UCONN

THE CATO T. LAURENCIN INSTITUTE FOR REGENERATIVE ENGINEERING

2023

ABOUT THE CEO
DR. CATO T. LAURENCIN

Cato T. Laurencin, M.D., Ph.D. earned his Bachelor of Science in Engineering (BSE) in Chemical Engineering from Princeton University, his MD, Magna Cum Laude, from Harvard Medical School (HMS), and his Ph.D. in Biochemical Engineering/Biotechnology from the Massachusetts Institute of Technology (MIT).

He is the pioneer of the field of Regenerative Engineering.

In receiving the Spingarn Medal, he was named the world's foremost engineer-physician-scientist. Dr. Laurencin pioneered the novel use of polymeric biomaterials for treating musculoskeletal conditions. In recognition of his breakthrough achievements, the American Institute of Chemical Engineers (AIChE) created the Cato T. Laurencin Regenerative Engineering Founder's Award.

Dr. Laurencin's work spans fundamental science, applied science, and technology translation. He has received the highest honors in all areas including Chemistry (Priestley Medal), Materials Science (Von Hippel Award), Biological Engineering (Jay Bailey Award), Medical and Biological Engineering (Pierre Galletti Award) and Surgery (Nicolas Andry Award).

In science, engineering, medicine, and innovation, he is an elected member of the National Academy of Sciences, the National Academy of Engineering, the National Academy of Medicine, and an elected Fellow of the National Academy of Inventors. He is the first surgeon in history to be elected to all four national academies. Dr. Laurencin received the Philip Hague Abelson Prize, the highest honor of the American Association for the Advancement of Science, for "signal contributions to the advancement of science in the United States" for his work in Regenerative Engineering. He is the first person to receive both the oldest/highest award from the National Academy of Engineering (the Simon Ramo Founder's Award) and one of the oldest/highest awards of the National Academy of Medicine (the Walsh McDermott Medal). In innovation, Dr. Laurencin was awarded the National Medal of Technology and Innovation, America's highest honor for technological advancement, by President Barack Obama in ceremonies at the White House.

Dr. Laurencin is the University Professor and Albert and Wilda Van Dusen Distinguished Endowed Professor at the University of Connecticut. He is the Chief Executive Officer of the Cato T. Laurencin Institute for Regenerative Engineering at the University of Connecticut.

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THE SIX PILLARS

The new Cato T. Laurencin Institute for Regenerative Engineering embraces the six pillars described by Dr. Laurencin:

Overwhelming Excellence in Science
Anti-Racism and Justice
Sponsorship and Mentorship
International, National, and Community Action
Transformative Technologies for Humanity
Entrepreneurship and Economic Value Creation

This new cross-campus Institute supports a core mission of UConn to foster new ways of thinking and new approaches to finding answers in medicine, science, engineering, and technology. The Institute reports to the Office of the Provost.

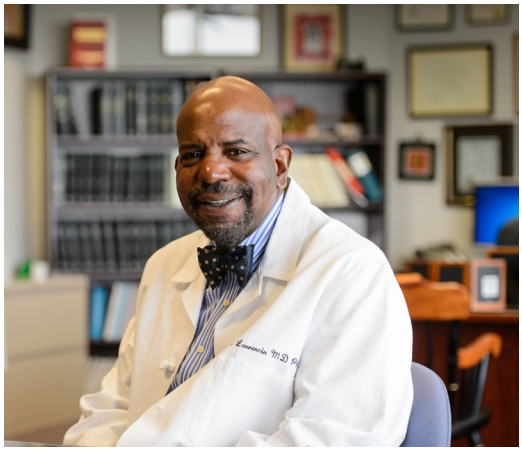
Regenerative engineering is a field founded by Professor Cato T. Laurencin. It is described as the convergence of advanced materials sciences, stems cell science, physics, developmental biology, and clinical translation for the regeneration of complex tissues and organ systems. The Cato T. Laurencin Institute for Regenerative Engineering represents a transdisciplinary effort at UConn with a focus on the musculoskeletal area.

The Institute integrates medicine, engineering, surgery, biology, physics, chemistry, and statistics/machine learning to enable a powerful platform for addressing scientific and medical problems in the regeneration and healing of complex tissues, organs, or organ systems.

OUR TEAM

CHIEF EXECUTIVE OFFICER

CATO T. LAURENCIN, MD, PH.D.



University Professor

Albert and Wilda Van Dusen Distinguished Professor of Orthopaedic Surgery

Professor of Chemical and Biomolecular Engineering

Professor of Materials Science and Engineering

Professor of Biomedical Engineering

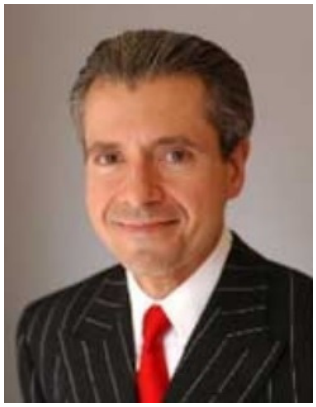
Our team consists of a talented group of leaders, program directors and staff who oversee and implement The Cato T. Laurencin Institute for Regenerative Engineering) initiatives and projects.
Members of leadership team have a wealth of experience, many of whom are NIH-funded and experts in their field, and reflect the diversity of clinical and translational research in the region.

INSTITUTE FACULTY

Lakshmi S. Nair, M.Phil., Ph.D.

James Grady, Dr.P.H.

Kevin Wai Hong Lo, Ph.D.



Gualberto Ruaño, MD, Ph.D.

Chia-Ling Kuo, Ph.D.

Yusuf Khan, Ph.D.

Howard A. Tennen, Ph.D.

Helen Wu, Ph.D.

INSTITUTE MISSION

The Cato T. Laurencin Institute for Regenerative Engineering fosters innovation in the field of regenerative engineering by strengthening established research endeavors and utilizing signature programs to enhance funding, research, and build the pipeline of students interested in careers in science and engineering.

Convergence is regarded as "The Third Revolution" in science, the coming together of insights from fields that were thought originally disparate. We look forward to making Connecticut a national leader in convergence and are committed to working with experts across different academic disciplines to foster new and exciting scientific advancements.

OUR FOUNDATION PRINCIPLES

INNOVATION

We believe that regenerative engineering offers solutions and hope for people who have ailments that today are beyond repair.

EDUCATION

We are committed to promoting the professional development of UConn faculty and students, embracing the diversity of human talent in our communities.

COLLABORATION

We are committed to collaboration, serving as a bridge across the wide range of disciplines dedicated to regenerative engineering research.

COMMUNITY ENGAGEMENT

We believe that interactive community engagement is fundamental to the fulfillment of its societal commitment to the resilience of human function.

AREAS OF RESEARCH FOCUS

The grand challenge to regenerate complex tissue and organ systems calls for a paradigm shift that requires a transdisciplinary approach. The field of regenerative engineering uses a convergence approach to create a regenerative toolbox to move beyond individual tissue repair to the regeneration of complex tissues and organ systems.

The Cato T. Laurencin Institute for Regenerative Engineering has defined regenerative engineering as a new field that convergences advanced materials sciences, stem cell sciences, physics, developmental biology, and clinical translation to foster scientific innovation.

THIS NEW FIELD INCLUDES THE FOLLOWING FIVE AREAS:

ADVANCED MATERIALS SCIENCES

The field of materials science has significantly advanced from the level of biodegradable polymers and ceramics to custom designed biomimetic inductive biomaterials with carefully modulated physical, mechanical, and biological properties to enhance the natural regenerative process of the body.

STEM CELL SCIENCES

The progress in the field of stem cells research represents great scope in regenerative engineering.

PHYSICS

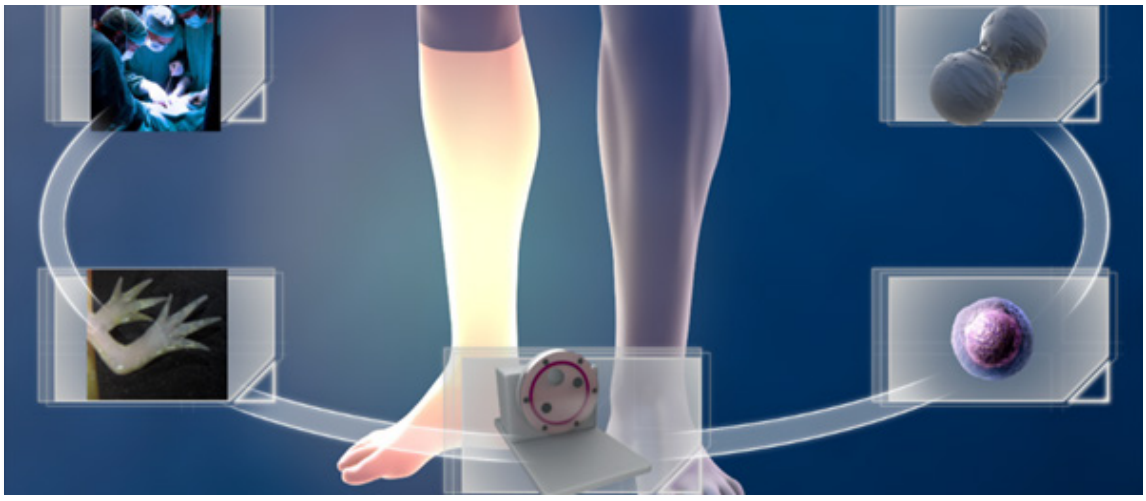
Physical forces play a subtle but crucial part in bio-fitness and resilience.

DEVELOPMENTAL BIOLOGY

Principles found in embryological development and in developmental morphogenesis will ultimately be critical for addressing grand challenges in regeneration.

CLINICAL TRANSLATION

The growing evidence of achieving better functional outcomes in larger animals using a biomaterial approach compared to smaller animals mirrors the translational potential of inductive biomaterials.



RECENT RESEARCH AND PUBLICATIONS

MICROSPHERE BASED NOVEL CALCIUM PEROXIDE/PLGA COMPOSITE MATRIX FOR BONE REGENERATION.

One of the main challenges hindering the clinical translation of bone tissue engineering scaffolds is the lack of establishment of functional vasculature. Insufficient vascularization and poor oxygen supply limit cell survival within the constructs resulting in poor osseointegration with the host tissue and eventually leading to inadequate bone regeneration. We engineered a composite matrix by incorporating calcium peroxide (CaO2) into poly(lactide-co-glycolide) (PLGA) microsphere-based matrices and sought to assess whether the delivery of the byproducts of CaO2 decomposition, namely O2, Ca2+, and H2O2 could enhance the regeneration of vascularized bone tissue. The in vitro cytocompatibility of the matrices and their ability to support osteogenic differentiation was confirmed using human adipose-derived stem cells. In vivo study was performed in a mouse critical-sized calvarial defect model to evaluate the capacity of these matrices in supporting vascularized bone regeneration. Results demonstrated that the presence of CaO2 increased cellularization and biological activity throughout the matrices.

The functional graphenic materials (FGMs) have demonstrated promising characteristics as a biomaterial in various scientific fields. Graphene-based bone composite polymers have demonstrated outstanding thermal, mechanical, and electrical characteristics and have been proposed as a novel generation of materials for regenerative engineering. Calcium phosphate graphene (CaPG) facilitates unprecedented regulation of GO functionalization endowing intrinsically osteoinductive properties to induce ectopic bone formation in vivo. Calcium peroxide (CaO2) hydrolytically decomposes into water, oxygen, H2O2, and calcium ions. Controlling the ions' burst release is essential to avoid cell death. Based on this information, our current research is aimed at fabrication of a novel matrix using CaO2/PLGA microspheres wrapped in GO and CaPG sheets that would provide a platform to control the burst release of oxygen and Ca2+ ions and would provide the necessary oxygen to combat hypoxia in the scaffold center to promote osteogenesis.

Recent Publications:

- Daneshmandi L, Holt BD, Arnold AM, Laurencin CT, Sydlik SA. Ultra-low binder content 3D printed calcium phosphate graphene scaffolds as resorbable, osteoinductive matrices that support bone formation in vivo. Sci Rep. 2022 Apr 28;12(1):6960. doi: 10.1038/s41598-022-10603-3. PMID: 35484292; PMCID: PMC9050648.
- Daneshmandi L, Barajaa M, Tahmasbi Rad A, Sydlik SA, Laurencin CT. GrapheneBased Biomaterials for Bone Regenerative Engineering: A Comprehensive Review of the Field and Considerations Regarding Biocompatibility and Biodegradation. Adv Healthc Mater. 2021 Jan;10(1):e2001414. doi: 10.1002/ adhm.202001414. Epub 2020 Oct 26. PMID: 33103370; PMCID: PMC8218309.
- Hosseini FS, Abedini AA, Chen F, Whitfield T, Ude CC, Laurencin CT. Oxygen-Generating Biomaterials for Translational Bone Regenerative Engineering. ACS Appl Mater Interfaces. 2023 Mar 29. doi: 10.1021/ acsami.2c20715. Epub ahead of print. PMID: 36988393.

POLYPHOSPHAZENES: ADVANCED BIOMATERIALS FOR REGENERATIVE ENGINEERING

An ideal synthetic scaffold for orthopaedic applications should be biocompatible, has desired mechanical properties, should degrade in a controlled fashion timed to match the rate of tissue integration and regeneration, has resorbable degradation products, be osteoconductive and osteoinductive, and allow for neovascularization. Thus, in the quest of designing advanced biomaterials for complex tissue regeneration, we have developed several novel Polyphosphazenes (PPHOS) and Polyphosphazene blends. Polyphosphazenes are linear polymers with alternating phosphorous and

nitrogen atoms in the backbone with two organic side groups. The nature and ratios of the side groups attached to the backbone can be dramatically altered providing synthetic flexibility while allowing polyphosphazenes with diverse properties including physical, chemical and biological. In our recent research, we developed dipeptide-based polyphosphazene and poly(lactide-co-glycolide) blend scaffolds (PPHOS-PLAGA) that have shown great potential in regenerative engineering. This generation of dipeptide-based PPHOS blends was designed to increase the miscibility between PPHOS and PLAGA by creating more H-bonding sites.

Our studies have demonstrated the feasibility of developing completely miscible blends with better physical, chemical, and mechanical properties than either PLAGA or the parent PPHOS. These blends can be developed with controlled degradation rates and near-neutral degradation products depending on the nature of polyphosphazene. We also demonstrated the feasibility of developing high-strength biodegradable blends compared to the parent polymers by designing polyphosphazenes that can exhibit unique molecular level interactions as well as by incorporating inflexible side groups. Some of the polymer blend scaffolds have a unique erosion profile, as it allows a gradual pore formation in situ during polymer erosion and resorption in vitro and in vivo, which accommodated the tissue ingrowth through the porous structures. This opens a new direction to developing bone scaffolds that can satisfy both the mechanical strength and the porosity needed for tissue engineering.

Recent Publications:

- Ogueri KS, Ogueri KS, Allcock HR, Laurencin CT. Polyphosphazene polymers: The next generation of biomaterials for regenerative engineering and therapeutic drug delivery. J Vac Sci Technol B Nanotechnol Microelectron. 2020 May;38(3):030801. doi: 10.1116/6.0000055. Epub 2020 Apr 9. PMID: 32309041; PMCID: PMC7156271.
- Ogueri KS, Ogueri KS, Ude CC, Allcock HR, Laurencin CT. Biomedical applications of polyphosphazenes. Med Devices Sens. 2020 Dec;3(6):e10113. doi: 10.1002/ mds3.10113. Epub 2020 Aug 2. PMID: 33889811; PMCID: PMC8059710.
- Ogueri KS, Ogueri KS, McClinton A, Kan HM, Ude CC, Barajaa MA, Allcock HR, Laurencin CT. In Vivo Evaluation of the Regenerative Capability of Glycylglycine Ethyl Ester-Substituted Polyphosphazene and Poly(lactic-coglycolic acid) Blends: A Rabbit Critical-Sized Bone Defect Model. ACS Biomater Sci Eng. 2021 Apr 12;7(4):1564-1572. doi: 10.1021/ acsbiomaterials.0c01650. Epub 2021 Apr 1. PMID: 33792283; PMCID: PMC8084594.
- Ogueri KS, Ogueri KS, Allcock HR, Laurencin CT. A Regenerative Polymer Blend Composed of Glycylglycine ethyl ester-substituted Polyphosphazene and Poly (lacticco-glycolic acid). ACS Appl Polym Mater. 2020 Mar 13;2(3):1169-1179. doi: 10.1021/ acsapm.9b00993. Epub 2020 Jan 8. PMID: 32699836; PMCID: PMC7375693.

SMALL MOLECULE-BASED COMPOUNDS IN BONE REGENERATIVE ENGINEERING

In clinical bone repair, the most widely used osteoinductive growth factor is recombinant human bone morphogenetic protein (rhBMP). However, disadvantages such as instability, low solubility, immunogenicity, and high production cost of these protein-based biofactors have hindered their widespread usage. As an alternative to rhBMP-2 treatments, osteoinductive small molecules are investigated. Of these targets, the cyclic adenosine 3',5'-monophosphate (cAMP) signaling pathway has been shown to promote osteogenic differentiation and mineralization of MSCs and osteoprogenitor cells through a PKA-pCREB dependent mechanism. Small molecule cAMP (cyclic Adenosine Monophosphate) analogues like Forskolin can retain the bioactivity of Forskolin through promoting osteogenic differentiation of BMSCs, while mitigating cytotoxic effects in vitro. When implanted in a rabbit radial criticalsized defect, the released Forskolin from the scaffolds also enhanced bone regeneration in vivo, while mitigating systemic off-target effects observed from elevated cAMP signaling. Thus, these small molecules have been proposed as novel biofactors for bone repair and regeneration.

Recent Publications:

- Awale GM, Barajaa MA, Kan HM, Seyedsalehi A, Nam GH, Hosseini FS, Ude CC, Schmidt TA, Lo KW, Laurencin CT. Regenerative engineering of long bones using the small molecule forskolin. Proc Natl Acad Sci U S A. 2023 May 30;120(22):e2219756120. doi: 10.1073/ pnas.2219756120. Epub 2023 May 22. PMID: 37216527; PMCID: PMC10235978.

BIOMIMETIC MATRIX FOR LIGAMENT REGENERATIVE ENGINEERING

The most accepted treatment for anterior cruciate ligament (ACL) reconstruction is the use of tendon autografts and allografts. However, donor site morbidity, potential disease transmission, and variable graft quality makes it a challenging procedure. In order to address these limitations, previously, we designed and developed of a cost-effective bench-top 3D braiding machine that fabricated scalable and tunable bioengineered ligaments. The machine created 3D braided scaffolds from biodegradable PLLA fibers. A rabbit ACL model was developed based on our past experiences in our laboratory. In designing our rabbit ACL reconstruction study, we wanted to assess the efficacy of the ACL Double Bundle Graft and enhance the biological fixation of the graft. To test whether by supplementing the ACL

matrix with growth factors (BMP2, FGF-2 and FGF 8) and bone marrow aspirate concentrate (BMAC), we could accelerate the rate of tissue regeneration using ACL matrix in vivo in a rabbit model. We also investigated whether strength retention of the bioengineered PLLA ACL matrix can be increased by incorporating non-biodegradable polyethylene terephthalate (PET) into the PLLA bioengineered ACL matrix to fabricate a "tiger graft." Our study showed that the tiger graft demonstrated superior osteointegration, making it an ideal bioengineered ACL matrix. The study also illustrated the beneficial effect of bioactive factors and PET incorporation have on ACL regeneration and shows a promising step toward the clinical translation of a functional bioengineered ACL matrix.

Recent Publications:

- Mengsteab PY, Otsuka T, McClinton A, Shemshaki NS, Shah S, Kan HM, Obopilwe E, Vella AT, Nair LS, Laurencin CT. Mechanically superior matrices promote osteointegration and regeneration of anterior cruciate ligament tissue in rabbits. Proc Natl Acad Sci U S A. 2020 Nov 17;117(46):28655-28666. doi: 10.1073/ pnas.2012347117. Epub 2020 Nov 3. PMID: 33144508; PMCID: PMC7682397.
- Yu X, Mengsteab PY, Narayanan G, Nair LS, Laurencin CT. Enhancing the Surface Properties of a Bioengineered Anterior Cruciate Ligament Matrix for Use with Point-of-Care Stem Cell Therapy. Engineering (Beijing). 2021 Feb;7(2):153161. Epub 2020 May 7. PMID: 34136308; PMCID: PMC8205060.

REGENERATION OF ROTATOR CUFF TEARS (RCTS) BY ENHANCING TENDON REGENERATION VIA REGENERATIVE ENGINEERING APPROACH

In adults, the third most common musculoskeletal complaint is shoulder pain. Shoulder stability and movement are controlled by a group of muscles whose tendons are collectively called the rotator cuff (RC). A large percentage of the shoulder pain that practitioners encounter consists of RC, thereby make RC repair surgeries one of the most widely performed musculoskeletal procedures. Rotator cuff tendon tear not only leads to pain, but can also cause tendon thinning and retraction, fatty infiltration as well as muscle atrophy, resulting in subsequent loss in shoulder stability and function. One of the challenges with rotator cuff repair is the high re-tear rate after surgery. Several factors such as patient age, tear size, fatty infiltration of muscle, tissue quality, and repair strategies influence the rate of re-tear.

We use electroconductive nanostructured scaffold to significantly reduce fatty infiltration/ fat expansion of muscles upon sub-acute rotator cuff tear. The cellular physical microenvironments can be mimicked by the hybrid electrospun fibers and electroconductive patch to generate a more robust and functional muscle construct for muscle regeneration. Recently we developed an

electroconductive matrix by incorporating graphene nanoplatelets (GnPs) into aligned poly (l-lactic acid) (PLLA) nanofibers (GnPs) into aligned poly (l-lactic acid) (PLLA) nanofibers with the potential to reverse muscle degenerative changes in vivo following massive RCT. GnP matrix to reverse the muscle atrophy, fat accumulation, and fibrosis in both supraspinatus and infraspinatus muscles at 24 and 32 weeks after the chronic MRCTs of the rat shoulder. The pathological evaluation of internal organs confirmed the long-term biocompatibility of the GnP matrix. We also showed that reversing the muscle degenerative changes improved the tendon morphology and tensile properties compared with the current surgical techniques. The long-term biocompatibility and the potential of the GnP matrix to treat muscle degeneration are promising results toward its clinical translation for MRCTs healing. This study represent a new treatment paradigm for massive RC tendon tears.

Recent Publications:

- Nikoo Saveh Shemshaki, Ho-Man Kan, Mohammed A. Barajaa, Amir Lebaschi, Takayoshi Otsuka, Neha Mishra, Lakshmi S. Nair, and Cato T. Laurencin. Efficacy of a Novel Electroconductive Matrix To Treat Muscle Atrophy and Fat Accumulation in Chronic Massive Rotator Cuff Tears of the Shoulder. ACS Biomaterials Science & Engineering 2023 9 (10), 5782-5792 DOI: 10.1021/acsbiomaterials.3c00585
- Saveh Shemshaki N, Kan HM, Barajaa M, Otsuka T, Lebaschi A, Mishra N, Nair LS, Laurencin CT. Muscle degeneration in chronic massive rotator cuff tears of the shoulder: Addressing the real problem using a graphene matrix. Proc Natl Acad Sci U S A. 2022 Aug 16;119(33):e2208106119. doi: 10.1073/ pnas.2208106119. Epub 2022 Aug 8. PMID: 35939692; PMCID: PMC9388153.
- Tang X, Saveh-Shemshaki N, Kan HM, Khan Y, Laurencin CT. Biomimetic electroconductive nanofibrous matrices for skeletal muscle regenerative engineering. Regen Eng Transl Med. 2020 Jun;6(2):228-237. doi: 10.1007/s40883019-00136-z. Epub 2019 Dec 3. PMID: 33426269; PMCID: PMC7793553.

BIOMIMETIC APPROACHES TO STRUCTURAL AND FUNCTIONAL MUSCLE REGENERATION USING PRECLINICAL VOLUMETRIC MUSCLE LOSS MODELS

Volumetric muscle loss (VML) is a common musculoskeletal condition characterized by a degree of tissue loss that exceeds the endogenous regenerative capacity of muscle, resulting in permanent functional deficits. Currently, no effective therapies can fully recover the functional impairment in VML patients. Specifically, hydrogel-based engineered skeletal muscle constructs (SMCs) hold great promise as regenerative tools for VML treatment due to the viscoelastic and biomimetic nature of hydrogels. Despite rapid progress, however, current hydrogel-based SMCs display limited regenerative capacity. In addition, scaling up the size of hydrogel-based SMCs to the human-scale (cm3) represents a major challenge that has not been met to date. In our preliminary studies, we developed a hydrogel directly derived from decellularized porcine skeletal muscle extracellular matrix (smECM) to provide a tissue-specific microenvironmental niche for enhanced muscle precursor cell growth and differentiation. This hydrogel served as a building block for the engineering of SMCs. We also developed a novel multi-module system (MMS) using a tethering method that readily (within ~ 30 minutes) enabled the generation of large-scale (mm3-cm3) hydrogel-based SMCs. The resultant constructs were aligned, multi-layered, and contained well-defined myo-bundle structures with conductivity and large pore volumes (microchannels) between the myobundles to facilitate the diffusion of oxygen and nutrients. Producing the SMCs within the short timeframe mentioned above prevented hypoxia generation and maintained the viability of the encapsulated cell during the fabrication process. Further, successful transplantation of these large-scale constructs into rodent tibialis anterior VML model in vivo by itself or laden with immortalized human muscle progenitor cells (hMPCs) could result in rapid restoration of muscle mass, structure, and function 8 weeks post-surgery comparable to sham. As a next step toward translation, we want to use a translatable source like induced pluripotent stem cells-derived muscle precursor cells and further translate to human scale. A scalable larger hydrogel muscle construct in a larger animal model would be beneficial.

Recent Publications:

- Barajaa, M.A., Ghosh, D. & Laurencin, C.T. Decellularized Extracellular Matrix-Derived Hydrogels: a Powerful Class of Biomaterials for Skeletal Muscle Regenerative Engineering Applications. Regen. Eng. Transl. Med.(2023). https://doi.org/10.1007/s40883-023-00328-8
- Barajaa, M.A., Nair, L.S. & Laurencin, C.T. Bioinspired Scaffold Designs for Regenerating Musculoskeletal Tissue Interfaces. Regen. Eng. Transl. Med. 6, 451–483 (2020). https://doi.org/10.1007/s40883-019-00132-3

SYNTHETIC ARTIFICIAL STEM CELLS

The stem cell secretome is one of the ways that stem cells are able to provide a therapeutic effect. We have used the concept of the secretome to make biodegradable polymeric microspheres that encapsulate key growth factors important to the therapeutic effect of the stem cell secretome. The spheres are the same size as that of a cell and the factors are completely synthetic, which allow us the flexibility to modify and design our synthetic secretome. We have designed SASC as an injectable therapy with controlled release of the formulated secretome. In vitro, SASC showed significant antiinflammatory and chondroprotective effects as seen by the up-regulation of SOX9 and reduction of nitric oxide, ADAMTS5, and PRG4 genes compared to ADSCs. In vivo, treatment with SASC and ADSCs significantly attenuated cartilage degeneration and improved the biomechanical properties of the articular cartilage in comparison to OA control.This SASC system demonstrates the feasibility of developing a completely synthetic, tailorable stem cell secretome which reinforces the possibility of developing a new therapeutic strategy that provides better control over targeted tissue engineering applications.

Recent publications:

- Shah S, Esdaille CJ, Bhattacharjee M, Kan HM, Laurencin CT. The synthetic artificial stem cell (SASC): Shifting the paradigm of cell therapy in regenerative engineering. Proc Natl Acad Sci U S A. 2022 Jan 11;119(2):e2116865118. doi:

  10.1073/pnas.2116865118. PMID: 34987101; PMCID: PMC8764679.
- Shah, S., Bhattacharjee, M., Kan, HM. et al. A Single Administration of Synthetic Artificial Stem Cells (SASC) Attenuates Osteoarthritis Progression. Regen. Eng. Transl. Med. (2023). https://doi.org/10.1007/s40883-023-00307-z

AMNION BASED INJECTABLE HYDROGEL AS A CELL DELIVERY CARRIER

Osteoarthritis (OA) is a chronic, painful diseases representing a major health issue with high economic burden. Current treatment strategies have failed to treat the pathogenesis of the disease or reversing the process of OA. We developed novel cell therapeutic approach with chondroprotective and immunomodulatory properties to prevent/delay OA progression. We developed injectable amnion hydrogel as a delivery system for adipose derived stem cell (ADSC) to treat OA. The unique advantages of both AM and ADSC showed a synergistic suppression of inflammation and cartilage degradation in rat osteoarthritic model thus presenting the potential to open new therapeutic avenues for OA. We investigated the potential of amnion hydrogel to maintain ADSC functions, the synergistic effect of AM with ADSC in preventing the catabolic responses of inflammation in stimulated chondrocytes.

Our studies have shown the feasibility of developing an AM-based injectable hydrogel and its efficacy of delivering and retaining ADSCs intra-articularly, and supporting cell viability, proliferation, and stemness. Our studies also showed the ability of AM hydrogel-ADSCs combinations to provide an immunomodulative and chondroprotective environment in vivo, demonstrating the unique advantages of using AM injectable hydrogels for cell therapy.

Additionally, we are exploring novel ways to use amnion membrane in knee osteoarthritis.

Recent Publications:

- Bhattacharjee M, Ivirico JLE, Kan HM, Bordett R, Pandey R, Otsuka T, Nair LS, Laurencin CT. Preparation and characterization of amnion hydrogel and its synergistic effect with adipose derived stem cells towards IL1β activated chondrocytes. Sci Rep. 2020 Oct 30;10(1):18751. doi: 10.1038/ s41598-020-75921-w. PMID: 33127964; PMCID: PMC7603317.
- Bhattacharjee M, Escobar Ivirico JL, Kan HM, Shah S, Otsuka T, Bordett R, Barajaa M, Nagiah N, Pandey R, Nair LS, Laurencin CT. Injectable amnion hydrogel-mediated delivery of adipose-derived stem cells for osteoarthritis treatment. Proc Natl Acad Sci U S A. 2022 Jan 25;119(4):e2120968119. doi: 10.1073/pnas.2120968119. PMID: 35046053; PMCID: PMC8794776.

BIOMIMETIC CHELATION THERAPY FOR FAILING JOINT IMPLANTS

Cobalt-containing alloys are useful for orthopedic applications due to their low volumetric wear rates, corrosion resistance, high mechanical strength, hardness, and fatigue resistance. Unfortunately, these prosthetics release significant levels of cobalt ions, which was only discovered after their widespread implantation into patients requiring hip replacements. These cobalt ions can result in local toxic effects-including peri-implant toxicity, aseptic loosening, and pseudotumor, as well as systemic toxic effects, including neurological, cardiovascular, and endocrine disorders. Failing metal-on-metal (MoM) implants usually necessitate painful, risky, and costly revision surgeries. To treat metallosis arising from failing MoM implants, a synovial fluid-mimicking chelator was designed to remove these metal ions. Hyaluronic acid (HA), the major chemical component of synovial fluid, was functionalized with British anti-Lewisite (BAL) to create a novel chelator (BAL-HA). Our recent results demonstrated that demonstrate that BAL-HA chelator system is biocompatible and capable of capturing significant amounts of cobalt ions from the hip joint within 30 min, with no risk of kidney failure. This new chelation therapy has the potential to mitigate cobalt toxicity from failing MoM implants through non-invasive injections into the joint.

Recent Publications

- Chinedu C. Ude, Stephen J. Schmidt, Samuel Laurencin, Shiv Shah, Jayson Esdaille, Ho-Man Kan, Brian D. Holt, Anne M. Arnold, Michelle E. Wolf, Lakshmi S. Nair, Stefanie A. Sydlik, Cato T. Laurencin. Hyaluronic acid – British anti-Lewisite (BAL-HA) as a safer chelation therapy for the treatment of arthroplasty-related metallosis. Proc Natl Acad Sci U S A. 2023 (in press)
- Chinedu C. Ude, Godwin K. Dzidotor, Kamsiyochukwu Iloeje, Lakshmi S. Nair, and Cato T. Laurencin. Corrosion of Metals During Use in Arthroplasty. ACS Applied Bio Materials 2023 6 (6), 2029-2042. DOI: 10.1021/acsabm.2c01082

GRID CELL RESEARCH

Mammalian regeneration capability is limited and inability to evoke epimorphic regeneration whereas complete and functional limb regeneration has been reported in salamanders. Ushing developmental cues, we have identified a unique subpopulation of heparan sulfate proteoglycan (HSPG) rich cells we termed “GRID (Groups that are Regenerative, Interspersed and Dendritic) cells” in axolotl limb, which may play a large role in limb regeneration. Most importantly we have identified “GRID cells” in neonatal mice, implying that mammals have a latent capability of complex tissue regeneration. Understanding the role of “GRID cells” in mammals may enable us to engineer a biomimetic GRID for enhanced regenerative therapies.

Recent Publications:

- Otsuka, T., Phan, A.Q., Laurencin, C.T. et al. Identification of Heparan-Sulfate Rich Cells in the Loose Connective Tissues of the Axolotl (Ambystoma mexicanum) with the Potential to Mediate Growth Factor Signaling during Regeneration. Regen. Eng. Transl. Med. 6, 7–17 (2020). https://doi.org/10.1007/s40883-019-00140-3
- Otsuka, T., Kan, HM. & Laurencin, C.T. Regenerative Engineering Approaches to Scar-Free Skin Regeneration. Regen. Eng. Transl. Med.
  8, 225–247 (2022). https://doi.org/10.1007/s40883-021-00229-8

Recent Doctoral Dissertation

1. Development of a Synthetic Artificial Stem Cell System as a Regenerative Therapy for Osteoarthritis (2022)
   Link: http://hdl.handle.net/11134/20002:860706854
2. Harnessing Cyclic AMP Signaling for Bone Regenerative Engineering (2022) Link: http://hdl.handle.net/11134/20002:860706969
3. Electroconductive Nanofiber Matrices to Treat Muscle Atrophy and Fat Accumulation in Chronic Massive Fullthickness Rotator Cuff Tears of the Shoulder (2022) Link: http://hdl.handle.net/11134/20002:860670836

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