (RCA)-based synthesis of 3D DNA hydrogels with rationally programmed sequences and tunable physical, chemical and biological properties. RCA is a simple and highly efficient isothermal enzymatic amplification strategy to synthesize ultralong single-stranded DNA that benefits from mild reaction conditions, and stability and efficiency in complex biological environments. Other available methods for synthesis of DNA hydrogels include hybridization chain reactions, which need a large amount of hairpin strands to produce DNA chains, and PCR, which requires temperature cycling. In contrast, the RCA process is conducted at a constant temperature and requires a small amount of circular DNA template. In this protocol, the polymerase phi29 catalyzes the elongation and displacement of DNA chains to amplify DNA, which subsequently forms a 3D hydrogel network via various cross-linking strategies, including entanglement of DNA chains, multi-primed chain amplification, hybridization between DNA chains, and hybridization with functional moieties. We also describe how to use the protocol for isolation of bone marrow mesenchymal stem cells and cell delivery. The whole protocol takes ~2 d to complete, including hydrogel synthesis and applications in cell isolation and cell delivery.

Zabka, A., et al. (2015). "The effects of anti-DNA topoisomerase II drugs, etoposide and ellipticine, are modified in root meristem cells of Allium cepa by MG132, an inhibitor of 26S proteasomes." Plant Physiol Biochem **96**: 72-82.

DNA topoisomerase II (Topo II), a highly specialized nuclear enzyme, resolves various entanglement problems concerning DNA that arise during chromatin remodeling, transcription, S-phase replication, meiotic recombination, chromosome condensation and segregation during mitosis. The genotoxic effects of two Topo II inhibitors known as potent anti-cancer drugs, etoposide (ETO) and ellipticine (EPC), were assayed in root apical meristem cells of Allium cepa. Despite various types of molecular interactions between these drugs and DNA-Topo II complexes at the chromatin level, which have a profound negative impact on the genome integrity (production of double-strand breaks, chromosomal bridges and constrictions, lagging fragments of chromosomes and their uneven segregation to daughter cell nuclei), most of the elicited changes were apparently similar, regarding both their intensity and time characteristics. No essential changes between ETO- and EPC-treated onion roots were noticed in the frequency of G1-, S-, G2-and M-phase cells, nuclear morphology, chromosome structures, tubulin-microtubule systems, extended distribution of mitosis-specific phosphorylation sites of histone H3, and the induction of apoptosis-like programmed cell death (AL-PCD). However, the important difference between the effects induced by the ETO and EPC concerns their catalytic activities in the presence of MG132 (proteasome inhibitor engaged in Topo II-mediated formation of cleavage complexes) and relates to the time-variable changes in chromosomal aberrations and AL-PCD rates. This result implies that proteasome-dependent mechanisms may contribute to the course of physiological effects generated by DNA lesions under conditions that affect the ability of plant cells to resolve topological problems that associated with the nuclear metabolic activities.

Zhang, L., et al. (2020). "Immunomodulatory role of mesenchymal stem cells in Alzheimer's disease." Life Sci **246**: 117405.

Alzheimer's disease (AD) is one of the most common causes of dementia and is characterized by gradual loss in memory, language, and cognitive function. The hallmarks of AD include extracellular amyloid deposition, intracellular neuronal fiber entanglement, and neuronal loss. Despite strenuous efforts toward improvement of AD, there remains a lack of effective treatment and current pharmaceutical therapies only alleviate the symptoms for a short period of time. Interestingly, some progress has been achieved in treatment of AD based on mesenchymal stem cell (MSC) transplantation in recent years. MSC transplantation, as a rising therapy, is used as an intervention in AD, because of the enormous potential of MSCs, including differentiation potency, immunoregulatory function, and no immunological rejection. Although numerous strategies have focused on the use of MSCs to replace apoptotic or degenerating neurons, recent studies have implied that MSC-immunoregulation, which modulates the activity state of microglia or astrocytes and mediates neuroinflammation via several transcription factors (NFs) signaling pathways, may act as a major mechanism for the therapeutic efficacy of MSC and be responsible for some of the satisfactory results. In this review, we will focus on the role of MSC-immunoregulation in MSC-based therapy for AD.

Zhang, X., et al. (2021). "Crosslinker-free silk/decellularized extracellular matrix porous bioink for 3D bioprinting-based cartilage tissue engineering." Mater Sci Eng C Mater Biol Appl **118**: 111388.

As cartilage tissue lacks the innate ability to mount an adequate regeneration response, damage to it is detrimental to the quality of life of the subject. The emergence of three-dimensional bioprinting (3DBP) technology presents an opportunity to repair articular cartilage defects. However, widespread adoption of this

technique has been impeded by difficulty in preparing a suitable bioink and the toxicity inherent in the chemical crosslinking process of most bioinks. Our objective was to develop a crosslinker-free bioink with the same biological activity as the original cartilage extracellular matrix (ECM) and good mechanical strength. We prepared bioinks containing different concentrations of silk fibroin and decellularized extracellular matrix (SF-dECM bioinks) mixed with bone marrow mesenchymal stem cells (BMSCs) for 3D bioprinting. SF and dECM interconnect with each other through physical crosslinking and entanglement. A porous structure was formed by removing the polyethylene glycol from the SF-dECM bioink. The results showed the SF-dECM construct had a suitable mechanical strength and degradation rate, and the expression of chondrogenesis-specific genes was found to be higher than that of the SF control construct group. Finally, we confirmed that a SF-dECM construct that was designed to release TGF-beta3 had the ability to promote chondrogenic differentiation of BMSCs and provided a good cartilage repair environment, suggesting it is an ideal scaffold for cartilage tissue engineering.

Zhang, Y., et al. (2022). "Facile fabrication of a biocompatible composite gel with sustained release of aspirin for bone regeneration." Bioact Mater **11**: 130-139.

Hydrogels are extracellular-matrix-like biomimetic materials that have wide biomedical applications in tissue engineering and drug delivery. However, most hydrogels cannot simultaneously fulfill the mechanical and cell compatibility requirements. In the present study, we prepared a semi-interpenetrating network composite gel (CG) by incorporating short chain chitosan (CS) into a covalent tetra-armed poly(ethylene glycol) network. In addition to satisfying physicochemical, mechanics, biocompatibility, and cell affinity requirements, this CG easily encapsulated acetylsalicylic acid (ASA) via electrostatic interactions and chain entanglement, achieving sustained release for over 14 days and thus promoting periodontal ligament stem cell (PDLSC) proliferation and osteogenic differentiation. In vivo studies corroborated the capacity of PDLSCs and ASA-laden CG to enhance new bone regeneration in situ using a mouse calvarial bone defect model. This might be attributed to PDLSCs and host mesenchymal stem cells expressing monocyte chemoattractant protein-1, which upregulated M2 macrophage recruitment and polarization in situ, indicating its appealing potential in bone tissue engineering.

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