OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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NAME: **Clinton Rubin, Ph.D.**

eRA COMMONS USER NAME (credential, e.g., agency login): CRUBIN

POSITION TITLE: SUNY Distinguished Professor, Department of Biomedical Engineering, and Director, Center for Biotechnology, Stony Brook University

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	1977	Biology
University of Bristol, Bristol, U.K.	Ph.D.	1983	Anatomy
Tufts Univ School of Medicine, Boston, MA	Res. Fellow	1983-1984	Cell Biology
Brigham & Women's Hospital, Boston, MA	Res. Fellow	1984-1985	Biomechanics

A. Personal Statement

My work is targeted towards understanding how mechanical factors influence the growth, healing, and homeostasis of musculoskeletal tissues such as bone, cartilage, tendon, ligament and muscle, as well as how they might suppress the formation of adipose tissue (fat). More specifically, this work focuses on how biomechanical stimuli mediate morphologic, cellular and molecular responses through the control of mesenchymal stem cell differentiation and proliferation. The clinical significance of this work is applicable to the inhibition and reversal of osteopenia, the promotion of bony ingrowth into implants, the acceleration of fracture healing, and the suppression/reversal of obesity and diabetes. I have been an investigator on a range of preclinical and clinical studies evaluating the ability of electric fields, ultrasound and low magnitude mechanical signals (LMMS) or low intensity vibration (LIV) to influence the quantity and quality of bone, muscle and postural stability, as well as the status of bone marrow derived stem cells. Ultimately, I hope our research represents a critical step towards the development of non-drug means for the treatment of disorders such as osteoporosis, diabetes and obesity. I hold over 30 patents in the area of wound repair, stem cell regulation, and treatment of bone disease, and am a founder of Exogen, Juvent, Marodyne Medical and Lahara Bio, each medical device companies which use physical signals to regulate biologic processes with focus on treating human disease.

In this specific proposal, I hope to leverage resources from the Center for Biotechnology (CfB) to accelerate the translation of basic and applied biomedical science into next generation therapeutics, diagnostics and medical devices. Through the CfB, we foster connections and partnerships with faculty to existing life sciences companies, as well as provide de-risking funding to promising, early-stage technologies. CfB will provide business support, including intellectual property analysis, market analysis, financial projections, and regulatory guidance for LINCATS research and technology development projects. Other CfB programs relevant to the LINCATS include SBIR/STTR workshops with 1:1 consulting, Bio-Strategy Sessions and the Innovation Boot Camp/Pre-Seed Workshop. These programs will introduce LINCATS investigators to potential investors and identify critical issues, highlight potential weaknesses, and provide actionable guidance. Finally, the CfB's Advanced Graduate Certificate in Life Sciences Innovation and Entrepreneurship will be open to CTSA participants, including medical and bio-centric grad students, interns, residents and faculty. The goal of this program is to introduce students to the 'real' life of bioscience industry, *with the majority of the curriculum taught by people from the life sciences industry.*

My efforts to translate our lab's basic science into medicine include:

1. **Bone Anabolism by LIV**: Rubin, C., Turner, S. Bain, S., Mallinckrodt, C. & McLeod, K. (2001) Anabolism: Low mechanical signals strengthen long bones. Nature 412:603-604.
2. **Use of Physical Signals as a Non-Drug Intervention for Osteoporosis**: Rubin, C.T., Recker, R., Raab, D., Ryaby, J., McCabe, J. & McLeod, K.J. (2004) Prevention of Post-Menopausal Bone Loss by a Low Magnitude, High Frequency Mechanical Stimuli; A Clinical Trial Assessing Compliance, Efficacy and Safety. J. Bone & Mineral Research. 19:343-351
3. **Ultrasound as a means of Accelerating Fracture Healing**: Rubin, C., Bolander, M., Ryaby, J. & Hadjiargyrou, M. (2001) The use of low intensity ultrasound to accelerate the healing of fractures. J. Bone & Jt. Surg. 83:259-70.
4. **Identifying Electric Field Parameters that Stimulate Bone Formation**: Rubin, C.T., McLeod, K.J., and Lanyon, L.E. (1989) Prevention of osteoporosis by pulsed electro-magnetic fields. J. Bone and Joint Surgery, 71A (3):411 418.

Ongoing Research Support

New York State Science and Technology Foundation (PI: C. Rubin) 07/01/1997 – 06/30/2025
(NYSTAR)
Title: **Center for Advanced Technology in Medical Biotechnology**
This funding is used to develop the biotechnology sector in New York State, and link academic centers to the biosciences industry. Ten-year re-designation just approved by NYSTAR.

Biomedical Advanced Research and Development Authority (BARDA) 06/01/2018 – 05/30/2023
HHS: (PI: C. Rubin)
Title: **Translating Biomedical Science into Health Security Innovations in New York Region.**
Funding used to identify early stage translation research in sepsis and infection.

Completed Research Support *(most recent 3 years)*

U.S. Economic Development Administration (PI: C. Rubin) 12/01/2016 – 12/31/2020
Title: **I6: Mentorship as a Driver of Entrepreneurship, Venture Creation, and SBIR/STTR Success in the Long Island, NY Region.**
Funding used to establish a training and mentor program in SBIR/STTR applications

BC150678 (PI: T. Guise) 02/01/2016 – 01/31/2020
Department of Defense / Breast Cancer Research Program (BCRP) Breakthrough Award
Title: **Effect of Low-Magnitude Mechanical Signals on Breast Cancer Bone Metastases.**
Support used to establish non-drug means of protecting the musculoskeletal system in a mouse model of breast cancer and consequences of aromatase treatment regimens.
Role: Co-Investigator

U01 HL127522 (PI: C. Rubin) 04/01/2015 – 08/31/2019
NIH-NHLBI
Title: **Establishing a Long Island Bioscience Hub**
A four-tiered approach to commercializing bio-based discoveries, using the foundation of Stony Brook University (public), Cold Spring Harbor Laboratory (private), Northwell Hospital (private) and Brookhaven National Laboratory (federal) as a source of technology capital.

B. Positions, Scientific Appointments, and Honors

Professional Experience:

2005- SUNY Distinguished Professor, State University of New York
2000-17 Professor and Chair (*founding*), Department of Biomedical Engineering

1997- Visiting Scientist, Brookhaven National Laboratory, Upton, NY
1997- Director, Center for Advanced Technology in Medical Biotechnology, New York State Science, Technology and Academic Research (NYSTAR)
1995-00 Director, Program in Biomedical Engineering, S.U.N.Y., Stony Brook.
1992- Professor of Orth., Anatomy, Biophysics & Genetics. S.U.N.Y., Stony Brook.
1987- Director, Musculo-Skeletal Research Laboratory, S.U.N.Y., Stony Brook.
1987-92 Assoc. Prof. of Orthopaedics, Anatomy, & Mechanical Eng, S.U.N.Y., Stony Brook.
1984-87 Assistant Prof of Anatomy & Cell Biol., Tufts Univ. School Med., Boston, Mass.

Selected Honors:

2020 Founder and Chief Scientific Officer, Lahara Bio, Inc.
2019 Fellow, Biomedical Engineering Society
2018 Fellow, American Society of Bone & Mineral Research
2017 Fellow, National Academy of Inventors
2016 Inductee, Long Island Technology Hall of Fame
2014 Fellow, American Association for Advancement of Science.
2012 Outstanding Clinical Investigator Award, Biomedical Eng. Soc. & Soc. Phys. Bio. Med.
2005 SUNY Distinguished Prof., highest rank in SUNY, as conferred by SUNY Trustees.
2009 Founder, Marodyne Medical, Inc.
2003 Fellow, American Institute for Medical and Biological Engineering.
2003 Elizabeth Lanier Kappa Delta Award, American Acad. Orthopaedic Surgeons.
2002 Calgary Award in Orthopaedic Biomechanics, IV World Cong. Biomechanics.
2001 Development Award, The Whitaker Foundation.
2001 NYSTAR Distinguished Prof of 2001, NY Science Tech. & Academic Research.
2000 Founder, Juvent, Inc.
2000 Giovanni Borelli Award, American Society of Biomechanics.
1997-08 Editorial Board, Journal of Bone & Mineral Research.
1997-06 The Whitaker Foundation, Fellowship Advisory Committee.
1998-04 Board of Directors, New York Biotechnology Association.
1996 Fuller Albright Award, American Society of Bone and Mineral Research.
1994 Founder, Exogen, Inc.
1993 John Charnley Award, The Hip Society, Amer. Acad. Orthop. Surgeons.
1990 Kappa Delta Award for Outstanding Research, Bioelectric Repair and Growth Soc.
1989-94 Comm. Space Biology & Medicine, Space Studies Board, National Res. Council.
1987-92 Presidential Young Investigator Award, National Science Foundation.
1986 European Society of Biomechanics Award for Excellence in Research.
1985 Kappa Delta Society Young Investigator Award, Amer. Academy Orthop. Surgeons.

C. Contributions to Science

1. Identifying specific mechanical parameters that drive adaptation in bone: We focus on the use of *in vivo* models of bone adaptation to identify specific mechanical signals which drive the 'form follows function' paradigm in the skeleton. While disuse in these models would result in a marked loss of bone, externally applied loading regimens, physiological in strain magnitude, could lead to significant increases in cross-sectional bone area, as dependent on changes in the magnitude and distribution generated within the bone tissue. The loading regimen must be dynamic (time-varying) in nature; static loads do not influence bone morphology. Perhaps most importantly, this work indicates the full osteogenic potential of a large amplitude (>2000 microstrain) regimen is realized following only an extremely short (< 1 min) exposure to this stimulus, suggesting that brief exposure to a specific signal can set off subsequent adaptive events.

a. Rubin, C.T. & Lanyon, L.E. (1984) Regulation of bone formation by applied dynamic loads. *J. Bone and Joint Surgery 66A:397-402.* PMID: 6699056

b. Pagnotti, G., Styner, M., Uzer, G., Patel, V. Ness, K., Guise, T., Rubin, J & Rubin, C.T. (2019) Combating osteoporosis and obesity with exercise: Harnessing cell mechanosensitivity. *Nature Reviews Endocrinology. 15:339-355* PMID: 30814687, PMCID: PMC6520125.
c. Fritton, S.P., McLeod, K.J., Rubin, C.T. (2000) Quantifying the strain history of bone: spatial uniformity and self-similarity of low magnitude strains. *J. Biomech. 33:317-326.* PMID: 10673115
d. Ozcivici, E., Luu, Y-K, Adler, B., Qin, Y-X, Rubin, J., Judex, S & Rubin, C.T. (2010) Mechanical Signals as Anabolic Agents in Bone. *Nature Reviews Rheumatology. 6:50-59 PMCID:* PMC3743048

2. Low magnitude mechanical signals are anabolic to the musculoskeletal system: Moving away from peak strain magnitudes, this work demonstrated that extremely small magnitude mechanical signals (<10 microstrain), if introduced at a relatively high frequency (>10Hz), were strongly anabolic to the skeleton. This work pointed towards the spectral content of muscle contraction, rather than peak impacts, as important signals in the achieving and retaining bone quality and quantity, even under conditions challenged by disuse or disease.

a. Rubin, C.T., Xu, G. & Judex, S. (2001) The anabolic activity of bone tissue, suppressed by disuse is normalized by brief exposure to extremely low magnitude mechanical stimuli. *The FASEB Journal. 15: 2225-2229* PMID: 11641249
b. Pagnotti, G., Thomson, W., Guise, T. & Rubin, C. (2021) Suppression of Cancer-Associated Bone Loss Through Dynamic Mechanical Loading. Bone 150:e-pub ahead of print. PMCID: 33971314
c. Goodship, A., Lawes, T. & Rubin, C. (2009) Low magnitude high frequency mechanical signals accelerate and augment endochondral bone repair. *J. Orth. Res. 27:922-930*
d. Pagnotti, G., Chan, M.E., Adler, B., Rubin, J., Shroyer, K. & Rubin, C.T. (2016) Low Intensity Mechanical Signals Mitigate Tumor Progression and Protect Bone Quantity and Quality in a Murine Model of Myeloma. *Bone* 90:69-79 PMCID: PMC4970889

3. Treatment of musculoskeletal disorders with non-invasive mechanical stimulation: Translating the musculoskeletal system's sensitivity to mechanical signals to the human, a series of double-blind, prospective clinical trials were performed to determine if low intensity vibration could serve as a non-drug means of stimulating growth of bone and muscle in those with poor bone quality.

a. Ward, K., Alsop, C., Brown, S., Caulton, J., Rubin, C., Adams, J. & Mughal, M. (2004) Low magnitude mechanical loading is osteogenic in children with disabling conditions. *J. Bone & Mineral Research: 19:360-369* PMID: 15040823
b. Gilsanz, V., Wren, T., Sanchez, M., Dorey, F., Judex, S. & Rubin, C.T. (2006) Low level, high frequency mechanical signals enhance musculoskeletal development of young women with low bone density. *J. Bone & Mineral Research 21:1464-1474* PMID: 16939405
c. Kiel, D.P., Hannan, M.T., Barton, B., Bouxsein, M.L., Sisson, E., Lang, T., Allaire, B., Dewkett, D., Carroll, D., Magaziner, J., Shane, E., Leary, E., Zimmerman, S. & Rubin, C.T., (2015). Low Magnitude Mechanical Stimulation to Improve Bone Density in Persons of Advanced Age: A Randomized, Placebo-Controlled Trial. *J. Bone & Mineral Research 30:1319-1328* PMCID*:* PMC4834704
d. Leonard, M., Shults, J., Long, J., Baldassanao, R., Brown, K., Hommel, K., Zemel, B., Mahboubi, S., Whitehead, K., Herskovitz, R., Lee, D. & Rubin, C.T. (2016). Effect of Low Magnitude Mechanical Stimulation on Bone Density and Structure in Pediatric Crohn Disease: A Randomized Placebo-Controlled Trial*. J. Bone & Mineral Research; 31:1177-1188* PMCID: PMC4891301

4. Mechanical biasing of stem cell differentiation to suppress adipogenesis: Honing in on the sensitivity of the musculoskeletal system to these low level mechanical signals, we have now demonstrated that these stimuli markedly bias mesenchymal stem cell differentiation towards osteoblastogenesis (bone formation), and away from adipogenesis (fat formation). Mechanosensitivity of the marrow cell population extends to hematopoietic stem cells, with our work now investigating the influence of these signals as a non-drug means of controlling obesity and T2 diabetes.

a. Luu, Y.K., Capilla, E., Pessin, J., Rosen, C., Gilsanz, V., Judex, S. & Rubin, C. (2009) Mechanical stimulation of mesenchymal stem cell proliferation and differentiation promotes osteogenesis while preventing dietary-induced obesity. *J. Bone & Min. Res. 24:50-61* PMCID*:* PMC2689082

b. Chan, M.E., Adler, B.J., Green, D.E. & Rubin, C.T. (2012) Bone Structure and B-Cell Populations, Crippled by Obesity, are Partially Rescued by Brief Daily Exposure to Low Magnitude Mechanical Signals *J. FASEB 26:4855-63* PMCID*:* PMC3509057
c. Adler, B., Kaushansky, K. & Rubin, C.T., (2014) Obesity Driven Disruption of Hematopoiesis and the Bone Marrow Niche. *Nature Reviews Endocrinology 10:737-748* PMID: 25311396
d. Frechette, D.M., Krishnamoorthy, D., Adler, B., Chan, M.E. & Rubin, C.T. (2015 Diminished satellite cells and elevated adipogenic gene expression in muscle as caused by ovariectomy are averted by low-magnitude mechanical signals. *J. Applied Physiology 119:27-36* PMCID*:* PMC4491530

5. Identifying molecular and physical pathways which foster mechanotransduction: This work, done in a long-term collaboration with Janet Rubin, is targeted towards determining key signal transduction pathways, as well as features of cell morphology, that allow the cell to perceive and respond to mechanical signals. By focusing on the molecular mechanisms responsible for mechanosensitivity, we are working towards a better understanding by which extremely low level signals can influence phenotype.

a. Sen, B., Styner, M., Xie, Z., Case, N., Rubin, C.T. & Rubin, J. (2010) Mechanical loading regulates NFATC1 and & β-catenin signaling through a GSK3 & β−control node*. J. Biol. Chem 284:34607-34617.* PMCID*:* PMC2787323
b. Sen, B., Guilluy, C., Xie, Z., Case, N., Syner, M., Thomas, J., Oguz, I., Rubin, C.T., Burridge, K. & Rubin, J. (2012) Mechanically induced focal adhesion assembly amplifies anti-adipogenic pathways in mesenchymal stem cells. *Stem Cells 29:1829-36* PMCID*:* PMC3588570
c. Yi, X., Wright, L., Pagnotti, G., Uzer, G., Powell, K., Wallace, J., Sankar, U., Mohammad, K., Rubin, C.T., Guise, T., Thompson, W. (2020) Mechanical Suppression of Breast Cancer Cell Invasion and Paracrine Signaling to Osteoclasts Requires Nucleo-Cytoskeletal Connectivity. *Bone Res **8,** 40-52* PMCID: PMC7673025
d. Uzer, G., Thompson, W.R., Sen, B., Xie, Z., Yen, S., Miller, S., Bas, G., Styner, M, Rubin, C.T., Judex, S., Burridge, K & Rubin, J. (2015) Cell mechanosensitivity to extremely low magnitude signals is enabled by a LINCed nucleus. *Stem Cells 33:2063-2076* PMCID*:* PMC4458857