Project Notes:

Project Title: Engineering Ionic Hydrogels to Overcome Charge and Size Barriers in Multi-Protein Co-Delivery
Name: Wheatley, Sam

Contents:

Knowledge Gaps:

This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

Knowledge Gap	Resolved By	Information is located	Date resolved
What hydrogels do	Researching their application and what they are composed of	https://www.sciencedirect.com	September 4th 2025
T cell Function	Looking up what they can contribute in certain environments (human, specific human, animal)	https://www.ncbi.nlm.nih.gov	September 18th 2025
T cell activity and why is it hard to regulate	Finding it within my readings then doing external research to understand it better	https://www.ncbi.nlm.nih.gov	September 25th 2025

Literature Search Parameters:

These searches were performed between 7/11/2025and XX/XX/2025.
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search
https://www.ncbi.nlm.nih.gov	Hydrogel, T cells, Cytokines, ECM	Interaction between T cells and hydrogels in osteoporotic bone
https://www.science.org/journal/science	Hydrogel, T cells, Cytokines, ECM	Interaction between T cells and hydrogels in osteoporotic bone, T cell knowledge gaps
https://www.sciencedirect.com	Hydrogel, T cells, Cytokines, ECM	cytokine and chemokine interactions in hydrogel-based microenvironments

Tags:

Tag Name	
#hydrogels, #cartilage,	#silkfibron #enzymaticcrosslinking #proteincrosslinking #molecularcharacterization
#immunotherapy #tcells #expansion #differentiation #ECM	#drugdelivery #news #biomimicry

Article #1 Notes: Title

Article notes should be on separate sheets

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Source Title	
Source citation (APA Format)	
Original URL	
Source type	
Keywords	
#Tags	
Summary of key points + notes (include methodology)	
Research Question/Problem/ Need	
Important Figures	
VOCAB: (w/definition)	
Cited references to follow up on	
Follow up Questions	

Article #1 Notes: Human cartilage repair with a photoreactive adhesive-hydrogel composite

Article notes should be on separate sheets

Source Title	NIH Public Access
Source citation (APA Format)	Sharma, Blanka. "Human Cartilage Repair with a Photoreactive Adhesive-Hydrogel Composite." *NIH Public Access*, 9 Jan. 2013, pmc.ncbi.nlm.nih.gov/articles/PMC3972413/pdf/nihms562655.pdf.
Original URL	Pmc.ncbi.nlm.nih.gov/articles/PMC3972413/pdf/nihms562655.pdf
Source type	Article
Keywords	Hydrogel, Cartilage
#Tags	#hydrogels, #cartilage
Summary of key points + notes (include methodology)	In this study, researchers developed a PEGDA hydrogel that promotes extracellular matrix deposition and stimulates cartilage growth in the presence of mesenchymal stem cells. Since this method is being applied to joints in particular, a chondroitin sulfate adhesive is added to strengthen the bond of the hydrogel with cartilage and bone. After an initial clinical trial of 15 participants was run, it showed better tissue fill and reduced pain compared to the typical surgery, suggesting that the biomaterials approach could enhance cartilage repair with further testing.
Research Question/Problem/ Need	Was there a more efficient way to carry out this process?
Important Figures	

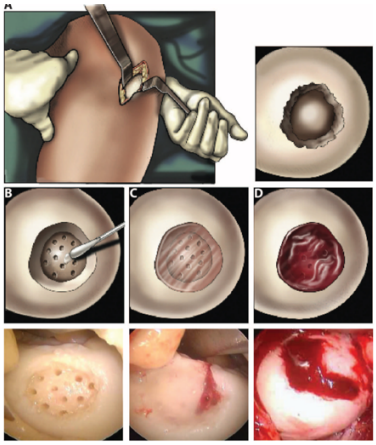


Figure 1: Hydrogel implantation procedure

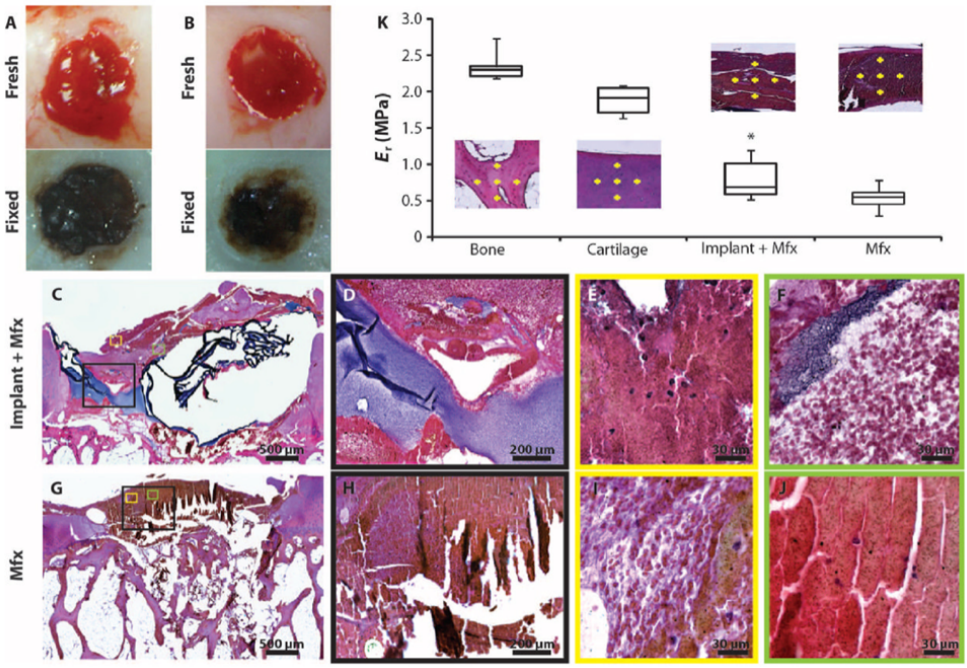


Figure 3: Hydrogel implantation in conjunction with microfracture

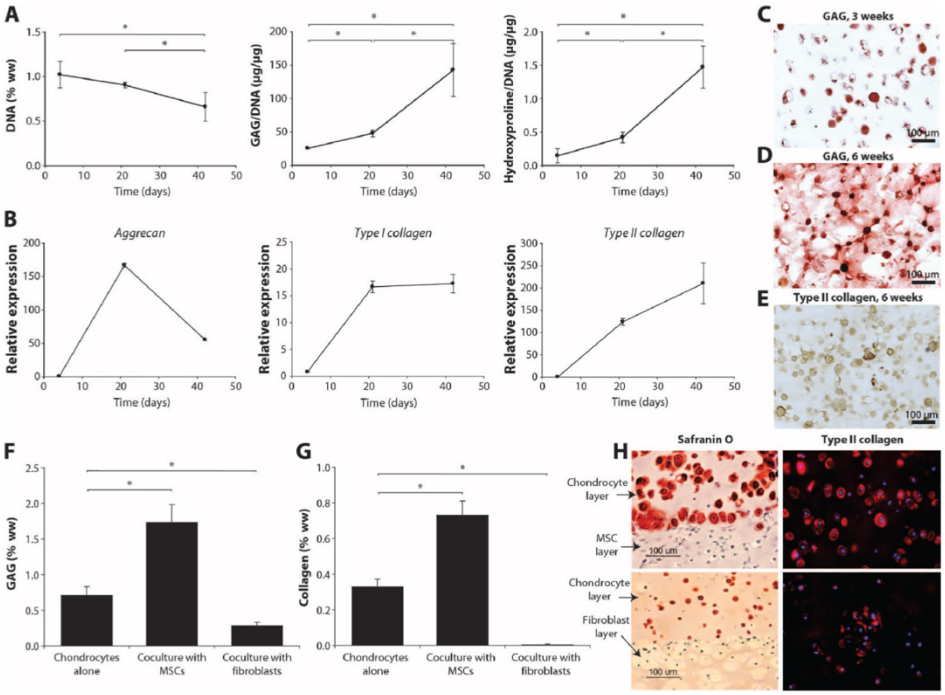


Figure 2: In vitro cartilage growth in hydrogels.

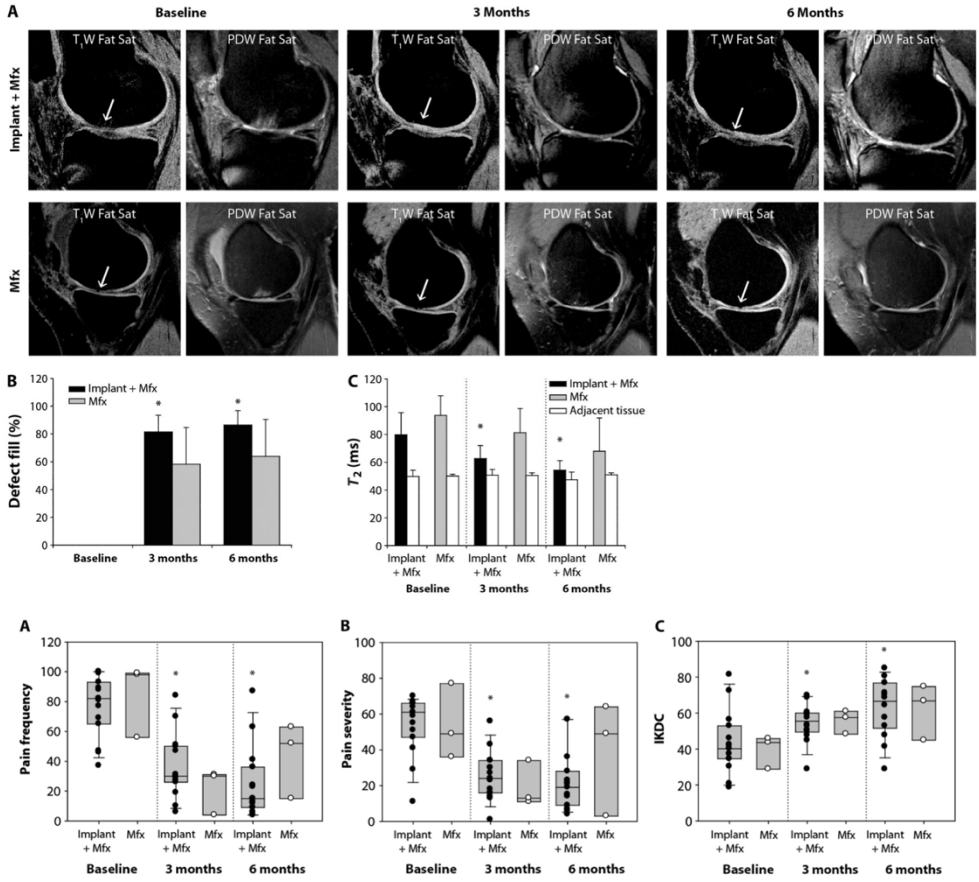
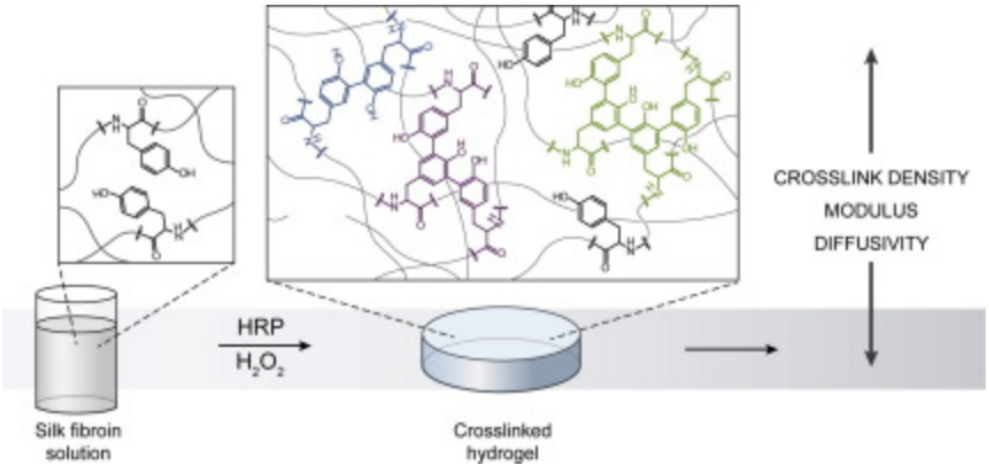


	Figure 4: Imaging and clinical evaluation of cartilage repair
VOCAB: (w/definition)	Articular cartilage - a smooth, resilient tissue covering the ends of bones within joints, acting as a shock absorber and enabling low-friction movement Avascular - something that lacks a direct blood supply Extracellular matrix - a complex meshwork of proteins and polysaccharides, primarily collagens and proteoglycans, that surrounds and supports cells, providing structural integrity, mechanical support, and an environment for cell signaling Chondrocytes - the sole cell type in cartilage, responsible for producing and maintaining its extracellular matrix (ECM), including collagens and proteoglycans, which gives cartilage its structural properties Osteoarthritis - the most common type of arthritis, causing the cartilage in joints to wear down over time, leading to pain, stiffness, and reduced mobility
Cited references to follow up on	Author links open overlay panelWenhao Liu a b 1, et al. "Time-Adaptable Alterations of the Extracellular Matrix during Chondrocyte Dedifferentiation." *Biomaterials Advances*, Elsevier, 11 June 2025, www.sciencedirect.com/science/article/abs/pii/S2772950825002109?fr=RR-2&ref=pdf_download&rr=9747dcda8df6e5ec.
Follow up Questions	What are the long-term effects of the surgery/how long does the implant last? How does the chondroitin sulfate adhesive impact the bond of hydrogel with cartilage versus bone? How does incorporating bioactive cues improve cartilage quality?

Article #2 Notes: Molecular and macro-scale analysis of enzyme-crosslinked silk hydrogels for rational biomaterials design

Source Title	Molecular and macro-scale analysis of enzyme-crosslinked silk hydrogels for rational biomaterial design
Source citation (APA Format)	McGill, M., Coburn, J. M., Partlow, B. P., Mu, X., & Kaplan, D. L. (2017). Molecular and macro-scale analysis of enzyme-crosslinked silk hydrogels for rational biomaterial design. *Acta Biomaterialia, 63*, 76-84. https://doi.org/10.1016/j.actbio.2017.09.020
Original URL	**https://www.sciencedirect.com/science/article/abs/pii/S1742706117305834?via%3Dihub**
Source type	Article
Keywords	• Hydrogels • Silk fibroin • Enzymatic crosslinking • Dityrosine bonds • Protein crosslinking • Bipolymer modification
#Tags	#silkfibron #enzymaticcrosslinking #proteincrosslinking #molecularcharacterization
Summary of key points + notes (include methodology)	The challenge that began this research was that the properties of hydrogels depend on how the silk molecules are linked, but in past work, it was all trial and error. There was a knowledge gap in the connection between molecular crosslinking and bulk performance quantification, so they decided to characterize how enzyme concentration, silk concentration and crosslinking affect crosslink density, mechanical stiffness, and diffusivity. To do this, they plan on building a framework for predictable material tuning. Many methods were used in this process. First, the silk fibroids needed to be extracted, then enzymatic crosslinking with horseradish peroxidase and H2O2 was used. This formed dityrosine bonds between tyrosine residues in silk fibrin. To quantify the degree of crosslinking, they used LC-MS/MS. Then, Rheology measured storage modulus for the stiffness and elasticity of the hydrogel. Diffusion testing, FRAP (Fluorescence Recovery After Photobeaching), was then used to measure molecular diffusivity inside the gel. After this procedure, the crossink density, mechanical strength, diffusion behavior, and structure and property relationship was found. The study concluded that enzymatic crosslinking of silk fibroin produced hydrogels with 28-56% of tyrosine residues forming dityrosine bonds, and that both higher silk and enzyme concentrations increased crosslink density. This means that the hydrogels were sitter, and that this stiffness can be tuned predictably by adjusting the formulation. It was also found that the diffusion decreases as silk concentration increases. Still, the relationship is nonlinear, as small competition changes can

	strongly affect molecular movement. In the end, this established the quantitative links between crosslinking and stiffness and silk concentration and diffusivity, as per the objective of the study. This took the silk hydrogel design from trial and error to actual engineering. This allows it to be translated to drug delivery systems, regenerative medicine, and tissue scaffolds.
Research Question/Problem/ Need	How does enzyme crosslinking change the strength and diffusion of silk hydrogels and how can this be expressed?
Important Figures	 Figure 1: Graphical Abstract of the experiment
VOCAB: (w/definition)	Crosslinking density - the concentration of covalent bonds (crosslinks) that connect individual polymer chains into a three-dimensional network structure Dityrosine bonds - covalent cross-links formed by the oxidative coupling of two tyrosine amino acid residues within or between proteins Enzymatic crosslinking - a biocatalytic process that uses enzymes to form stable covalent bonds between polymer chains, creating a three-dimensional network Empirical - deriving knowledge and conclusions from direct observation, measurement, and verifiable evidence gathered through experimentation or real-world experience, rather than from theory or personal belief FRAP - (Fluorescence Recovery After Photobleaching) is a microscopy technique that uses a high-intensity laser to photobleach (destroy the fluorescence of) a specific area of a fluorescently labeled sample, then observes the rate at which unbleached, fluorescent molecules move into the bleached region to recover fluorescence intensity Horseradish peroxidase - a highly stable, heme-containing enzyme found in the roots of the horseradish plant, widely used in biotechnology and diagnostics for its ability to catalyze the oxidation of various substrates, particularly chromogenic and fluorogenic compounds, in the presence of hydrogen peroxide

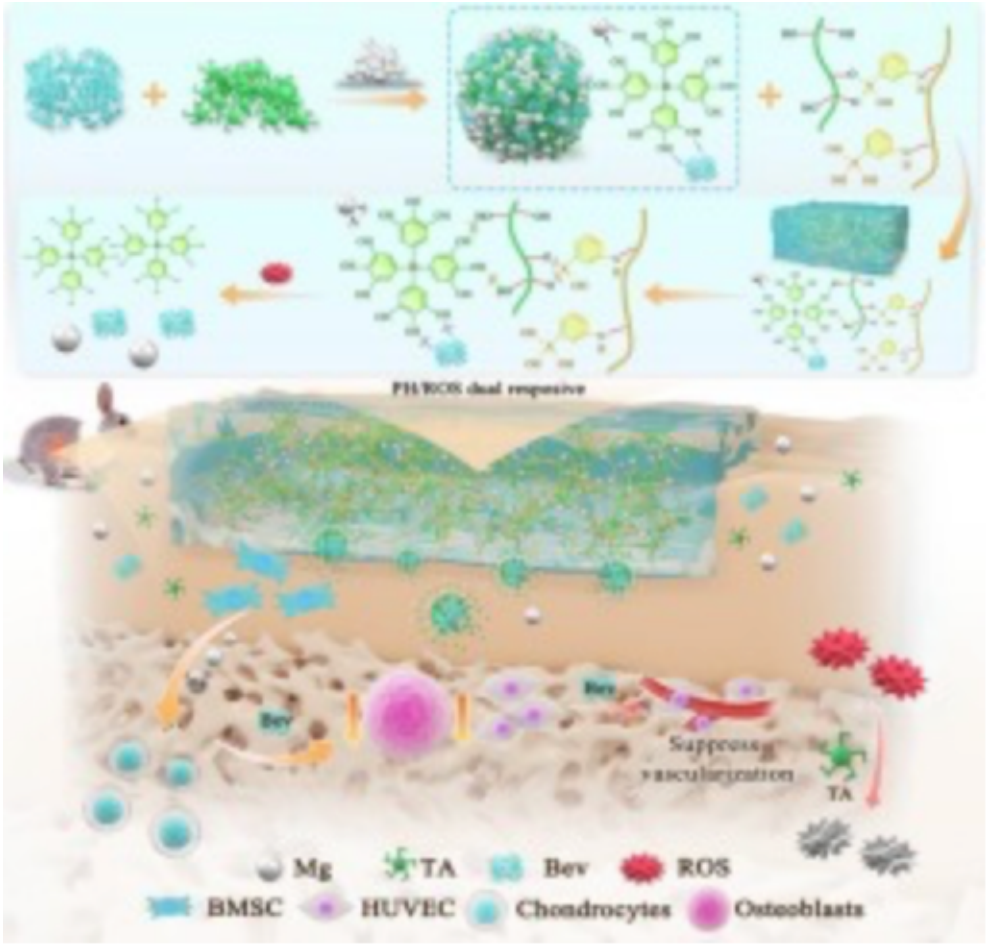
	LC-MS/MS - liquid chromatography-tandem mass spectrometry, is a powerful analytical technique that separates and identifies compounds in a sample with high specificity and sensitivity Mechanical stiffness - a critical parameter in bioresearch, impacting cell differentiation, tissue fibrosis, and disease progression by influencing cell metabolism and function Rheology - the science that studies the flow and deformation of matter, such as liquids, semisolids, and even solids under stress Silk fibroin - the main protein of natural silk, known for its excellent mechanical strength, biocompatibility, and tunable degradation rate, making it a promising biomaterial for various applications, especially in tissue engineering and drug delivery
Cited references to follow up on	*Altman, G. H., Diaz, F., Jakuba, C., Calabro, T., Horan, R. L., Chen, J., … & Kaplan, D. L. (2003).* Silk-based biomaterials. *Biomaterials, 24*(3), 401–416.
Follow up Questions	• Are there others tools that could give you even more insight on the analysis? • How precise are these tools? • Can these hydrogels be modified so that you can specialize the scenario in which these are used?

Article #3 Notes: Inflammatory responsive hydrogels incorporated with bevacizumab-loaded infinite coordination nanopolymers for accelerating cartilage repair

Source Title	Inflammatory responsive hydrogels incorporated with bevacizumab-loaded infinite coordination nanopolymers for accelerating cartilage repair
Source citation (APA Format)	Chen, H., Tao, X., Liu, J., Kong, Q., Wang, L., Zhao, Y., Jiang, C., Song, Y., Xu, X., Zhu, J., Wang, Y., Du, F., Chen, B., & Wu, J. (2025). *Inflammatory responsive hydrogels incorporated with bevacizumab-loaded infinite coordination nanopolymers for accelerating cartilage repair*. *Journal of Colloid and Interface Science*. Advance online publication. https://doi.org/10.2139/ssrn.5290785
Original URL	https://www.sciencedirect.com/science/article/abs/pii/S0021979725018752?fr=RR-2&ref=pdf_download&rr=9853de3f4ee1d687
Source type	Article
Keywords	hydrogels, ROS, bevacizumab, VEGF, ICNPs, cartilage repair, sustained release
#Tags	#hydrogels #cartilage repair #ROS

Summary of key points + notes (include methodology)	• Intro:
	  • Cartilage lacks blood vessels and does not heal well after an injury
	  • The inflammation after the injury causes an excessive ROS (reactive oxygen species) and acidic microenvironments
	  • Abnormal angiogenesis destroys cartilage structure and leads to bone-lile tissue
	  • Bevacizumab can inhibit this angiogenesis but it needs a sustained and localized delivery
	• Knowledge Gaps
	  • The biomaterials we have now do not respond dynamically to inflammation to control drug release
	  • The current anti-angiogenic therapies are poorly retained in cartilage and will degrade quickly
	  • The understanding of how to combine aint-angiogensis with cartilage regeneration instead of impairing it is limited
	• Methods
	  • The synthesis of ICNPs were conducted through metal-ligand coordination chemistry which optimized for high drug loading and controlled release
	  • A hydrogel matrix was designed with ROS
	  • Morphology
	  • Rheology for mechanical strength testing
	  • These were multiple trials of the drug release under different conditions such as in under inflamed and normal conditions

	• Results
	  • Because the hydrogel mixed evenly with the bevacizumab-loaded nanopolymers when placed in an inflamed environment with high ROS or low pH, meaning it it softened and degraded faster, it showed that it responded directly to the inflammation
	  • In the vitro design, the material stopped blood vessels cells from spreading or forming tubes and the cartilage cells continues to grow and make a normal cartilage matrix
	  • This was biocompatible, stable, and effective for joint healing

Research Question/Problem/ Need	How can inflammation-responsive hydrogels help cartilage heal faster after injury?
Important Figures	 Figure 1: Graphical Abstract of the experiment
VOCAB: (w/definition)	ROS - reactive oxygen species, chemically reactive molecules that contain oxygen, formed as normal byproducts of cellular metabolism and other processes, or from external sources like UV radiation and pollution

	Crosslinking - the process of chemically connecting two or more biomolecules, such as proteins or nucleic acids, via covalent bonds, often using a bifunctional reagent Bevacizumab - a monoclonal antibody medication used to treat certain types of cancer. It works by blocking the growth of new blood vessels that tumors need to survive and spread VEGF - Vascular Endothelial Growth Factor, is a crucial signaling protein that promotes the formation of new blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis). It is essential for normal physiological processes like embryonic development and wound healing, but it also drives pathological conditions, particularly in cancer, where it promotes tumor growth by supplying blood, and in age-related eye diseases. VEGF binds to specific receptors (VEGFRs) on endothelial cells, triggering a cellular response that leads to vessel formation ICNP - an amorphous, extended network formed by the coordination of metal ions with organic ligands Chondrocyte - the single type of cell found in cartilage, responsible for producing and maintaining the cartilage's extracellular matrix (ECM). These specialized cells secrete substances like type II collagen and proteoglycans, which give cartilage its strength and flexibility Collagen Type II - a primary structural protein in the extracellular matrix of cartilage, providing tensile strength and elasticity to joints and enabling them to resist compressive and shearing forces. Also known as cartilage collagen, it is the major collagen synthesized by chondrocytes (cartilage cells) and forms the bulk of the cartilage structure, but it is also found in the vitreous humor of the eye and intervertebral discs Aggrecan - a large proteoglycan in cartilage and other tissues that binds water via its attached glycosaminoglycan (GAG) chains (like chondroitin sulfate and keratan sulfate) to provide tissue hydration and resistance to compressive forces. GAGs - long, negatively charged polysaccharide chains that attract water, creating an osmotic pressure that is essential for the mechanical properties of cartilage and intervertebral discs Angiogenesis - the physiological process by which new blood vessels form from pre-existing vessels Hyaline cartilage - a type of connective tissue that covers the ends of bones in joints, providing a smooth, low-friction surface for movement Histology - the branch of biology that studies the microscopic anatomy of tissues, examining their cellular and structural organization to understand their function and detect diseases
Cited references to follow up on	Zhao, X., et al. (2021). Smart injectable hydrogels with pH/ROS dual sensitivity for on-demand drug release. Biomaterials Science, 9(5), 1640–1655
Follow up	• Can this therapy improve long-term cartilage function? • Can this process be scaled for large scale cartilage repair implants?

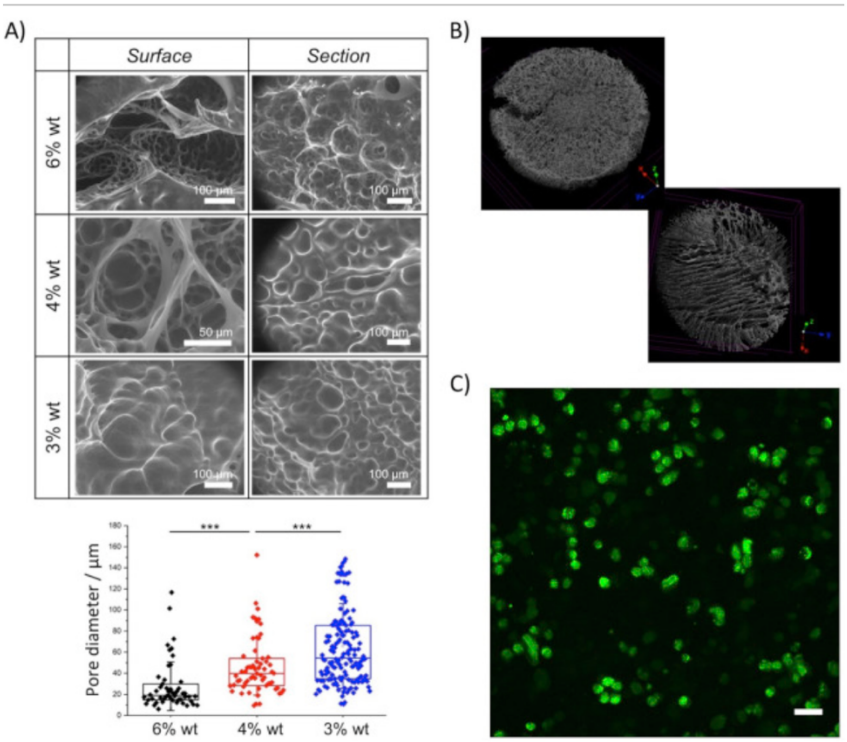
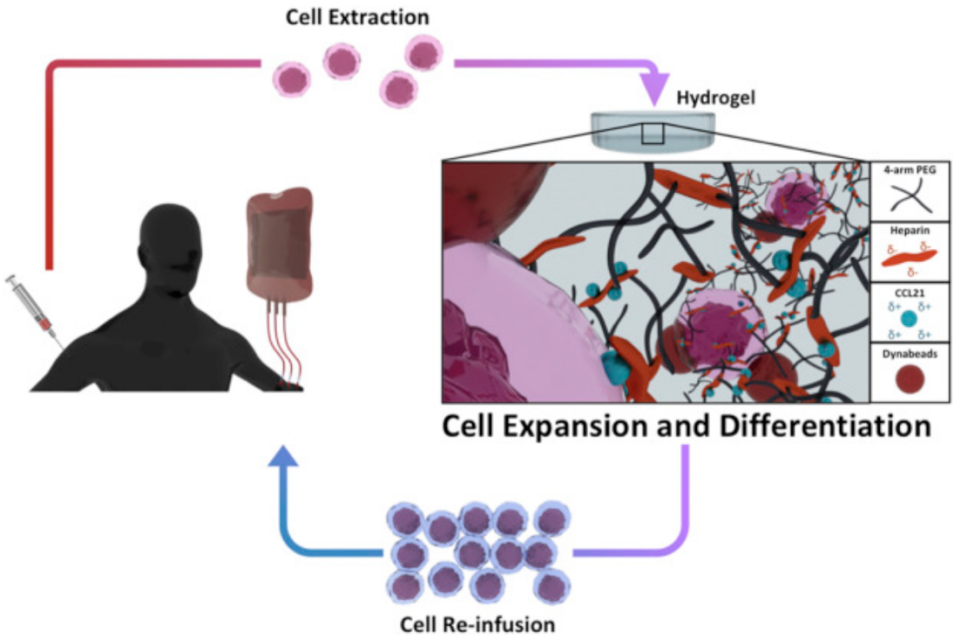
Questions	• How can the hydrogel be optimized so it can release the agents only when needed?

Article #4 Notes: CCL21-loaded 3D hydrogels for T cell expansion and differentiation

Source Title	CCL21-loaded 3D hydrogels for T cell expansion and differentiation
Source citation (APA Format)	Pérez del Río, E., Santos, F., Rodriguez Rodríguez, X., Martínez-Miguel, M., Roca-Pinilla, R., Arís, A., Garcia-Fruitós, E., Veciana, J., Spatz, J. P., & Ratera, I. (2020). *CCL21-loaded 3D hydrogels for T cell expansion and differentiation. Biomaterials*, 259, 120313. https://doi.org/10.1016/j.biomaterials.2020.120313
Original URL	https://www.sciencedirect.com/science/article/pii/S0142961220305597
Source type	Article
Keywords	3D hydrogels T cells, cytokines, proliferation, lymph nodes, adoptive cell therapy
#Tags	#immunotherapy #hydrogels #tcells #expansion #differentiation

Summary of key points + notes (include methodology)	• Goal
	  • The goal of this research is to improve the t cell growth and differentiation to advance adoptive immunotherapy
	• Problem
	  • The problem they ran into was that the regular culture methods don't mimic the lymph node environment properly
	• Process
	  • They decided to make PEG-heparin hydrogels that can cold CCL21 to guide the T cells
	  • They tested the different gel stiffness and pore sizes
	  • Soluble and immobilized CCL21 forms were compared to see which one supports T cells
	• Results
	  • The 3D hydrogels loaded with the CCL21 increased the T cell proliferation, viability, and the effector memory differentiation
	  • The T cells in the gels has less dead calls and divided/multiplies more times than in the typical liquid culture
	  • It was seen that the CCL21 that was attached to the gel worked better than the freely dissolved CCL21.

Research Question/Problem/ Need	How can the mimicking of lymph node improve T cell growth and function for immunotherapy?

Important Figures	 Figure 1: Structural properties of PEG-Hep hydrogels  Figure 2: T cell expansion in a CCL21-loaded PEG-Hep hydrogel as part of an ACT process
VOCAB: (w/definition)	PEG-heparin - conjugates where polyethylene glycol (PEG) is combined with heparin, an anticoagulant, to create new biomaterials like hydrogels or coatings for various biomedical applications, including drug delivery, tissue engineering, and enhancing the biocompatibility of medical devices

	CCL21 - a chemokine that binds to the receptor CCR7, guiding immune cells, especially T cells and dendritic cells, to lymph nodes and other lymphoid tissues to trigger adaptive immunity and central self-tolerance CCR7 - a G protein-coupled receptor that plays a crucial role in the immune system by controlling the migration of B and T lymphocytes to secondary lymphoid organs and draining lymph nodes, as well as guiding dendritic cells Dynabeads - superparamagnetic polystyrene microspheres Naive T Cell - an immune cell that has developed in the thymus but has not yet encountered and responded to a specific antigen Central Memory T Cell - a type of long-lived immune cell that resides in lymph nodes and other secondary lymphoid organs, patrolling for known pathogens to provide long-term immunosurveillance Effector Memory T Cell - a subset of long-lived T lymphocytes that play a crucial role in the immune response to infections and other immune challenges Storage Modulus - a mechanical property of a material that measures its ability to store energy when deformed, reflecting its elastic or "solid-like" behavior Loss Modulus - quantifies a material's capacity to dissipate energy as heat when deformed, representing its viscous behavior 3D Cell Culture - allows cells to grow and organize in a three-dimensional environment, mirroring in vivo tissue structures, unlike traditional 2D cultures
Cited references to follow up on	Zhao L, Shireman J, Probelsky S, Rigg B, Wang X, Huff WX, Kwon JH, Dey M. CCL21 *Induces Plasmacytoid Dendritic Cell Migration and Activation in a Mouse Model of Glioblastoma. Cancers (Basel)*. 2024 Oct 12;16(20):3459. doi: 10.3390/cancers16203459.
Follow up Questions	How can this be scaled? How long will this last? How long does it take for it to start degrading? If it does start degrading, what would the next steps be? Can the degradation be mitigated?

Article #5 Notes: Time-adaptable alterations of the extracellular matrix during chondrocyte dedifferentiation

Source Title	Time-adaptable alterations of the extracellular matrix during chondrocyte dedifferentiation
Source citation (APA Format)	Liu, W., Liu, Z., Chen, H., Shan, J., Li, X., Hu, X., Cui, H., Yu, Y., & Wen, G. (2025). *Time-adaptable alterations of the extracellular matrix during chondrocyte dedifferentiation*. Biomaterials Advances, 177, 214383. https://doi.org/10.1016/j.bioadv.2025.214383
Original URL	https://www.sciencedirect.com/science/article/abs/pii/S2772950825002109?fr=RR-2&ref=pdf_download&rr=9853e00e09d0d687
Source type	Article
Keywords	chondrocyte dedifferentiation, extracellular matrix, decolorized chondrocyte, cartilage repair, nuclear deformation, tissue engineering
#Tags	#cartilagerepair #ECM #chondrocyte

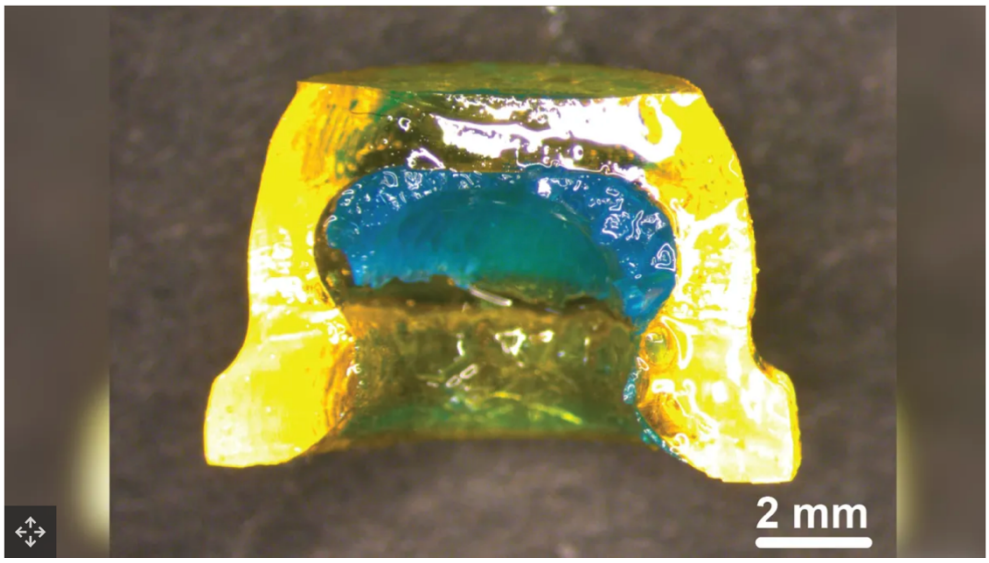
Summary of key points + notes (include methodology)	• Research Goal:
	  • The goal of this study was to map how ECM structure and functions change over time during chondrocyte dedifferentiation
	  • They also wanted to see how these changes affect the performance of sCS (decellularized chondrocyte sheets)
	  • They wanted to address how the dedifferentiation a;lters the unseful part of the chondrocyte-derived ECM in terms of cartilage repair
	  • They wanted to kind ket regulators that think the ECM properties, such as molecular, structural, and mechanical, to cell behaviours
	• Methods
	  • The primary mouse chondrocytes were isolated, then these cells were expanded to a few passages of progressive dedifferentiation stages
	  • The dCS were prepared for each stage
	  • There was lots of differ characterization that took place
	  • Morphology used for nuclear deformation imaging
	  • Mechanical testing to get the ultimate tensile strength and collagen fiber alignment
	  • Physicochemical and proteomic analysis
	  • Cellular assays for the migration, proliferation, and chondrogenic potential, especially with the mesenchymal stem cells
	  • They also tested Fmod supplementation to assess the effects on the already late-stage ECM function
	• Results
	  • There were signs of morphological evolution
	  • In the early stages of the chondrocytes, they were round and polygonal, which are healthy phenotypes

	• In the late stages, they were elongated and amoeboid like, which means they were dedifferentiated. • This nuclear deformation increased as the dedifferentiation progressed • The randomness of collagen fiber direction decreased, meaning they became more aligned as the dedifferentiation advanced • There was found to be correlation with ultimate tensile strength meaning a stronger dCS • The Fibromodulin seemed to mirror the ECM's functional changes. Adding it to the late-stage dCS improved it's biological regulation and it enhanced its chondrogenic potential and mimicked the early-stage ECM behavior • • Conclusions • The properties are the dCS are time-adaptable • The temporal evolution of the ECM determines its value for it's regenerative applications • The Fmod can somewhat "reverse" the deficiencies in the late stages • This provides a step forward in the optimization of chondrocyte-derived ECM in cartilage repair
Research Question/Problem/ Need	How does the chondrocyte dedifferentiation alter the eCM structure and function?
Important Figures	n/a
VOCAB: (w/definition)	Dedifferentiation - a biological process where a specialized cell loses its specialized characteristics and reverts to a more primitive, less differentiated state, often to facilitate cell proliferation and tissue regeneration Decellularized chondrocyte sheet - a sheet-like biological scaffold made from the extracellular matrix (ECM) left behind after cells (chondrocytes) have been removed from a chondrocyte cell sheet grown in a dish Fibromodulin - a small proteoglycan protein that plays a crucial role in the extracellular matrix (ECM) of various tissues, including connective tissues, cartilage, and bone Ultimate Tensile Strength - the maximum pulling stress a material can withstand before it begins to neck and then fracture Time-lapse atlas - various applications of time-lapse technology to create visual atlases of change over time Chondrocyte - a cell which has secreted the matrix of cartilage and become embedded in it Passage - the number of times cells have been subcultured or transferred Nuclear deformation - the change in the shape of a cell's nucleus in response to mechanical forces or other stimuli

	Elastic modulus - a measure of a material's stiffness, quantifying its resistance to non-permanent (elastic) deformation when a stress is applied Cell migration - a fundamental process in which cells move from one location to another Proliferation - the process of cells increasing in number through growth and division, driven by signals like growth factors and regulated by a tightly controlled cell cycle Chondrogenic differentiation - the biological process by which precursor cells, typically mesenchymal stem cells (MSCs), mature into chondrocytes (cartilage cells)
Cited references to follow up on	Pei, M., & He, F. (2012). *Extracellular matrix deposited by synovium-derived stem cells delays replicative senescence and dedifferentiation of chondrocytes.* Biomaterials.
Follow up Questions	Are there other correlations? What if the stages were combined? What happens between the two stages? How similar are the ECMs of the mouse are to human?

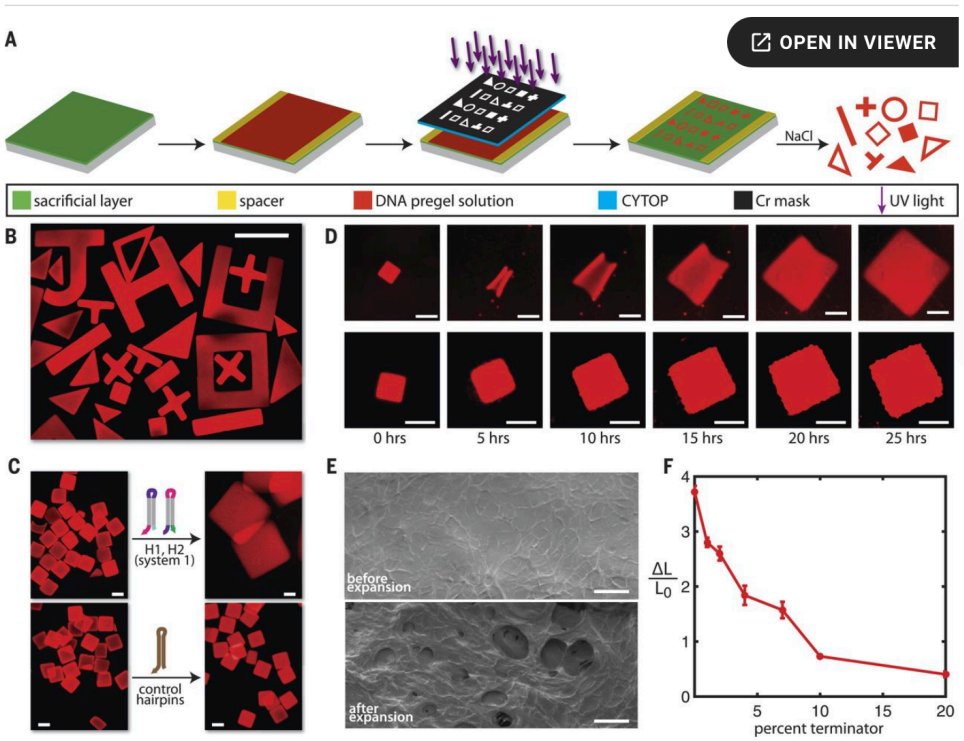
Article #6 Notes: Octopus sucker-inspired patch delivers drugs into the body without needles or pills

Source Title	Octopus sucker-inspired patch delivers drugs into the body without needles or pills
Source citation (APA Format)	Cooke, E. (2023, September 27). *Octopus sucker-inspired patch delivers drugs into the body without needles or pills*. LiveScience. https://www.livescience.com/health/medicine-drugs/octopus-sucker-inspired-patch-delivers-drugs-into-the-body-without-needles-or-pills
Original URL	https://www.livescience.com/health/medicine-drugs/octopus-sucker-inspired-patch-delivers-drugs-into-the-body-without-needles-or-pills
Source type	Science news article
Keywords	drug delivery, microneedle patch, octopus, noninvasive, biomimicry
#Tags	#drugdelivery #news #biomimicry
Summary of key points + notes (include methodology)	This octopus sucker-inspire patch is a new type of drug delivery system that offers an alternative to using pills or needles to take medication. This patch is pressed onto the inner lining of the cheek, containing the medication inside. Previous testing in dogs showed successful delivery of two drugs: desmopressin and semaglutide. A trial was also conducted on people using patches without the drugs. The subjects were able to talk, move, and rinse their mouths without the patch falling off. More tests run and improvements are still needed, but this technology may be a huge improvement for larger drugs that have difficulty being absorbed when taken orally, and for helping those who struggle with infections. It could also serve as an alternative to using nasal medication and is less invasive than the use of microneedles. While still in the trial stage, the end goal is to deliver large molecules effectively through this method. There are also some concerns about the possibility of the patch being accidentally swallowed, but further testing will address this issue.
Research Question/Problem/ Need	How can medicine be delivered into the body without the use of needles or pills?

Important Figures	 Figure 1: the patch after being loaded with the drug
VOCAB: (w/definition)	Biomimicry - a design philosophy and scientific field that emulates nature's strategies, forms, and processes to solve human design challenges and promote sustainability Transdermal Drug Delivery - a method of delivering medication through the skin into the systemic circulation, typically using a skin patch, to treat various conditions PDMS - polydimethylsiloxane, a silicone polymer with a wide range of applications, including in cosmetics for moisturizing skin, as a component in industrial lubricants and sealants, and for its use in lab-on-a-chip devices for analytical chemistry Localized Delivery - an advanced method of administering therapeutic agents directly to a specific target site in the body Sustained Release - focuses on developing technologies to deliver drugs over an extended period, which helps maintain a steady therapeutic concentration in the bloodstream Thermosensitive Material - a smart polymer that undergoes significant changes in its physical properties in response to temperature fluctuations
Cited references to follow up on	Hwang, J. M., Lee, S. H., Baek, E. J., Kim, H.-R. C., Oh, J.-H., Lee, J. S., & Lee, S.-H. (2025). Comparison of the effects of fractional microneedle radiofrequency and microneedling on modulating the senescent fibroblast milieu in aged skin. *Scientific Reports*, 15(1), 18296. https://doi.org/10.1038/s41598-025-02545-3
Follow up Questions	Can it be adjusted to hold larger molecules? How many can be used at a time? What would it cost on a grand scale? Is it really that much more effective?

Article #7 Notes: DNA sequence–directed shape change of photopatterned hydrogels via high-degree swelling

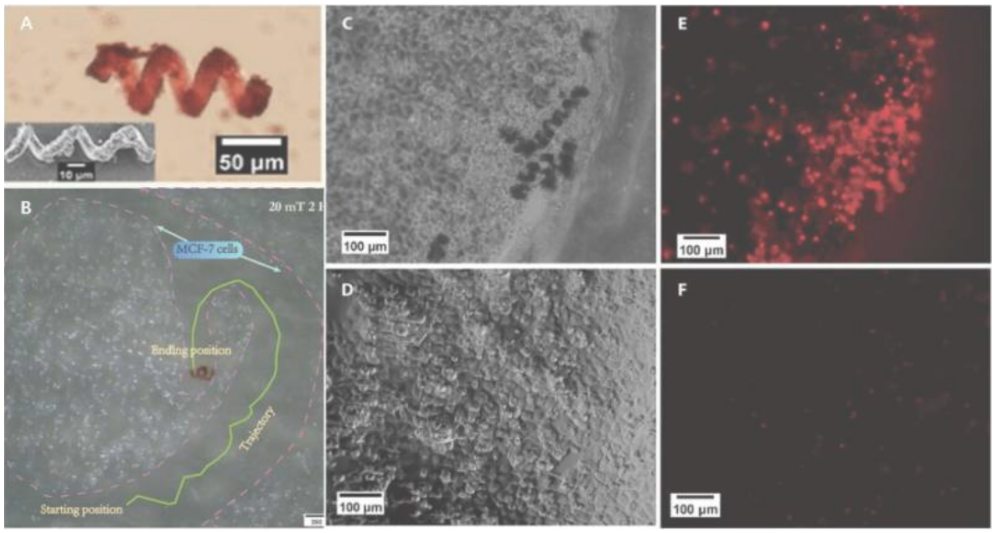
Source Title	DNA sequence-directed shape change of photopatterned hydrogels via high-degree swelling
Source citation (APA Format)	Angelo Cangialosi, Chang Kyu Yoon, Jiayu Liu, Qi Huang, Jingkai Guo, Thao D. Nguyen, David H. Gracias, Rebecca Schulman. *Science* 357 (6356), 1126–1130 (15 September 2017). DOI: 10.1126/science.aan3925
Original URL	https://www.science.org/doi/10.1126/science.aan3925
Source type	Research article
Keywords	DNA-programmed materials, programmable matter, soft robotics, photopatterning, molecular programing
#Tags	#biomaterials #programmablematter #bioengineering #softrobotics
Summary of key points + notes (include methodology)	In this study, researchers wanted to design a programmable material capable of changing shape in response to stimuli. They decided to use hydrogels as the base material and DNA as the programmable component because of its binding capability. To carry out this experiment, the researchers designed photopatterned hydrogels with DNA strands embedded in certain areas using UV light and photolithography. This approach allowed for control in both the crosslinking density and the distribution of DNA within the gel. Once the hydrogel was exposed to complementary DNA solutions, it absorbed the water and swelled unevenly, causing it to change shape. This reaction was caused by the DNA strands inside the gel hybridizing with the complementary strands in the solution, creating osmotic pressure and selective swelling. These findings show potential for designing materials with multi-responsive behaviors that can be programmed to change based on molecular signals. This approach could eventually lead to biocompatible and programmable materials that self-assemble in response to targeted DNA sequences.
Research Question/Problem/ Need	How can materials be designed to respond to a specific molecular signal in order to make the shape change programmable and predictable?

Important Figures	 Figure 1: The photopatterning and hydrogel expansion
VOCAB: (w/definition)	Photopatterning - a technique that uses light to create specific spatial distributions of materials, often by projecting a pattern onto a photosensitive material Programmable matter - materials whose physical properties, such as shape, density, conductivity, or optical characteristics, can be intentionally and dynamically changed based on user input or autonomous sensing DNA Strand Displacement - a process where one DNA or RNA strand invades and replaces another pre-existing strand that is partially or fully complementary Cross-linker - a reagent or molecule that forms chemical bonds between other molecules, such as proteins or polymers, to create a more stable, network-like structure with enhanced properties Strand hybridization - the process where two single strands of DNA or RNA bond together to form a double-stranded molecule through complementary base-pairing, like a zipper Polyarcryamide - a water-soluble synthetic polymer used in agriculture as a soil amendment to reduce erosion, in water treatment to remove suspended particles, and in the biomedical field for drug delivery systems and protein separation gel electrophoresis
Cited references to follow up on	Cheng, E., et al. (2009). *DNA-based responsive hydrogels. Angewandte Chemie International Edition.*

Follow up Questions	What could the applications of this be in the medical or environmental fields? Is there a way to make something to predict the sequences for the desired shapes? What are the energy and scalability limits compared to other similar methods?

Article #8 Notes: Team develops magnetic microrobots with folate to promote targeted drug delivery to cancer cells

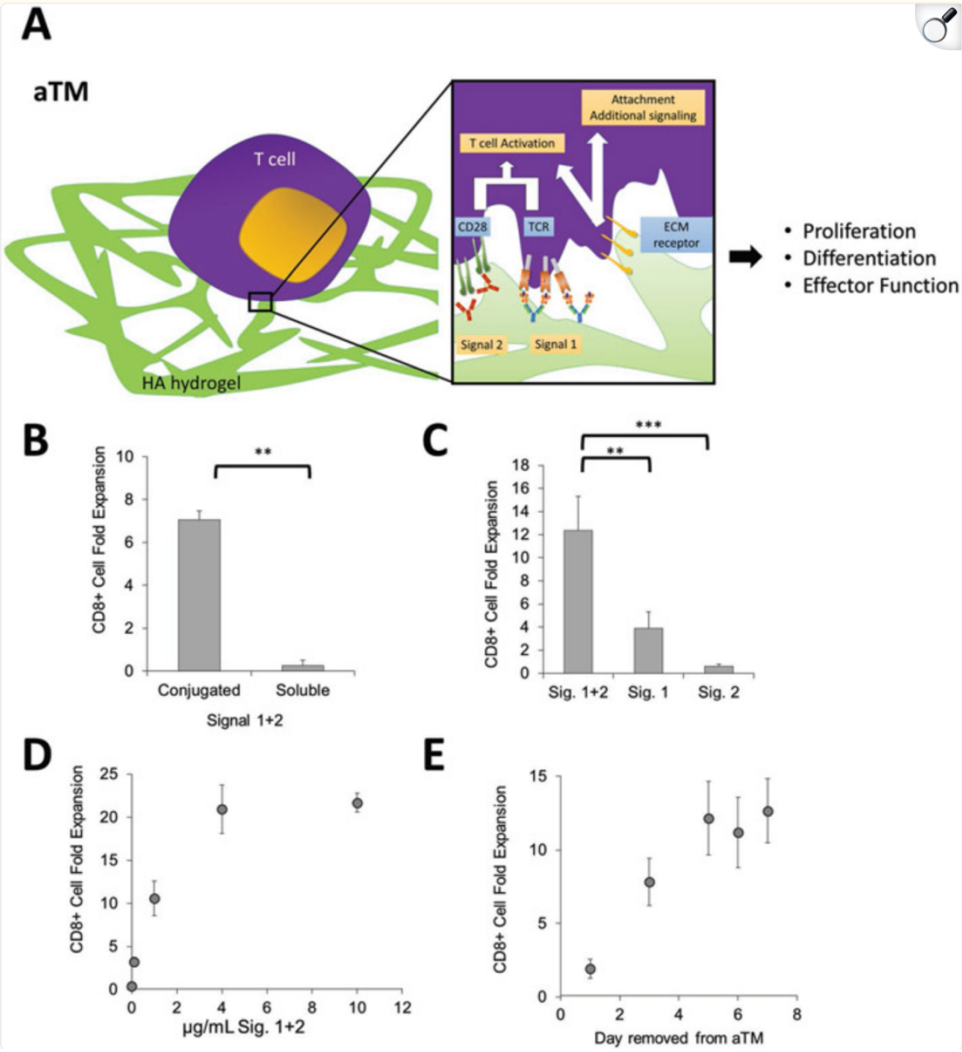
Source Title	Team develops magnetic microrobots with folate to promote targeted drug delivery to cancer cells
Source citation (APA Format)	Min Ye et al, *Magnetic Microrobots with Folate Targeting for Drug Delivery, Cyborg and Bionic Systems* (2023). DOI: 10.34133/cbsystems.0019
Original URL	**https://phys.org/news/2023-06-team-magnetic-microrobots-folate-drug.html**
Source type	Science news article
Keywords	drug delivery, magnetic microbots, targeted therapy, cancer treatment, cell culture, in vitro
#Tags	#biotechnology #cancer #drugdelivery
Summary of key points + notes (include methodology)	To address the side effects of chemotherapy, a group of researchers decided to utilize magnetic microbots coated in folic acid to navigate to cancerous tumors and deliver drugs properly to treat them. These microbots are functionalized with folate to target cancer cells that overexpress folate receptors. The ability to externally manipulate the magnetic field allows for the controlled navigation through biological environments. Because of the folate-mediated binding, the microbots can perform selective attachment to the tumor cells. Once at the tumor site, the microbots will release the therapeutic payloads they were carrying directly. This targeted release will help minimize off-target toxicity and protect the healthy tissue surrounding the tumor. Due to the size of the microbot, it is able to move through microvasculature and other complex anatomical spaces. This approach to cancer treatment has only been done in a lab and requires further preclinical and clinical validation. But, there is potential to advance these minimally invasive, site-specific cancer treatment modalities.
Research Question/Problem/ Need	How can microrobots navigate to cancer cells AND the drug uptake in tumor cells?

Important Figures	 Figure 1: The introduction of FA improved the tumor targeting ability of the microrobots
VOCAB: (w/definition)	Microbot - a tiny robotic device, often a few micrometers to a few hundred micrometers in size, designed for tasks within the human body or other micro-scale environments Nanomedicine - uses nano-scale materials (1-100 nanometers) and devices to diagnose, treat, and prevent disease Metal-organic framework - crystalline, porous materials built from metal ions and organic linkers that form sponge-like, 3D structures with exceptionally high surface areas DOX - doxorubicin, a chemotherapy drug used to treat various types of cancer, including: breast cancer, lymphoma, leukemia, ovarian cancer, and soft tissue sarcoma Endocytosis - the process by which a cell takes in materials from its surroundings by engulfing them with its cell membrane, forming a vesicle Folate Receptor - a protein found on the surface of cells that plays a crucial role in the transport and metabolism of folate, a water-soluble vitamin essential for cell growth, development, and DNA synthesis
Cited references to follow up on	Xu, T., Yu, J., Yan, X., Choi, H., & Zhang, L. (2017). *Magnetic actuation of microrobots for biomedical applications.Advanced Functional Materials*, 27(30), 1604761
Follow up Questions	Could this system deliver multiple drugs at the same time? How are these microbots expelled from the body after, if they are? If not, why not and what are those effects? Would these microbots degrade in the body over time?

Article #9 Notes: Engineering an Artificial T-Cell Stimulating Matrix for Immunotherapy

Source Title	Engineering an Artificial t-Cell Stimulating Matrix for Immunotherapy
Source citation (APA Format)	Hickey JW, Dong Y, Chung JW, Salathe SF, Pruitt HC, Li X, Chang C, Fraser AK, Bessell CA, Ewald AJ, Gerecht S, Mao HQ, Schneck JP. *Engineering an Artificial T-Cell Stimulating Matrix for Immunotherapy. Adv Mater.* 2019 Jun;31(23):e1807359. doi: 10.1002/adma.201807359.
Original URL	https://pmc.ncbi.nlm.nih.gov/articles/PMC8601018/
Source type	Article
Keywords	adoptive T cell therapy, artificial matrix, extracellular matrix, hydrogel, immunotherapy, mechanotransduction, t cell stimulation
#Tags	#tcells #ECM #hydrogel #simulation

Summary of key points + notes (include methodology)	Key points:
	• An artificial matric was created help activate the t cells for cancer immunotherary
	• This matrix mimics how the T cell would typically interact with APCs (antigen-presentings cells)
	• It provides biochemical signals and physical cues
	  • Biomechanical signals involved molecules
	  • The physicals cues were traits like stiffness
	• After adjusting the stiffness of the gel, it was found that the t cells respond differently to different levels of stiffness
	  • It affects how the t cells activate
	• They found a way to help the t cells grow and stay active for even longer than the culture plates that were used before
	• They allows for improvement of t cell preparation for various treatments, such as CAR-T therapy
	Methods:
	• The design of the matrix
	  • They needed to create a hydrogels that mimics how t cell behave
	• Ligand attachment
	  • This method was used to add the biochemical signals onto the gel
	• T-cell culture
	  • Allowed for the t cells to interact with the matrix
	  • Used to manipulate the conditions and the amount of time for the interaction
	• The variables were continuously manipulate so that the difference in behavior sound be observed
	  • Things such as stiffness levels and densities
	• Measurements taken:
	  • T-cell activation markers
	  • Proliferation (cell growth)
	  • Cytokine release
	  • Microscopy

	• Used to see how the t cells interacted • Comparison to the standard activation methods
Research Question/Problem/ Need	Need: A material that can mimic a cell environment to help the T cells function more effectively to improve cancer treatment
Important Figures	 Figure 1: An artificial T cell stimulating matrix is engineered by conjugating T cell stimulating signals to a hydrogel
VOCAB: (w/definition)	Proliferation - the multiplication or reproduction of cells, leading to an increase in cell number Mechanotransduction - the process by which cells convert mechanical forces into biological and chemical responses Antigen-preseting cell - an immune cell that captures, processes, and displays fragments of antigens (such as from viruses or bacteria) on its surface, activating other immune cells, especially T cells

	T Cell receptor - a protein complex on the surface of T-cells that identifies and binds to foreign peptides presented by major histocompatibility complex (MHC) molecules on other cells, thereby initiating an immune response Cytokine - small proteins secreted by cells of the immune system and other cell types that play a crucial role in intercellular communication and immune regulation Peptide-MHC - a molecule where a short peptide fragment binds to a Major Histocompatibility Complex (MHC) molecule, forming a complex that is displayed on a cell's surface Co-stimulatory Molecule - cell-surface proteins that, along with T-cell receptor (TCR) signaling, are essential for activating T cells and initiating a full immune response
Cited references to follow up on	Yuan D.J., Shi L., Kam L.C. Biphasic response of T cell activation to substrate stiffness. *Biomaterials*. 2021 Jun;273(120797). doi: 10.1016/j.biomaterials.2021.120797.

Follow up Questions	• Can this be used to help grow t-cells?
	  • If so, can it adjust its traits?
	• Will other treatments be needed to give to the patient for this to work?
	  • If so, are they harmful?
	  • Is there a way to make it all one treatment?
	• What is the cost comparison to the current methods?
	• Can this method be used for other immune cells?

Article #10 Notes: Tumor Microenvironment: A Complex Landscape of Cancer Development and Drug Resistance

Source Title	Tumor Microenvironment: A Complex Landscape of Cancer Development and Drug Resistance
Source citation (APA Format)	Fatima, S. (2025, April 11). *Tumor microenvironment: A complex landscape of cancer development and drug resistance*. Cureus. https://pmc.ncbi.nlm.nih.gov/articles/PMC12066109/
Original URL	https://pmc.ncbi.nlm.nih.gov/articles/PMC12066109/
Source type	Article
Keywords	cancer cell, stromal cells, immune calles, ECM, cytokines, chemokines, microenvironments
#Tags	#tumor #immunecellls #ECM #cancer

Summary of key points + notes (include methodology)	Key points:
	• A TME (tumor microenvironment) has cancer cells, stromal cells, immune cells, ECM, and other soluble factors
	• These parts influence each other greatly and are the reason for the growth, spread, and response the cancer
	• These cancer cells can also affect the cells around them as they release cytokines to create a suitable environment for itself
	• Immune cells can act very different, some can fight the cancer while other suppress the immune response
	• Blood vessels with tumors have uneven oxygen supply
	  • In these hypoxic conditions, tumor cells before more aggressive and drug-resistant
	  • Due to the cellular changes, the ECm becomes stiffer and more disorganized
	• TME is a shield but it also is an enabler
	• There have been many emerging therapeutic strategies that are trying to normalize the TME
	  • Ex: altering the ECM stiffness
	  • Improving immune infiltration
	• For long term success, cancer therapy needs to take both the tumor and its microenvironment into account
	Methods:
	• Summaries of recent finding on how TME components were included
	• Comparisons
	  • Analysis of how the interactions differed between cell times, such as immune and stromal
	  • How these cells influences the outcomes of cancer
	• Molecular
	  • Linking signaling pathways to angiogenesis, inflammation, and resistance
	  • In vitro models

<table>
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2D cancer-stromal co-cultures
ECM mimicking hydrogels

In vivo models

Mouse xenograft used to study tumor angiogenesis and immune cell infiltration
Natural tumor evaluation

Results:

TME components contribute to tumor growth with the use of cytokines and chemokines
Cancer associated fibroblasts were shown to help cancer cell survival due to it’s ability to remodel the ECM
Potential therapeutic solutions were found

Modifying immune cell behavior
ECM targeting
Microenvironment remodeling

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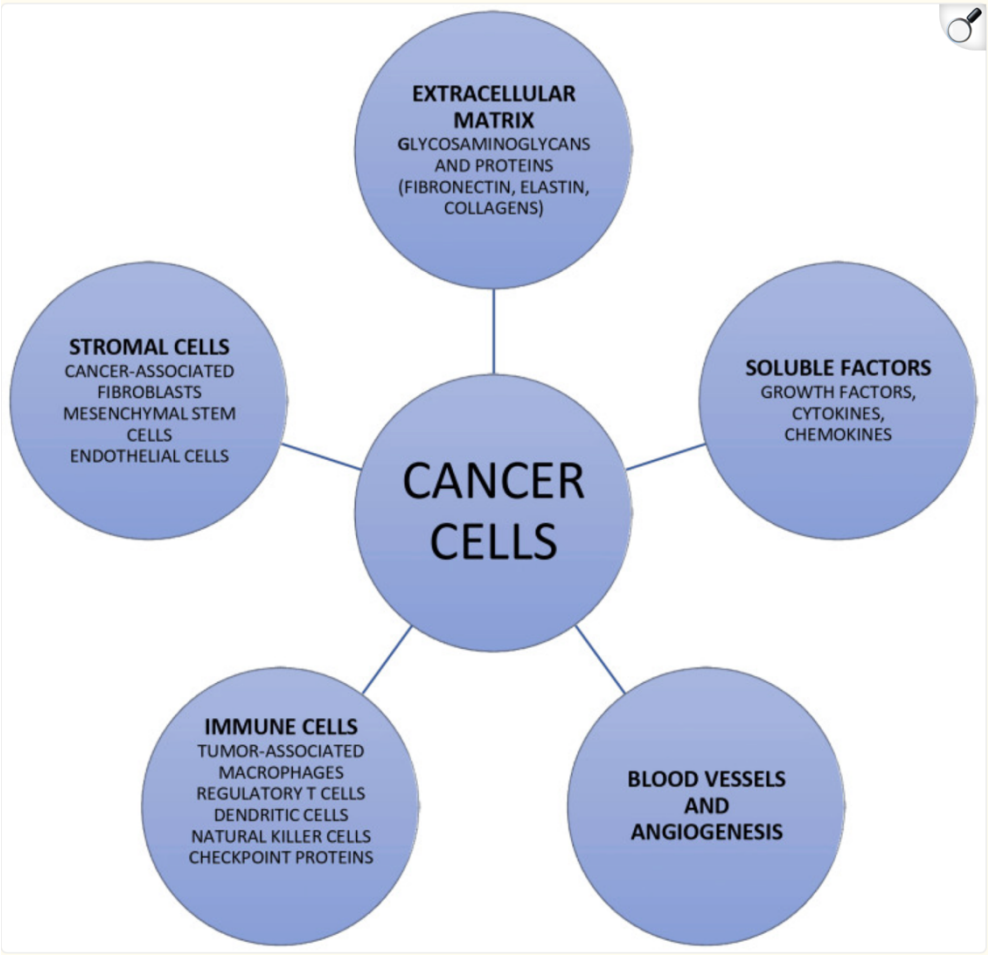
<tr><td>Research Question/Problem/ Need</td><td>How do the cells and molecules around tumors affect how it grows and responds to therapy?</td></tr>
<tr><td>Important Figures</td><td> 

Figure 1: Components of TME</td></tr>
</table>

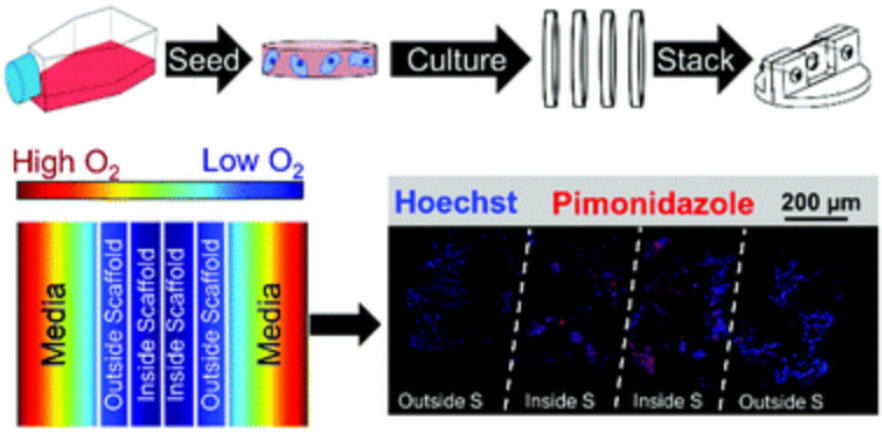
VOCAB: (w/definition)	TME - tumor microenvironment, the complex network of cells, extracellular matrix (ECM), and signaling molecules that surround and interact with tumor cells CAFs - cancer-associated Fibroblasts, a type of fibroblast that plays a crucial role in the development and progression of cancer ECM - extracellular matrix, a non-cellular network of proteins and polysaccharides that surrounds and supports cells in tissues and organs Angiogenesis - the process of forming new blood vessels from existing ones Hypoxia - a condition where there is an inadequate supply of oxygen to the body's tissues Immune Evasion - refers to the strategies that infectious pathogens and cancer cells use to avoid being detected, recognized, and destroyed by the host's immune system Cytokines - small proteins secreted by immune and other cells that act as chemical messengers, coordinating and regulating various immune and inflammatory responses Tumor Heterogeneity - the variability in the genetic, molecular, and phenotypic characteristics of cancer cells within a tumor or between different tumors in the same patient MMPs - matrix metalloproteinases, zinc-dependent enzymes that break down components of the extracellular matrix (ECM) and are involved in tissue remodeling, wound healing, angiogenesis, and immune responses
Cited references to follow up on	Prakash, J., & Shaked, Y. (2024). *The interplay between extracellular matrix remodeling and cancer therapeutics*. *Cancer Discovery*, 14(8), 1375-1388. https://doi.org/10.1158/2159-8290.CD-24-0002
Follow up Questions	• Could a model be made that deals with both immune suppression and hypoxia? • Can modifying the tumor vasculature do anything? • What external influences could there be and what can be done to address the as well?

Article #11 Notes: Development of a stacked, porous silk scaffold neuroblastoma model for investigating spatial differences in cell and drug

Source Title	Development of a stacked, porous silk scaffold neuroblastoma model for investigating spatial differences in cell and drug responsiveness
Source citation (APA Format)	Ornell, K. J., Mistretta, K. S., Ralston, C. Q., & Coburn, J. M. (2021). Development of a stacked, porous silk scaffold neuroblastoma model for investigating spatial differences in cell and drug responsiveness. *Biomaterials Science, 9*(4), 1272–1290. https://doi.org/10.1039/D0BM01153C
Original URL	https://pubs.rsc.org/en/content/articlelanding/2021/bm/d0bm01153c
Source type	Research Article
Keywords	silk scaffold, 3D tumor model, hypoxia gradients, drug responses, neuroblastoma
#Tags	#3Dcellculture #model #tumormodel #gradient #hypoxia #drugrespose

Summary of key points + notes (include methodology)	• Goal: to make a 3D mm neuroblastoma tumor model that has spatial heterogeneity and allows for layer by layer analysis of the cells and their response to drugs
	• They make thin porous silk fibrin scaffolds using lyophilization
	• They made a scaffold holder using COMSOL modeling to stack scaffold layers
	  • Enabled diffusion of nutrients
	  • Established cell-driven gradients
	• Used COMSOL to simulate different oxygen profiles through the stacks
	  • This model guides the design of the holder with things such as channel depth and spacing to it can yield gradients
	• They seed neuroblastoma cell lines onto the scaffold
	  • Cells are seeded onto both faces of each scaffold to promote infiltration
	• After culture, they separate the stack back into individual layers and analyze each layer for DNA content, gene expression, and viability
	• They also had to make sure there was actually a hypoxia gradient
	  • They did this with pimonidazole staining
	  • The interior layer need to show higher hypoxia marker expression, lower DNA content, and gene expression comparable to cells in 1% O2 conditions and the outer layers need to resemble closer to 21% O2 conditions

	• To prove that this gradient matters biologically, they tested tirapazamine, a hypoxia-activated drug, on a 4 layer model
	  • The interior layers showed a much greater reduction in DNA and viability than the outer layers
	  • This supported that the model can detect spatially distinct drug responses
	• This showed how the scaffold stacking approach allowed for controlled, cell-driven microenvironments and region-specific analysis for drug screenings

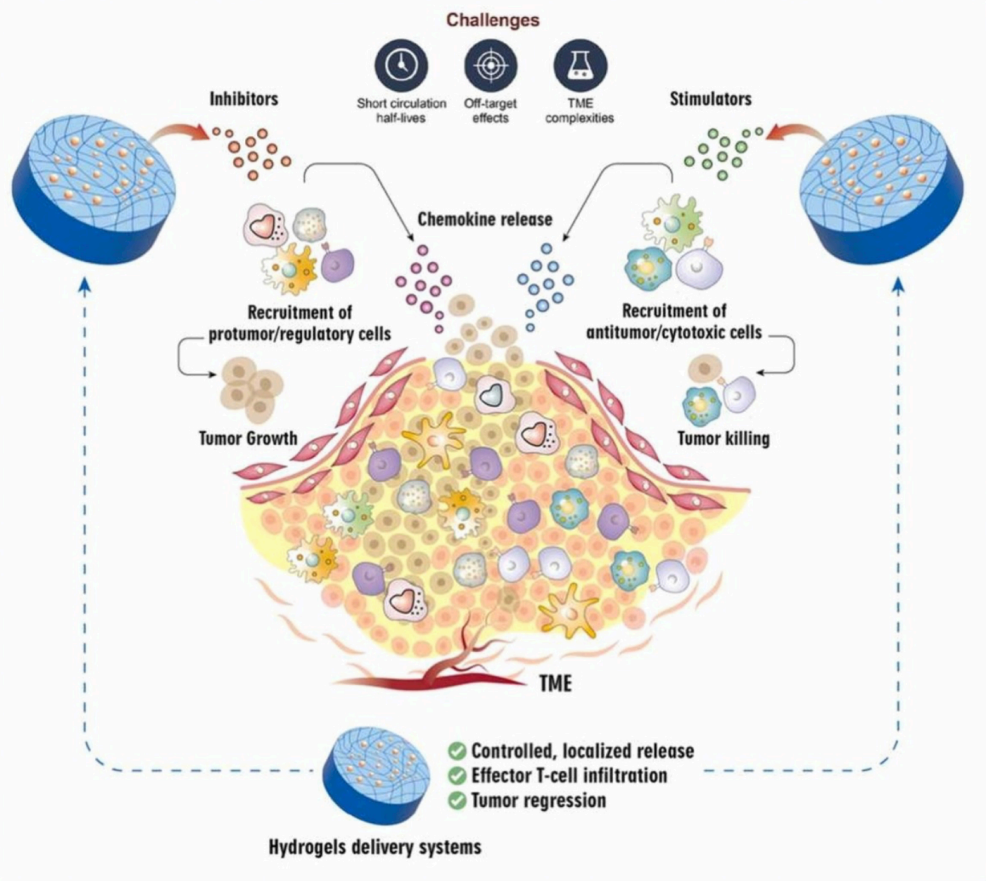
Research Question/Problem/ Need	Can stacked silk scaffolds be used to model spatial differences in oxygen levels in neuroblastoma tumors?
Important Figures	 Figure 1: The graphical abstract of the study
VOCAB: (w/definition)	Lyophilization - a low-temperature dehydration process that removes water from a product by freezing it and then reducing the pressure to allow the ice to sublimate directly into vapor Scaffold - a 3D structure that supports cell growth and mimics the physical environment of tissues Silk Fibrin - a protein from silkworm cocoons used as biocompatible and tunable biomaterials for tissue engineering Pimonidazole - a chemical marker that kinds in hypoxic cells and is used to visualize low-oxygen regions COMSOL - a software used for computer simulations of physical phenomena like diffusion and oxygen transport Gradient - spatial variation across a structure Finite element modeling - a computational method that divides complex structures into small sections to simulate physical processes

	Gene expression - when cells convert genetic information into proteins VEGF - a protein that stimulates blood vessel formation CAIX - helps cells adapt to acidic conditions caused by low oxygen Tirapazamine - an experimental anticancer drug that targets hypoxic (low-oxygen) tumor cells Spatial heterogeneity - the variation of a system's variables across space, such as differences in landscape features, habitat patchiness, or population density Tumor gradient model - a research tool or system that simulates the gradients of molecules like oxygen and nutrients found in the tumor microenvironment
Cited references to follow up on	Jung, P., & Wolpaw, A. J. (2025). *Three-Dimensional Culture Systems in Neuroblastoma Research*. *Organoids, 4*(2), 10. https://doi.org/10.3390/organoids4020010
Follow up Questions	• How would this model behave after a longer culture, like a week or a month? • Can you stack it beyond the 8 layers? • Can this be generalized across different tumor types? • Could you use something other than tirapazamine to test this model?

Article #12 Notes: Fighting cancer smarter: Using hydrogel delivery systems to target chemokines

Source Title	Fighting cancer smarter: Using hydrogel delivery systems to target chemokines
Source citation (APA Format)	Khorramdelazad, H., Yaraghi, P., et al. (2025). Fighting cancer smarter: Using hydrogel delivery systems to target chemokines. *Biomedicine & Pharmacotherapy*. https://doi.org/10.1016/j.biopha.2025.118601
Original URL	https://www.sciencedirect.com/science/article/pii/S0753332225007954
Source type	Review article
Keywords	Chemokine, hydrogel, immunotherapy, nanosystems
#Tags	#TME #chemokines #hydrogel #delivery #immunotherapy

Summary of key points + notes (include methodology)	• Chemokines are critical regulators of immune cell trafficking in the TME
	  ○ Some recruit effector immune cells
	  ○ Others support immunosuppressive myeloid populations
	• There are limitations to the systemic administration of chemokines
	  ○ Rapid degradation, off-target effects, difficulty penetrating the TME (hypoxia and acidity)
	  ○ Hydrogels can control the release of chemokines
	  ▪ Improves stability, spatial confinement, and gradients favorable for immune cell infiltration
	• this review surveyed different types of hydrogel design strategies
	  ○ stimuli-responsive, degradable linkers, crosslink density tuning, loading, combining with different agents
	• with in vitro and in vivo evidence, it says that hydrogel-mediated chemokine delivery can enhance infiltration of effector t cells and improve responses when they are combines with ICIs
	• there are some safety issues with this
	  ○ immune overstimulation, toxicity
	• there are also challenges
	  ○ scaling, stability, regulation
	*because this is a review article, the methodology is synthesis of studies
	• found relative studied on hydrogels and chemokines
	• compared the designs and outcomes of these studies

	• identified the challenges of this process • suggested some ideas for the future of the research of this topic
Research Question/Problem/ Need	How can hydrogel delivery systems be engineered to be more precise and effective when targeting chemokines in the TME and treatment?
Important Figures	 Figure 1: The graphical abstract of the study

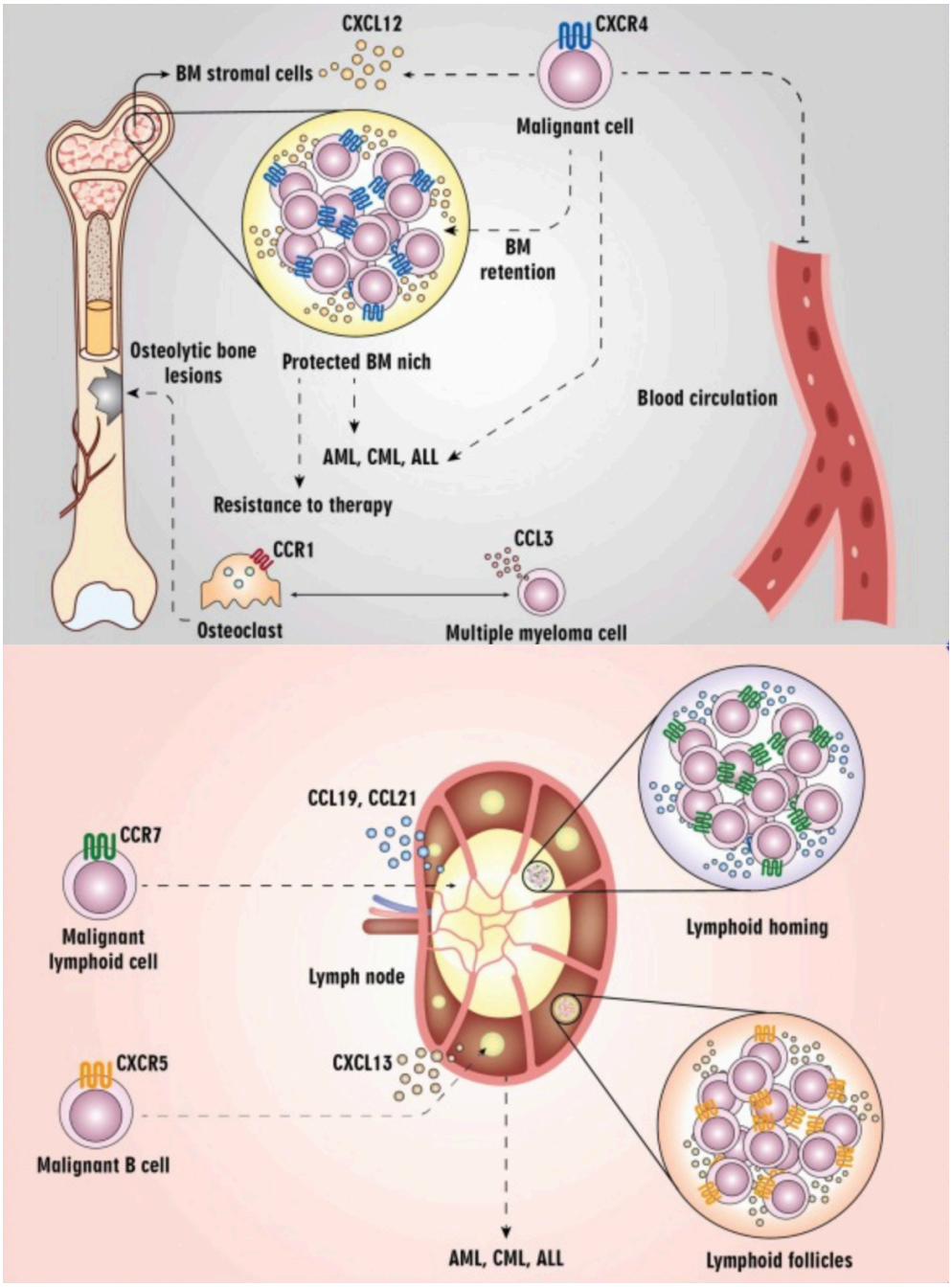


Figure 2: Bone marrow and lymph node niches highlighting stromal cell interactions and chemokine signaling

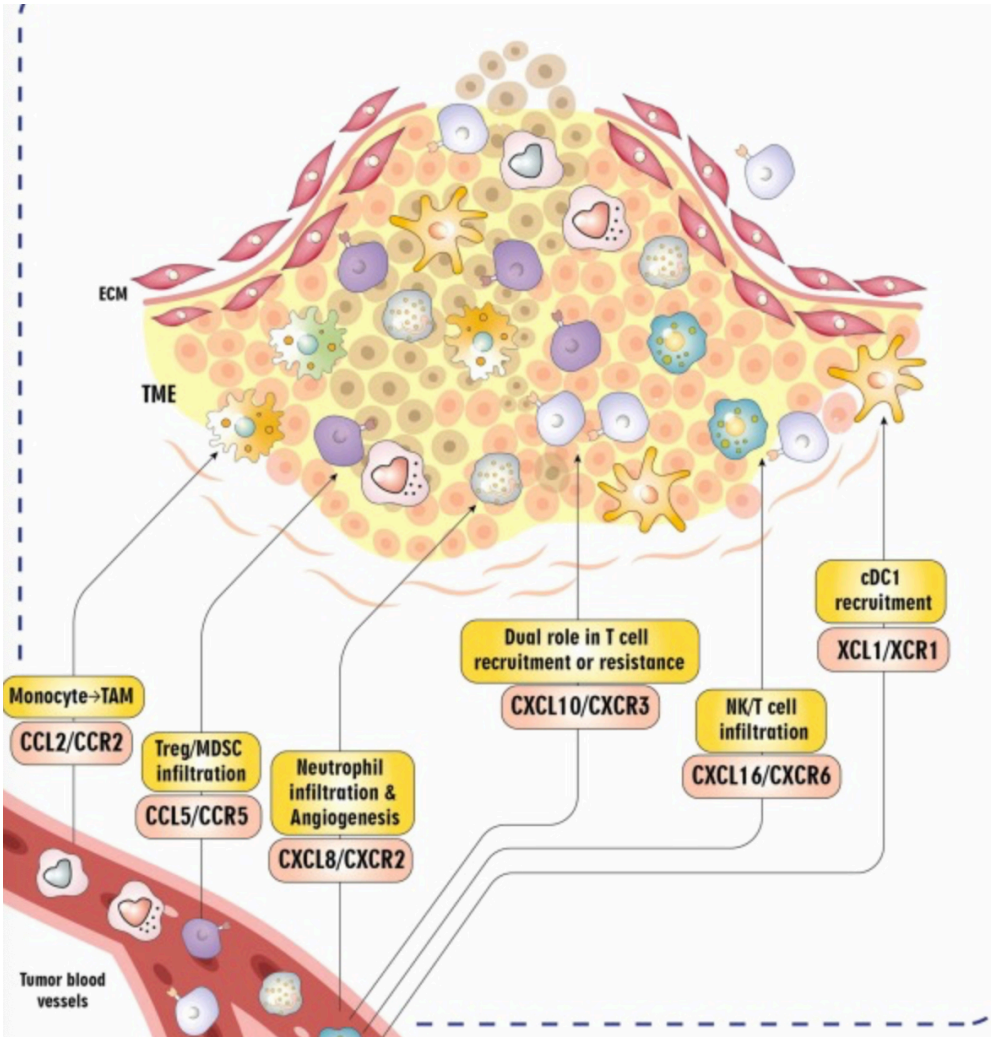


Figure 3: Tumor microenvironment with extracellular matrix interactions and immune cell infiltration

VOCAB: (w/definition)

Chemokine – small signaling proteins that direct the movement of immune cells (type of cytokine)

Cytokine – signaling molecules that regulate immune responses

Biocompatibility – the ability of a material to be compatible with tissue without rejecting or causing harm

ICI – immune checkpoint inhibitor, a drug that blocks proteins which normally suppress the immune system and allow t cells to attack tumors

Localized delivery – treatment that targets a specific area to increase effectiveness and reduce the side effects

	Biodegradability – the ability for a material to naturally break down in the body over a period of time Angiogenesis – the formation of new blood vessels, for cancer, this can help tumors grow and spread Metastasis – when cancer cells spread from the original tumor site to different parts of the body Immunomodulation – the adjusting or controlling of immune repose that could either enhance it or suppress it
Cited references to follow up on	Li, J. Y., Mooney, D. J., & Lee, K. Y. (2022). Designing hydrogels for controlled drug delivery. Nature Reviews Materials, 7(1), 24–39. https://doi.org/10.1038/s41578-021-00333-1
Follow up Questions	What time of chemokines are most promising when delivered via hydrogel? / the ones the enhance or suppress? Do different types of tumors affect the efficiency and process of the chemokine-releasing hydrogels? Are there risks, such as over activation or cytokine storm, and if so, how can they be mitigated?

Article #13 Notes: Preparation and Characterization of TPP-Chitosan Crosslinked Scaffolds for Tissue Engineering

Article notes should be on separate sheets

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Source Title	Preparation and Characterization of TPP-Chisosan Crosslinked Scaffolds for Tissue Engineering
Source citation (APA Format)	Silvestro, I., Francolini, I., Di Lisio, V., Martinelli, A., Pietrelli, L., Scotto d'Abusco, A., Scoppio, A., & Piozzi, A. (2020). Preparation and characterization of TPP-chitosan crosslinked scaffolds for tissue engineering. *Materials*, *13*(16), 3577. https://doi.org/10.3390/ma13163577
Original URL	https://pmc.ncbi.nlm.nih.gov/articles/PMC7475966/
Source type	Peer-reviewed scientific journal article
Keywords	Chitosan, tripolyphosphate, scaffolds, tissue engineering, crosslinking, mechanical properties
#Tags	#chitosan #biomaterials #crosslinking
Summary of key points + notes (include methodology)	- the goal of this study was to see how chitosan and TPP concentration as well as allowed cross-lining time influenced the structure of the scaffold - this scaffold is to be used in tissue engineering applications Methodology: - chitosan solutions with 1% and 2% concentrations were prepared and formed into scaffolds using freeze-drying to create porous 3D structures - these scaffolds were then ionically crossed with tripolyphosphate (TPP) at 1% and 2% concentrations - measurements were taken at 2, 4, and 6 hours to see if there were time-dependent effects - FTIR spectroscopy was used to examine the chemical interactions between the chitosan and TPP - Scanning Electron Microscopy was used to analyze the pore size and interconnectivity

	- Compression testing measured the mechanical strength and stiffness of the gels - Thermogravimetric analysis was used to evaluate the thermal stability - The swelling behavior was quantitatively measured - The osteoblast ess viability assays were conducted to asses prelim biocompatibility Key finding: - The lower the chitosan concentration, the better pore interconnectivity - The higher the TPP concentraition, the longer cross-linking time was ended up increasing the mechanical strength and thermal stability - He best balance was with the 1% chitosan, 2% TPP, and 8-hour crosslinking period - This balanced had the best strength, porosity, and cell compatibility
Research Question/Problem/ Need	How does chitosan concentration, TPP concentration, and cross-linking time affect the physical and mechanical properties of chitosan and TPP scaffolds?

Important Figures

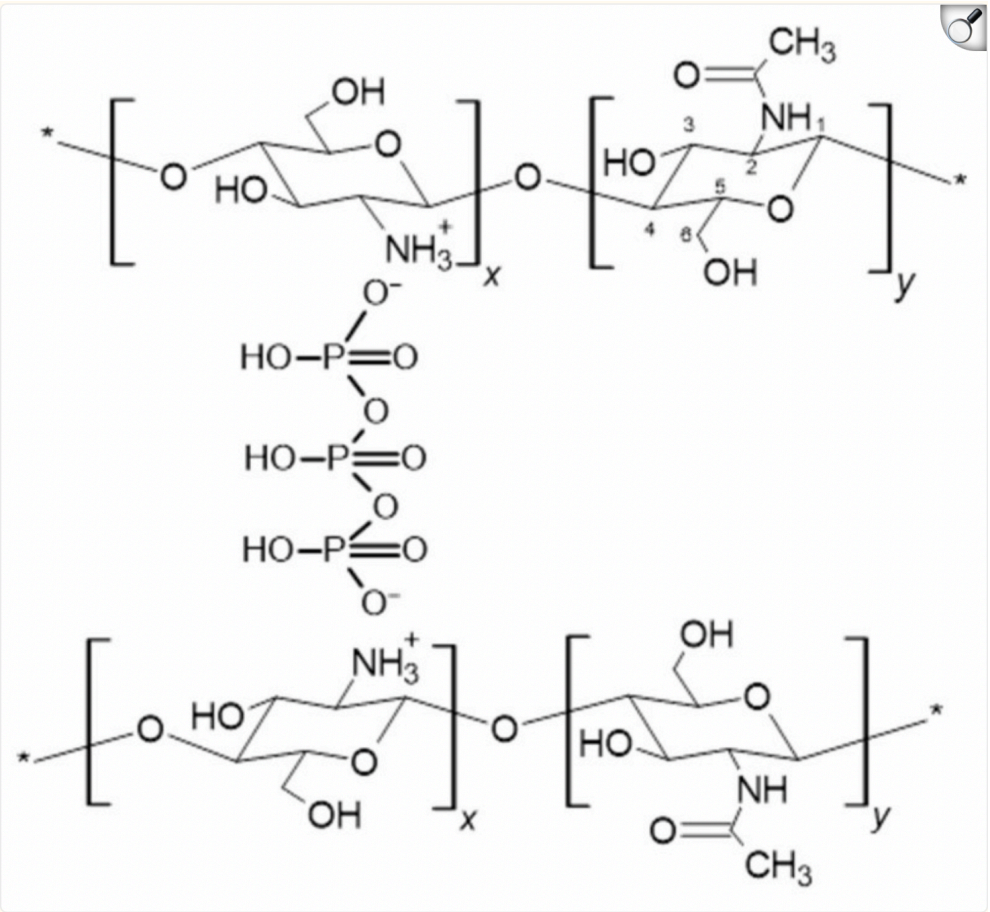
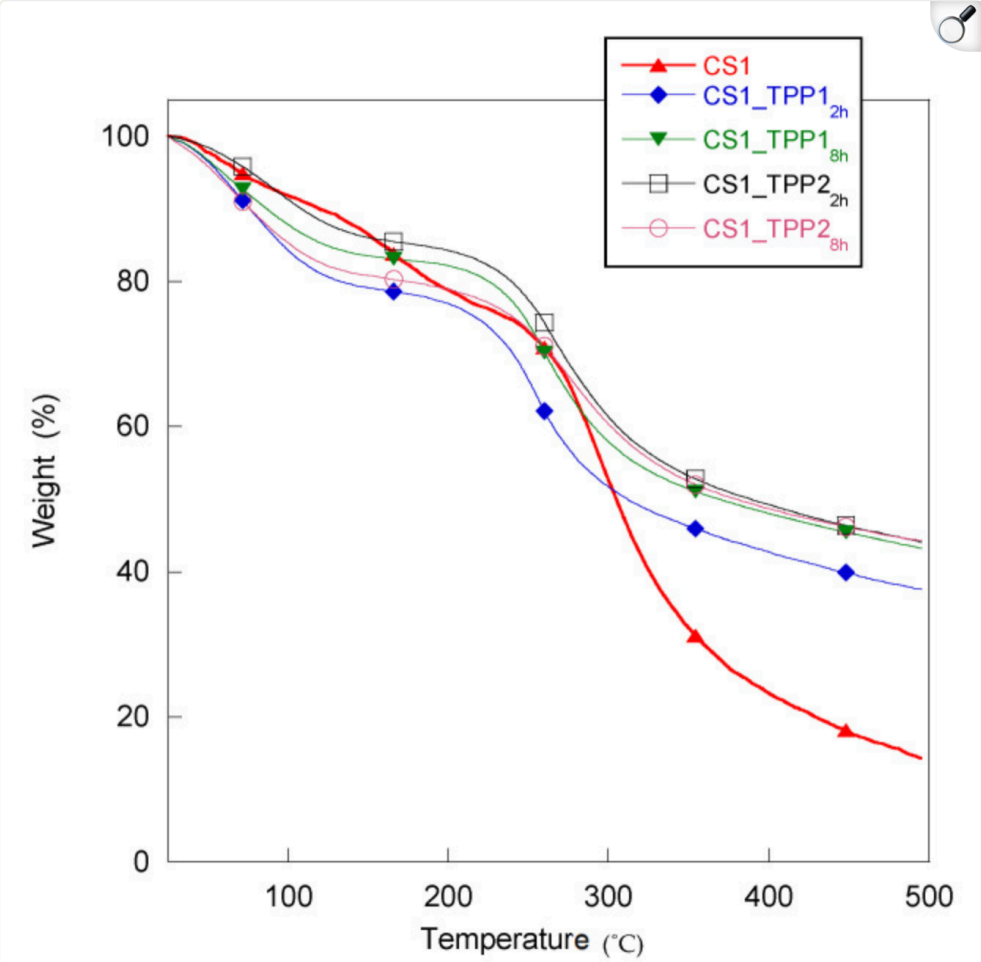


Figure 2: Ionic interactions of CS with TPP polyanion

Sample	CS Concentration (w/v %)	TPP Concentration (w/v %)	Cross-Linking Time (h)	Td (°C)	CM (MPa)	Pore Size (μm)	Pore Regularity
CS1	1	-	-	285	0.06 ± 0.01	80–180	Good
CS2	2	-	-	290	0.2 ± 0.05	130–250	Good
CS1_TPP12h	1	1	2	255	0.2 ± 0.05	50–200	Low
CS1_TPP18h	1	1	8	262	0.5 ± 0.05	50–180	Low
CS1_TPP22h	1	2	2	270	0.6 ± 0.05	80–100	Good
CS1_TPP28h	1	2	8	277	1.2 ± 0.05	60–100	Good
CS2_TPP12h	2	1	2	262	0.3 ± 0.05	70–100	Good
CS2_TPP18h	2	1	8	247	0.9 ± 0.05	90–110	Good
CS2_TPP22h	2	2	2	282	1.8 ± 0.05	100–120	Good
CS2_TPP28h	2	2	8	273	4.7 ± 0.05	200–300	Low

Table 1: Shows composition, mechanical and structural outcomes of all the samples

	 Figure 4: Thermogravimetric curves of CS1 and CS1_TPP scaffolds obtains at different cross-lining conditions
VOCAB: (w/definition)	Chitosan – a natural polymer delivered from chitin Tripolyphosphate (TPP) – an anionic cross-linker used to bind chitosan chains ioniclly Porosity – the percentage of void space in a scaffold Interconnectivity – how well pores are connected FTIR Spectroscopy – technique to identify chemical bonds using infrared light absorption Compression modulus - a measure of how much a material resists deformation under compression
Cited references to follow up on	Loh, Q. L., & Choong, C. (2013). Three-dimensional scaffolds for tissue engineering applications: Role of porosity and pore size. *Tissue*

	Engineering Part B: Reviews, *19*(6), 485–502. https://doi.org/10.1089/ten.teb.2012.0437 Abdelaziz, A. G., Nageh, H., Abdo, S. M., Abdalla, M. S., Amer, A. A., Abdal-hay, A., & Barhoum, A. (2023). A review of 3D polymeric scaffolds for bone tissue engineering: Principles, fabrication techniques, immunomodulatory roles, and challenges. *Bioengineering*, *10*(2), 204. https://doi.org/10.3390/bioengineering10020204
Follow up Questions	How do the different pore sizes affect cell migration? Can chitosan be crossed with anything else to gel?> What is the long-term degradation profile within physiological environments?

Article #14 Notes: Crosslinking of Chitosan with Dialdehyde Chitosan as a New Approach for Biomedical Applications

Article notes should be on separate sheets

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Source Title	Crosslinking of Chitosan with Dialdehyde Chitosan as a New Approach for Biomedical Applications
Source citation (APA Format)	Wegrzynowska-Drzymalska, K., Grebicka, P., Mlynarczyk, D. T., Chelminiak-Dudkiewicz, D., Kaczmarek, H., Goslinski, T., & Ziegler-Borowska, M. (2020). Crosslinking of Chitosan with dialdehyde chitosan as a new approach for biomedical applications. *Materials*, *13*(15), 3413. https://doi.org/10.3390/ma13153413
Original URL	https://pmc.ncbi.nlm.nih.gov/articles/PMC7435867/
Source type	Peer-reviewed scientific journal article
Keywords	Dialdehyde chitosan, chitosan, crosslinking, biomaterials, mechanical properties
#Tags	#Chitosan #DialdehydeChitosan #Crosslinking #Biomaterials
Summary of key points + notes (include methodology)	This study explores using dialdehyde chitosan as a natural-crosslinking agent for chitosan Conventional agents may be toxic, so this is a natural alternative that may reduce the toxicity Methodology: - Chitosan was oxidized with sodium periodate by varying the oxidant rations to produce the dialdehyde chitosan - Films were made from chitosan and were corrliked with DACS, DAS, or Glu, at 5%, 10%, 15% weight ratios - To characterize the properties: ▪ ATR-FTIR was used to confirm chemical modifications ▪ SEM and AFM for the surface morphology ▪ Swelling tests within PBS mircotox toxcitiy testing

	Findings:
	- The optimized oxidation methods produced DACS with up to 58% aldehyde group content in 3hrs
	- All the cross-linked films were homogeneous
	  ▪ The surface morphology was influences the type and amount of crosslinker
	- The increased DACS content improved tensile strength
	- The DACS and DAS crosslinked films showers much greater welling than the glutaraldehyde-cross-linked film
	  ▪ This indicated that higher hydrophilic and potential biological fluid interactions within
	- The DACS crossed materials show LOWER toxicity compared to the glu crossed films

Research Question/Problem/ Need	Can dialdehyde chitosan be a less toxic cross-linking agent for chitosan film compared to the current commonly used agents?
Important Figures	

Sample	CS:OA	ALD, %
$DACS_1$	1:0.5	22
$DACS_2$	1:0.7	29
$DACS_3$	1:0.9	35
$DACS_4$	1:1	58

Table 1: shows the degree of oxidation of dialdehyde chitosan

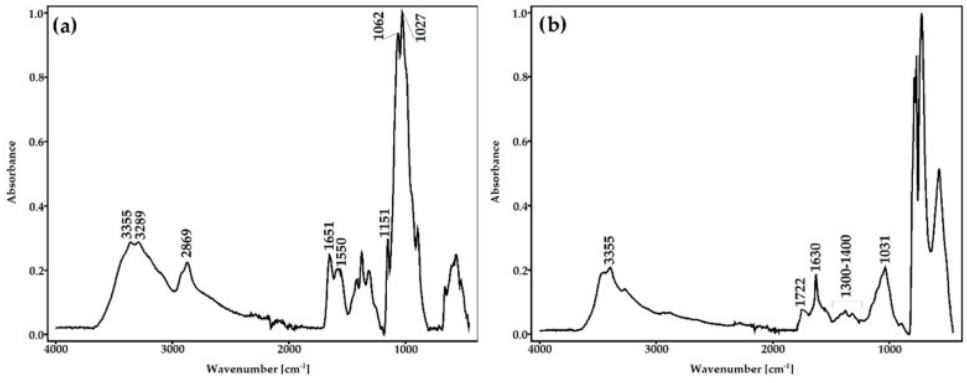
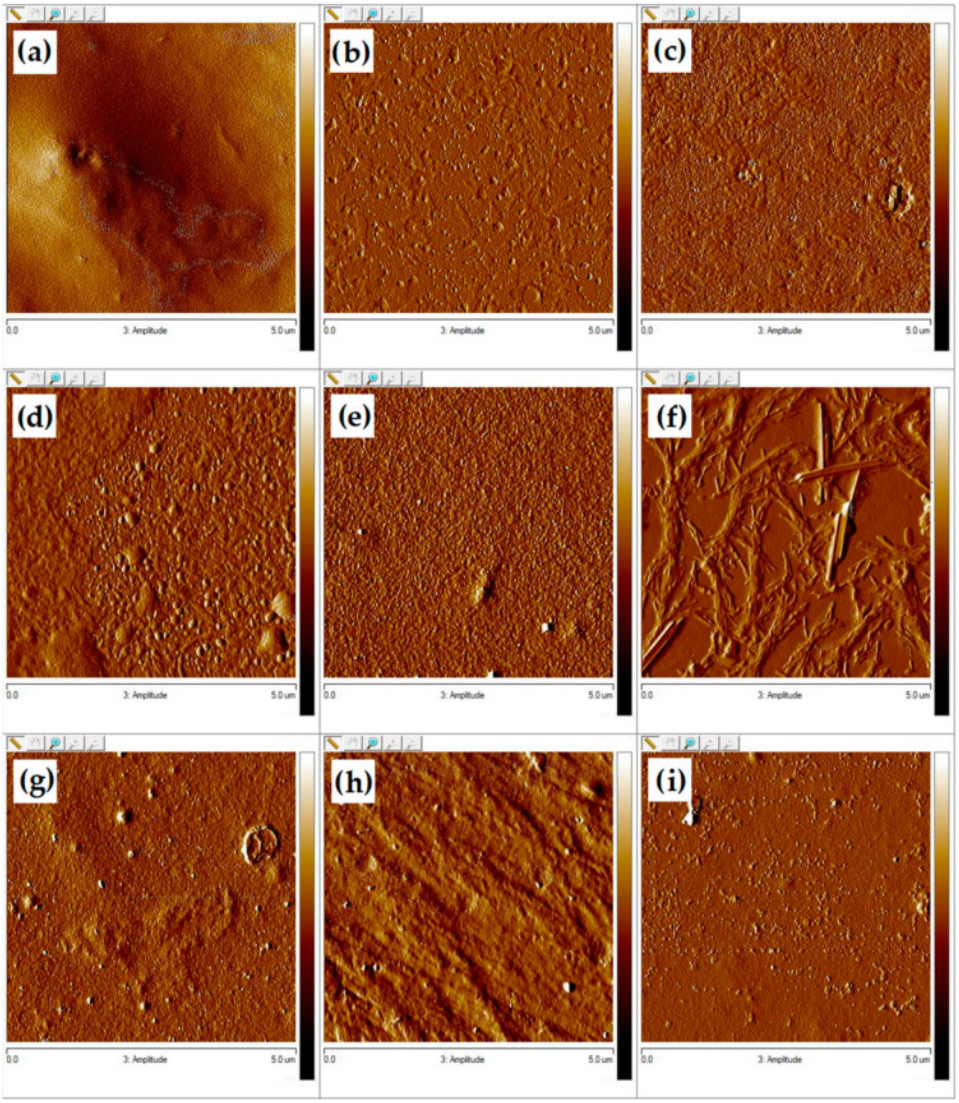


Figure 4: the ATR-FTIR spectra of chitosan and dialdehyde chitosan

	 The 2D scale of chitosan films with the crosses of DACS DAS and Glu
VOCAB: (w/definition)	Dialdehyde Chitosan – chitosan that is chemically oxidized to introduce aldehyde functional groups Schiff base – a covalent imine linkage formed between an aldehyde and an amine group during crosslinking DAS – oxidized starch with aldehyde groups used as an alternative polysaccharide cross-linker Glutaraldehyde – a small molecule cross linker commonly used but known to be highly cytotoxic Microtox test – a bioluminescence-based assay to assess acute toxicity using bacteria

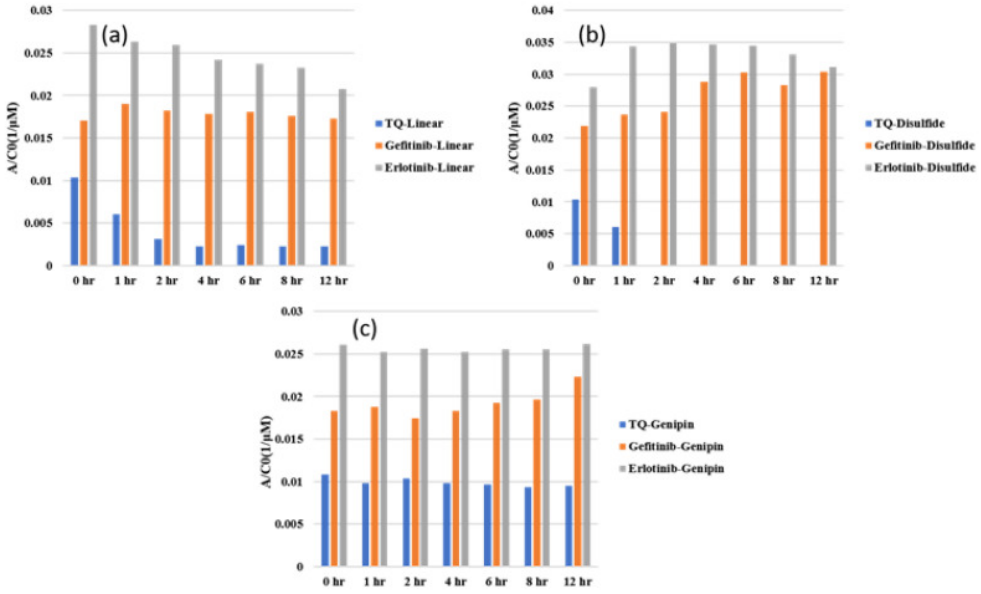
Cited references to follow up on	Lin, C. Y., Kikuchi, N., & Hollister, S. J. (2004). A novel method for biomaterial scaffold internal architecture design to match bone elastic properties with desired porosity. *Journal of Biomechanics*, *37*(5), 623–636. https://doi.org/10.1016/j.jbiomech.2003.09.029
Follow up Questions	How does the degree of oxidation in DACS effect cell proliferation? What is the degradation profile of DACS crossed materials In physiological environments?

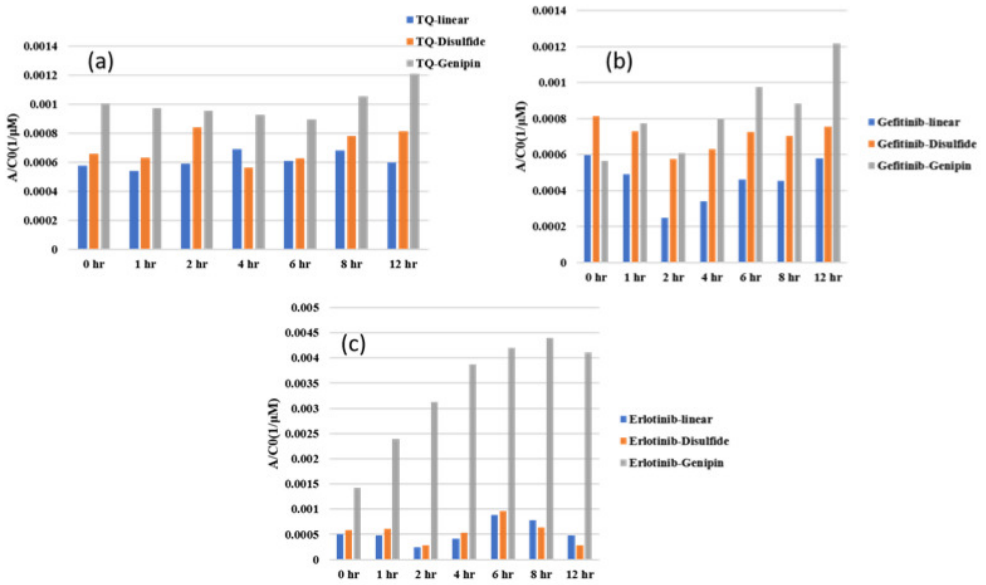
Article #15 Notes: Effect of Crosslinking Agents on Chitosan Hydrogel Carriers for Drug Loading and Release for Target Drug Delivery

Article notes should be on separate sheets

KEEP THIS BLANK AND USE AS A TEMPLATE

Source Title	Effect of Crosslinking Agents on Chitosan Hydrogel Carriers for Drug Loading and Release for Target Drug Delivery
Source citation (APA Format)	Uddin, M. S., Khand, S., & Dong, C. (2024). Effect of crosslinking agents on chitosan hydrogel carriers for drug loading and release for Targeted Drug Delivery. *Gels*, *10*(7), 421. https://doi.org/10.3390/gels10070421
Original URL	https://pmc.ncbi.nlm.nih.gov/articles/PMC11276364/
Source type	Peer-reviewed scientific journal article
Keywords	Chitosan, crosslinking, drug loading, druge release, disulfide crosslinking, agents, target deliverey
#Tags	#ChitosanHydrogel #DrugDelivery #Crosslinking #PharmaceuticalBiomaterials
Summary of key points + notes (include methodology)	The purpose of this study was to see how different crosslinking agents, such as genipin and disulfide, affect the drug loading and release in chitosan hydrogels that are used for target drug delivery Methodology: - Three chitosan hydrogels systems were made: ▪ Non crossed ▪ Genipin ▪ Disulfide - They were loaded with three different types of drugs: ▪ Thymoquinone ▪ Gefitnib ▪ Erlotinib HCl - They were submerged in the drugs, allowing for the absorption - The loading was measured over time with UV-Vis

	spectroscopy - The loaded gels were then incubated in PBS Finding: - Thymoquinone showsd the lowest loading efficiency in all of the systems - Gefitnib showed stable loading and release across all systems - Erlotinib had the highest loading and release over all ▪ But its release fluctuated in linear in disulfide ▪ Genipen had the most consistent drug performance
Research Question/Problem/ Need	How do different crosslinking agents influence the drug loading and release of chitosan hydrogels?
Important Figures	 Figure 6: comparison of loading of different drugs in different systems

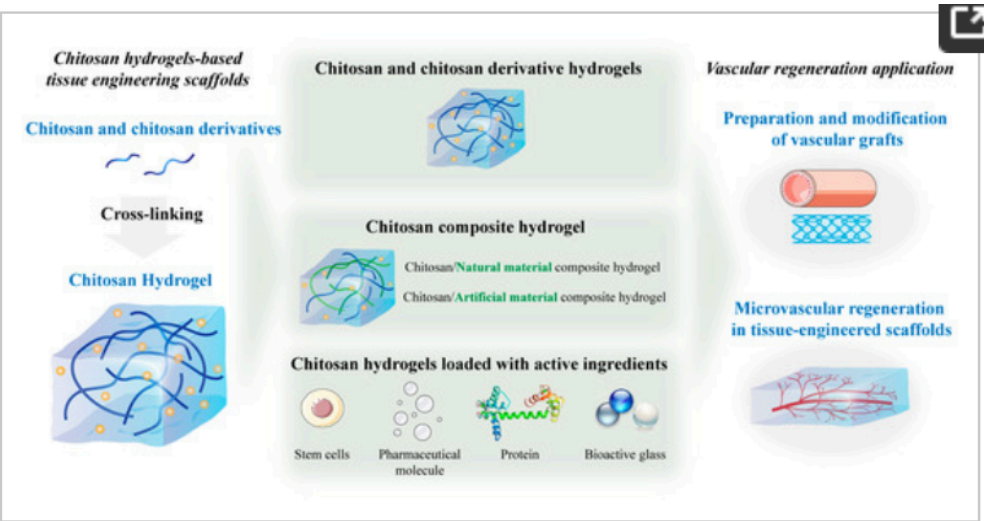
	 Figure 9: comparison of release of different drugs in different systems
VOCAB: (w/definition)	Genipin – natural crosslinker used to form stable gels with low toxicity Disulfide crosslinking – formation of covalent bons between sulfur groups to stabilize gels UV-Vis spectroscopy – analytical technique that measures absorption of light to quantify drug loading Molecular diffusivity – how fast a drug molecules moves though the hydrogel network
Cited references to follow up on	Prabaharan, M., & Mano, J. F. (2004). Chitosan-based particles as controlled drug delivery systems. *Drug Delivery*, *12*(1), 41–57. https://doi.org/10.1080/10717540590889781
Follow up Questions	How does the degree of crosslinking affect the drug release kinetics? How does the hydrogel mesh size correlate with loading efficiency for different drug sizes?

Article #16 Notes: Chitosan Hydrogel as Tissue Engineering Scaffolds for Vascular Regeneration Applications

Article notes should be on separate sheets

KEEP THIS BLANK AND USE AS A TEMPLATE

Source Title	Chitosan Hydrogel as Tissue Engineering Scaffolds for Vascular Regeneration Applications
Source citation (APA Format)	Wang, Q., Wang, X., & Feng, Y. (2023). Chitosan hydrogel as tissue engineering scaffolds for vascular regeneration applications. *Gels*, *9*(5), 373. https://doi.org/10.3390/gels9050373
Original URL	https://www.mdpi.com/2310-2861/9/5/373
Source type	Peer Reviewed Article
Keywords	Chitosan, hydrogel, tissue engineering, vascular regeneration, angiogenesis, scaffold materials, extracellular matrix mimicry
#Tags	#ChitosanHydrogel #VascularRegeneration #TissueEngineering #ScaffoldMaterials #Angiogenesis #Biomaterials #ECM
Summary of key points + notes (include methodology)	this is a comprehensive review of how chitosan hydrogels are used within the field of tissue engineering and terms of scaffolds for vascular regeneration across numerous studied the advantages, progress, modification strategies, and future prospects of chitosan hydrogel usage d as discussed within this article Main points: - Hydrogels are ideal scaffolds because their 3D network mimics the extracellular matrix, holds water, and supports cell movement and nutrient transport - Vascular regeneration requires scaffolds that support growth of both large vessels and micro vessels and that have suitable mechanical, biological, and porous properties - Chitosan hydrogels are tunable by chemical modification and cross-linking - Future prospects include optimizing physical structure and bioactivity - There is an aim for clinical translation

	Methodology: - Since this is a review, there are no new experiments, it just summarizes and compares the results from other published work
Research Question/Problem/ Need	What are the current applications, modification, and challenges of using chitosan hydrogels scaffold for vascular regeneration.
Important Figures	 Figure 1. Chitosan hydrogels and their applications in vascular regeneration.
VOCAB: (w/definition)	Angiogenesis – formation of new blood vessels Hydrophilicity – the tendency of a material to interact with and hold water Vascular regeneration – the process of repairing or regrowing blood vessels
Cited references to follow up on	Application of chitosan-based biomaterials in tissue engineering. (2016). *Chitosan-Based Hydrogels*, 417–478. https://doi.org/10.1201/b11048-12
Follow up Questions	How do different chemical modifications of chitosan angiogenic outcomes? What role do growth factors loaded into chitosan hydrogels play in in-vivo vascular regeneration?

Article #17 Notes: Mechanical Properties of Alginate Hydrogels Cross-Linked with Multivalent Cations

Article notes should be on separate sheets

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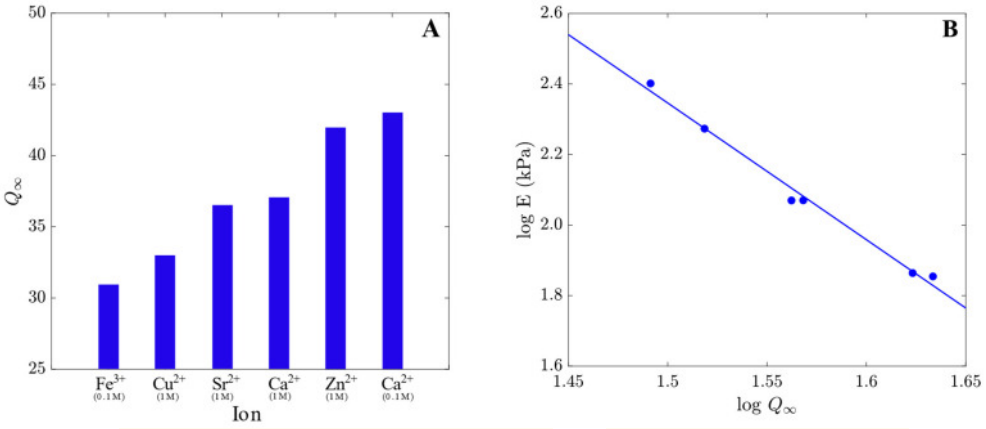
Source Title	Mechanical Properties of Alginate Hydrogels Cross-Linked with Multivalent Cations
Source citation (APA Format)	Malektaj, H., Drozdov, A. D., & deClaville Christiansen, J. (2023). Mechanical properties of alginate hydrogels cross-linked with multivalent cations. *Polymers*, *15*(14), 3012. https://doi.org/10.3390/polym15143012
Original URL	https://pmc.ncbi.nlm.nih.gov/articles/PMC10386690/
Source type	Peer-reviewed scientific research article
Keywords	Alginate hydrogel, multivalent cations, ionic crosslinking, mechanical properties, swelling, polymer network
#Tags	#AlginateHydrogel #Crosslinking #MultivalentCations #HydrogelMechanics #Swelling #PolymerNetwork #Biomaterials

Summary of key points + notes (include methodology)	The purpose of this article is to look at different multivalent cations influence the mechanical properties and swelling behavior of alginate hydrogels
	Methodology:
	- Prepared alginate hydrogels by ionic cross-linking with various cations
	  ▪ divalent: Ca^{2+}, Sr^{2+}, Cu^{2+}, Zn^{2+}
	  ▪ trivalent: Fe^{3+}
	- Controlled concentrations of salts were used to crosslink sodium alginate solutions
	- Swelling degrees were quantified in solvent media
	- The stress-strain and swelling data were fitted to network models to quantify elastic modulus and structural inhomogeneity
	Findings:
	- Some crosslinking cation significantly affects mechanical stiffness and swelling

	▪ Trivalent Fe^{3+} generally produced hydrogels with higher elastic moduli than divalent ions at similar concentrations ▪ Different ions' binding affinity and ionic radius influence how tightly the polymer network is cross-linked - The mechanical relationships differ compared to covalently crossed gels ▪ This indicated that ionic interactions have a role in tuning properties - The equilibrium swelling and elastic modulus exhibited trends that correlate with ionic strength and cross-link density ▪ This will be useful when designing materials for biomedical use
Research Question/Problem/ Need	How does the type of multivalent cation alter the swelling and mechanical properties of alginate hydrtogels?
Important Figures	 Figure 3: Equilibrium degree of swelling $Q\infty$ of alginate hydrogels cross-linked with various cations and The elastic modulus *E* versus equilibrium degree of swelling $Q\infty$
VOCAB: (w/definition)	Multivalent cation - An ion with more than one positive charge (e.g., Ca^{2+}, Fe^{3+}) used to cross-link polyanionic polymers. Elastic modulus - A measure of a material's stiffness; higher values indicate a stiffer hydrogel Dynamic mechanical analysis (DMA) - A technique that measures mechanical response under oscillatory deformation Viscoelasticity - Material behavior that shows both elastic (solid-like) and viscous (fluid-like) responses to deformation

Cited references to follow up on	Ye, R., Liu, S., Zhu, W., Li, Y., Huang, L., Zhang, G., & Zhang, Y. (2023). Synthesis, characterization, properties, and biomedical application of chitosan-based hydrogels. *Polymers*, *15*(11), 2482. https://doi.org/10.3390/polym15112482
Follow up Questions	How do biological ions in physiological conditions affect the mechanical stability of ionically cross-linked hydrogels in vivo? How does cross-linker concentration influence long-term degradation and mechanical integrity?

Article #18 Notes: Multi-Layered Hydrogels for Biomedical Applications

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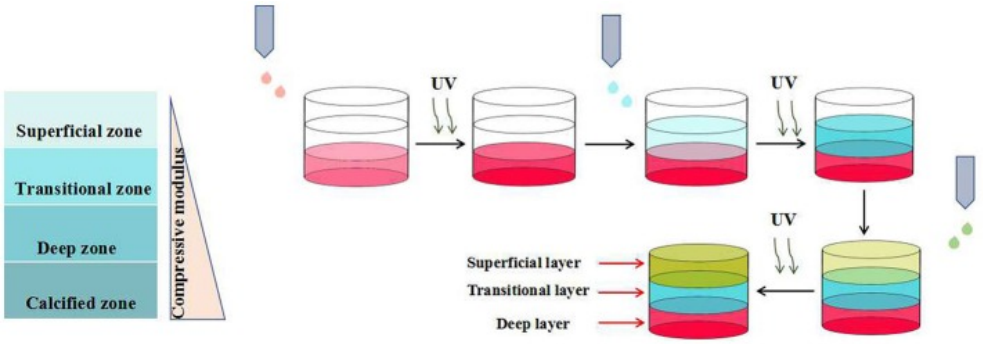
Source Title	Multi-Layered Hydrogels for Biomedical Applications
Source citation (APA Format)	Liu, G., Ding, Z., Yuan, Q., Xie, H., & Gu, Z. (2018). Multi-layered hydrogels for biomedical applications. *Frontiers in Chemistry*, *6*. https://doi.org/10.3389/fchem.2018.00439
Original URL	https://pmc.ncbi.nlm.nih.gov/articles/PMC6167445/
Source type	Peer-reviewed scientific journal article
Keywords	Multi-layered hydrogel, layer-by-layer self-assembly, step-wise fabrication, sequential electrospinning
#Tags	#MultiLayeredHydrogels #BiomedicalApplications #HydrogelFabrication #LayerByLayer
Summary of key points + notes (include methodology)	This is a review of multi-layers hydrogels and how they are fabricated using different techniques Topics Covered: - There basics of hydrogels where they talk about how hydrogels are 3D polymer networks that absorb large amounts of water and mimic soft tissues - Talks about why multi-layered designs matter ▪ Hydrogels do not always adequately mimic the anatomical and functional complexity of tissues ▪ Multi-layered structures can provide gradients in properties that better match natural tissues - Goes over different fabrications techniques: ▪ Layer-by-Layer (LBL) Self-Assembly: Builds precise alternating layers of materials based on electrostatic or other molecular interaction ▪ Step-Wise Technique: Sequential gelation processes that create “onion-like” multi-layered hydrogels ▪ Photo-Polymerization: Uses light to cross-link layers with spatially controlled properties ▪ Sequential Electrospinning: Produces fibrous multi-layered hydrogel mats with distinct mechanical and

	release profiles - Discusses the applications of layered gels ▪ Uses in drug delivery, tissue regeneration, particulaly where gradients matter, such as skin, cartilage, or vasculature, and as coatings for implants that can control bioactive release - Challenges: ▪ Highlights fabrication limitations, scalability challenges, and opportunities like 3D bioprinting for producing complex multi-layered hydrogel systems
Research Question/Problem/ Need	What are the fabrication strategies for multi layered hydrogels?
Important Figures	 Figure 5: Schematic representation of three-layered hydrogels with spatially-varying mechanical properties by photo-polymerization technique  Figure 6: Schematic representation of four-layered hydrogels with time-programmed combination release behavior by sequential electrospinning technique.
VOCAB: (w/definition)	Layer-by-Layer Self-Assembly - Sequential adsorption of alternating materials to build layered structures at the nanoscale Step-wise technique - A fabrication method where layers are formed sequentially by controlled gelation processes Sequential Electrospinning - A technique that produces layered fibrous mats by spinning polymers layer by layer

Cited references to follow up on	Ahmed, E. M. (2015). Hydrogel: Preparation, characterization, and applications: A Review. *Journal of Advanced Research*, *6*(2), 105–121. https://doi.org/10.1016/j.jare.2013.07.006
Follow up Questions	How do mechanical gradients in multi-layered hydrogels affect cell behavior during tissue regeneration? Can multi-layered hydrogel systems be made stimulus-responsive to enable triggered drug delivery?

Article #19 Notes: Nonlinear Dynamics and Chaos Theory: Concepts and Applications Relevant to Pharmacodynamics

Article notes should be on separate sheets

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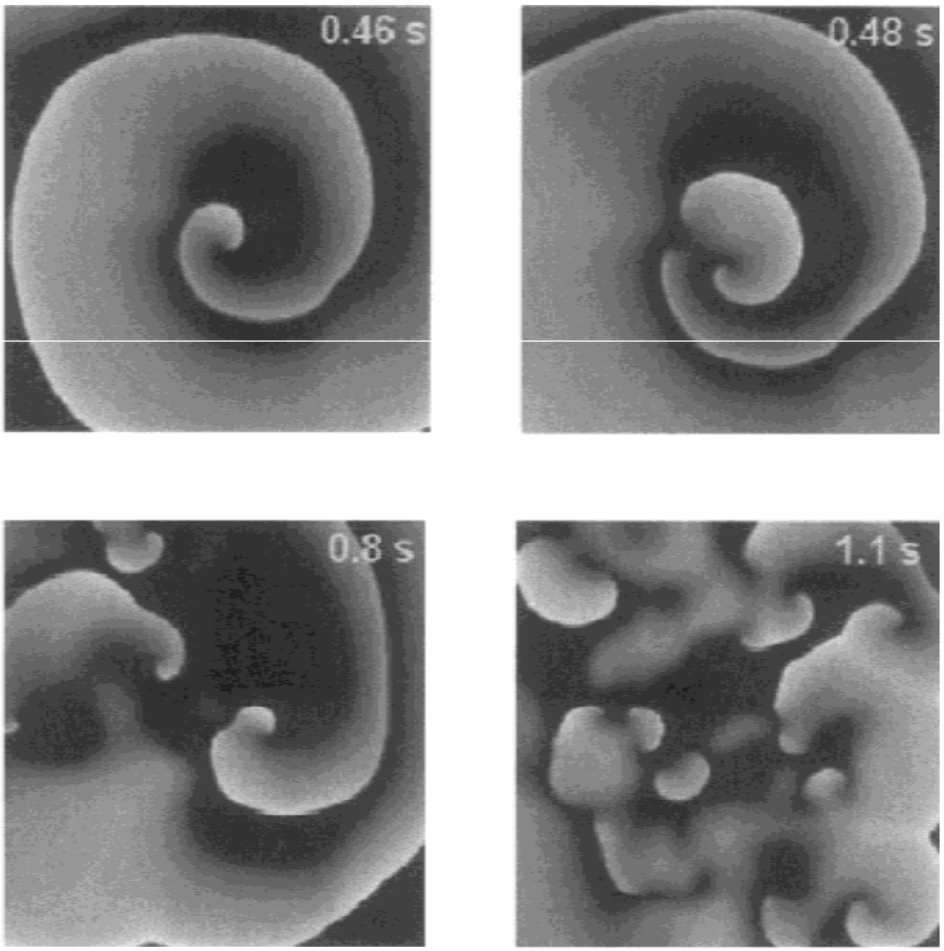
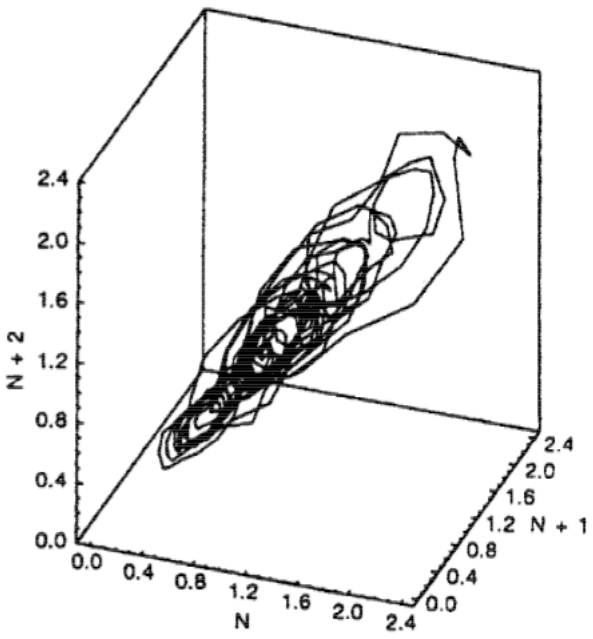
Source Title	Nonlinear Dynamics and Chaos Theory: Concepts and Applications Relevant to Pharmacodynamics
Source citation (APA Format)	Dokoumetzidis, A., Iliadis, A., & Macheras, P. (2001). Nonlinear Dynamics and Chaos Theory: Concepts and applications relevant to pharmacodynamics. *Pharmaceutical Research*, *18*(4), 415–426. https://doi.org/10.1023/a:1011083723190
Original URL	https://link.springer.com/article/10.1023/A:1011083723190#citeas
Source type	Peer-reviewed scientific journal article
Keywords	Pharmacodynamics, chaos, cardiovascular drugs, CNS drugs, hormones
#Tags	#ChaosTheory #NonlinearDynamics #Pharmacodynamics #BiologicalComplexity
Summary of key points + notes (include methodology)	This paper goes over the concepts of nonlinear dynamics and chaos theory within the context of biological and pharmacodynamic systems Background/purpose: - Biological systems exhibit complex, and seemingly, random dynamics that be determined by certain principles - Chaos theory provides tools to analyze behaviors like these - It also offers alternative interpretations to classical pharmacodynamic models Concepts: - Nonlinear systems, also including sensitive to initial conditions - Attractors, bifurcations, and phase space representations - Lyapunov stability, referencing how small differences in initial states evolve over time - Application of chaos theory to pharmacodynamics ▪ Drug-receptor interaction models, physiological

	oscillations "Methodology": - It analyses and synthesizes mathematical models of dynamical systems ▪ It really hits on how chaos theory principles can be used to interpret biological signal behavior ▪ It reviews other published pieces on complex dynamics and interprets it within biological scenarios ▪ Endocrine rhythms, pharmacokinetic responses Concussion: - The author argue that nonlinear and chaotic dynamics are essential to understanding many biological phenomena ▪ Believes that it may improve model predictions in pharmacodynamics ▪ Chaos theory could offer new frameworks for analyzing variability and complexity beyond traditional linear models
Research Question/Problem/ Need	How can principles of nonlinear dynamics and chaos theory be applied to biological systems and pharmacodynamics?

Important Figures	 The four snapshots show the evolution and break up of a spiral wave pattern in 2D simulated cardiac tissue (300 × 300 cells). The chaotic regime shown in the final snapshot, corresponds to fibrillation.

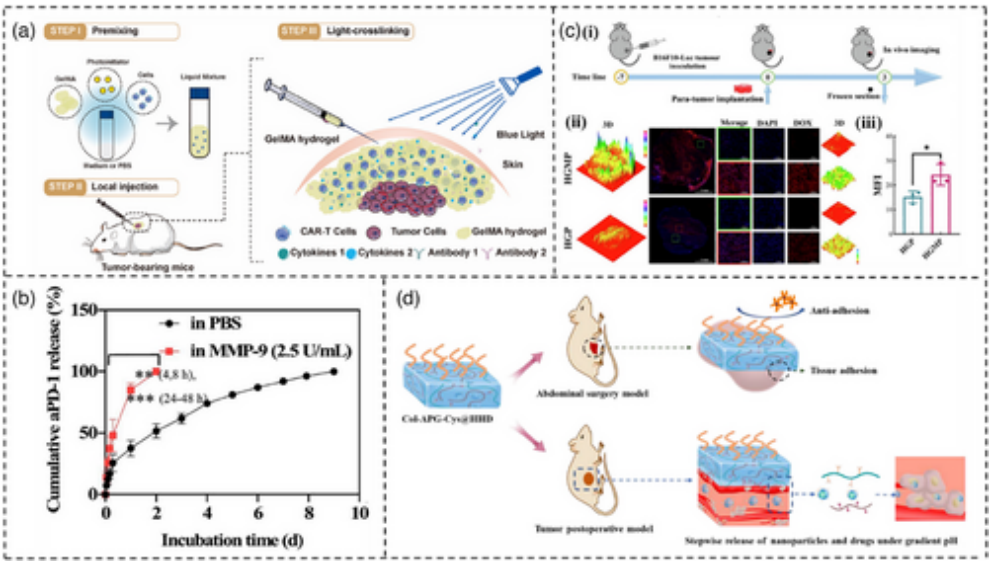
	 Sketch of the 3D attractor of prolactin generated by the data of plot A. The dimension of the attractor was found to be fractional, namely D0 1.66, indicating that diurnal prolactin secretion is governed by nonlinear dynamics.
VOCAB: (w/definition)	Deterministic chaos - Behavior that appears random despite being governed by deterministic rules Phase space - A multidimensional space where all possible states of a system are represented Attractor - A set of system states toward which a system tends to evolve Bifurcation - A qualitative change in system behavior due to a parameter change Phase portrait - A visual representation of trajectories in phase space
Cited references to follow up on	Nježić, S., Radulović, J., Živić, F., Mirić, A., Jovanović Pešić, Ž., Vasković Jovanović, M., & Grujović, N. (2022). Chaotic model of Brownian motion in relation to drug delivery systems using ferromagnetic particles. *Mathematics*, *10*(24), 4791. https://doi.org/10.3390/math10244791
Follow up Questions	How can chaos theory improve predictive pharmacokinetic/pharmacodynamic models compared to linear

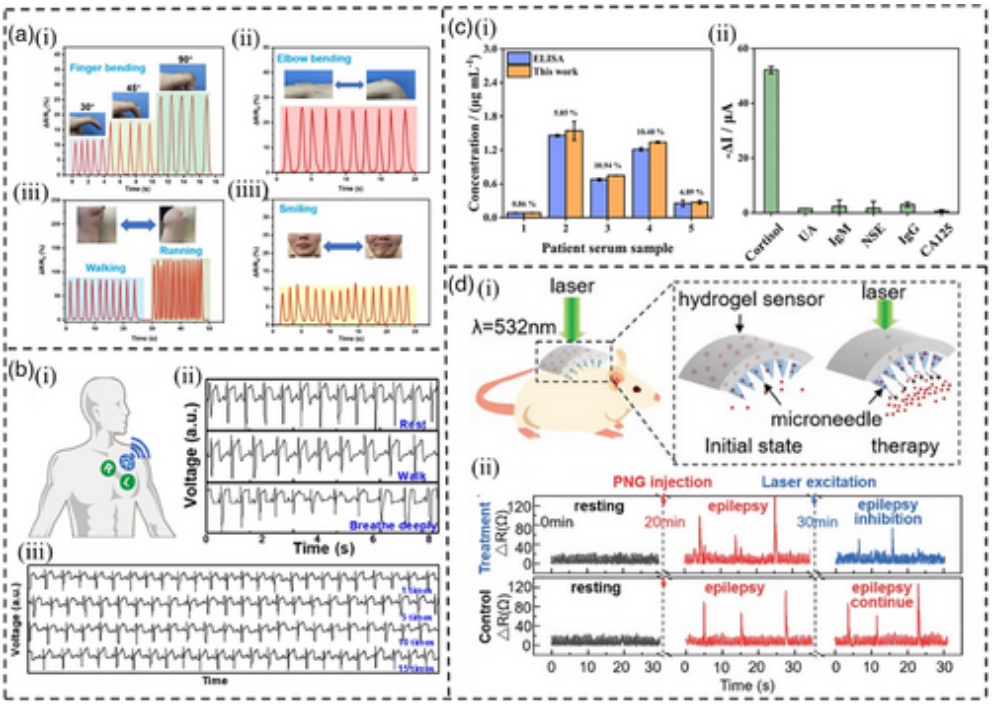
	approaches? How might nonlinear models of drug response explain variability in patient outcomes?

Article #20 Notes: A Comprehensive Review on Protein-Based Hydrogels: From Structure Modification to Applications

KEEP THIS BLANK AND USE AS A TEMPLATE

Source Title	A Comprehensive Review on Protein-Based Hydrogels: From Structure Modification to Applications
Source citation (APA Format)	Gou, Y., Wang, A., Ding, L., Yang, X., Lu, X., Qi, Q., Wang, L., Nan, G., Zhang, R., Duan, S., & Ren, C. (2025). A comprehensive review on protein-based hydrogels: From structure modification to applications. *ChemistrySelect*, *10*(14). https://doi.org/10.1002/slct.202405618
Original URL	https://chemistryeurope.onlinelibrary.wiley.com/doi/full/10.1002/slct.202405618?saml_referrer
Source type	Peer-reviewed scientific journal article
Keywords	Protein-based hydrogels, structure modification, mechanical properties, drug delivery
#Tags	#ProteinHydrogels #DrugDelivery #TissueEngineering
Summary of key points + notes (include methodology)	This article is a review of protein-based hydrogels and how protein structure can be modified to tailor hydrogel properties Background: - Hydrogels are soft, water-rich 3D polymer networks that mimic many aspects of the natural extracellular matrix - Protein-based hydrogels combine high biocompatibility, biodegradability, and multiple functional possibilities based on protein chemistry *there is no real methodology since this is a review article Key points: - Protein-based hydrogels are highly promising biomaterials because they closely mimic the extracellular matrix - Modifying the structure of a gel is essential to overcome their natural weaknesses, like mechanical strength

	- By tuning cross-linking density and protein chemistry, protein hydrogels can be engineered with tailored mechanical, swelling, and degradation properties for specific biomedical applications - This technique is used in drug delivery, tissue engineering, wound healing, 3D bioprinting, and biosensors - Hybrid gels improve stability and functionality compared to single-component systems - As advantages are they are, there are still challenges in scalability, reproducibility, and long-term mechanical performance
Research Question/Problem/ Need	What strategies have been developed to modify protein-based hydrogels and how to they influence the properties of the gels?
Important Figures	 Figure 2: The applications of drug delivery with protein-based hydrogels. (a) The schematic diagram of preparation and applications of the GelMA hydrogels delivery system

	 Figure 6: The biosensors application of protein-based hydrogels
VOCAB: (w/definition)	Methacryloylation - A chemical modification that adds methacryloyl groups to proteins to enable photo-cross-linking Gelation Kinetics - The rate and mechanism by which a liquid precursor transforms into a gel network Cytocompatibility - A specific aspect of biocompatibility referring to a material's ability to support cell survival and normal cellular behavior
Cited references to follow up on	Liu, G., Ding, Z., Yuan, Q., Xie, H., & Gu, Z. (2018a). Multi-layered hydrogels for biomedical applications. *Frontiers in Chemistry*, *6*. https://doi.org/10.3389/fchem.2018.00439
Follow up Questions	How do mechanical gradients in multi-layered hydrogels affect cell behavior during tissue regeneration? What are the scalability challenges for producing multi-layered hydrogel implants with consistent performance? What role do layer composition and interface properties play in the long-term?

Patent #1 Notes: Hydrolysable hydrogels for controlled release US6497903B1

Article notes should be on separate sheets

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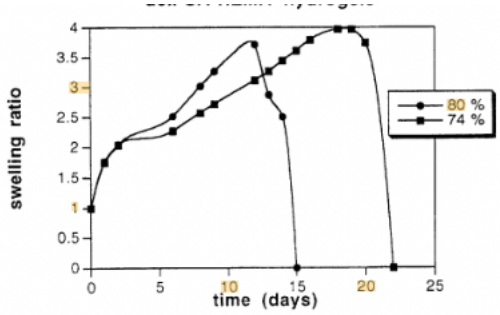
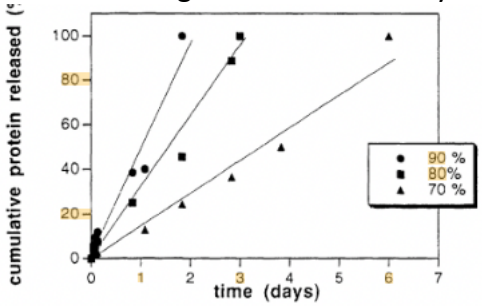
Source Title	Hydrolysable hydrogels for controlled release US6497903B1
Source citation (APA Format)	Hennink, W. E. (2017, December 24). Hydrolysable hydrogels for controlled release.
Original URL	https://patents.google.com/patent/US6497903B1/en
Source type	Patent
Keywords	Controlled release, polymer cross-linking, hydrolysable hydrogel, biodegradable material
#Tags	#Hydrogel #ControlledRelease #Patent #Biodegradable #Polymer #DrugDelivery #Crosslinking
Summary of key points + notes (include methodology)	- The invention covers hydrolysable hydrogel compositions designed for controlled release of active agents - These hydrogels are made up of polymer networks that have hydrolysable bonds ▪ These bonds break down over time when exposed to moisture or physiological conditions - The system allows tunable release profiles by adjusting polymer composition, cross-link density, and hydrolysable linker chemistry - This invention helps toward the analysis of non-degradable hydrogels in terms of predictable breakdown and elimination from the body Methodology: - A water-soluble polymer backbone was selected - The polymer was chemically modify to introduce hydrolysable spacer groups - Polymer chains were crosslinked to form the hydrogel network - Therapeutic or bioactive agents were incoperated into the solution prior to gelation - Hydrogels were formed under controlled conditions - The hydrolysable bonds gradually cleave when explosed to

	water, causing network degradation - Drug or agent release occurs as a function of bond hydrolysis rate and network breakdown rather than simple swelling alone
Research Question/Problem/ Need	To create biodegradable hydrogel materials that can gradually break down in a body environment, allowing for a controlled and sustained release of drugs.
Important Figures	 Figure 4: Swelling behaviors of the hydrogels  Figure 5: Release of IgG from degrading hydrogels
VOCAB: (w/definition)	Lactate Ester - A hydrolysable chemical group formed from lactic acid and alcohol components Hydrolysable Linkages - Chemical bonds within the polymer network designed to be broken by water, enabling gradual material degradation
Cited references to follow up on	Knipe, J. M. (2016, July 21). Hydrogels for delivery of therapeutic compounds.
Follow up Questions	How do hydrolysable bonds influence the release profile of drugs from hydrogels compared to non-hydrolysable hydrogels? How do cross-link density and hydrolysis rate correlate with the release kinetics of the drugs? What other materials can be used to create biodegradable controlled-release hydrogels?

Patent #2 Notes: Hydrogels for delivery of therapeutic compounds

Article notes should be on separate sheets

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Source Title	Hydrogels for delivery of therapeutic compounds
Source citation (APA Format)	Knipe, J. M. (2016, July 21). Hydrogels for delivery of therapeutic compounds.
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Source type	Patent
Keywords	Controlled drug delivery, pH-responsive, therapeutics
#Tags	#Hydrogel #DrugDelivery #Patent #ControlledRelease #pHResponsive #Biomaterials

Summary of key points + notes (include methodology)	Purpose: to make a hydrogel designed to deliver therapeutic compounds with controlled release triggered by environmental conditions
	Key points:
	- The hydrogels are pH-responsive, remaining compact in acidic environments and swelling at neutral pH
	  ▪ An example of acidic is the stomach
	  ▪ An example of the neutral pH
	- Enzymatically cleavable peptide crosslinks are incorporated to enable site-specific degradation
	- This method is made to protect sensitive therapeutics during transit and release
	- The hydrogel platform is modular, allowing different drugs, linkers, and formulations
	Methodology:
	- A copolymer backbone is selected for pH sensitivity
	- Polymer chains are crosslinked using peptide linkers
	- The therapeutic agents are loaded before or during gel formation
	  ▪ These include proteins and nucleic acids
	- The hydrogel is processed into particles or a dosage that can be taken orally
	- When the gels were exposed, the findings showed that:
	  ▪ A. low pH caused the gel to remain collapsed

	▪ A neautral pH and an enzyme allowed for the gel to well and degrade - It was found that drug release occurs through combined swelling and enzymatic breakdown
Research Question/Problem/ Need	How can hydrogel networks be engineered to protect therapeutic compounds to be delivered orally and release at the proper time in a controlled manner using pH and enzymatic triggers.
Important Figures	N/A, the only figures are the compound of what they used, nothing procedural or on the findings
VOCAB: (w/definition)	Peptide Crosslinker - A short amino-acid sequence used to link polymers and enable enzymatic cleavage Bioavailability - The proportion of a therapeutic compound that successfully reaches systemic circulation and can produce a biological effect Enzyme-Cleavable Linker - A molecular connector designed to break when exposed to specific enzymes, enabling targeted degradation of a polymer network
Cited references to follow up on	Musuc, A. M., Mititelu, M., & Chelu, M. (2024). Hydrogel for sustained delivery of therapeutic agents. *Gels*, *10*(11), 717. https://doi.org/10.3390/gels10110717
Follow up Questions	How does enzymatic crosslink cleavage compare to purely hydrolytic degradation? How could this design be adapted for injectable rather than oral delivery? How does this approach compare to TPP-crosslinked chitosan hydrogels in release control?