University of Virginia
Orthopaedic Surgery

New World Biology of Flexor Tendon Repairs

Tendon Tissue Engineering

Bobby Chhabra, MD

Lillian T. Pratt Distinguished Professor

Chair, Department of Orthopaedic Surgery

University of Virginia Health System

Disclosures

- Speaker, Miller Orthopaedic Review Course
- Royalties, W. B. Saunders & Elsevier Publishing
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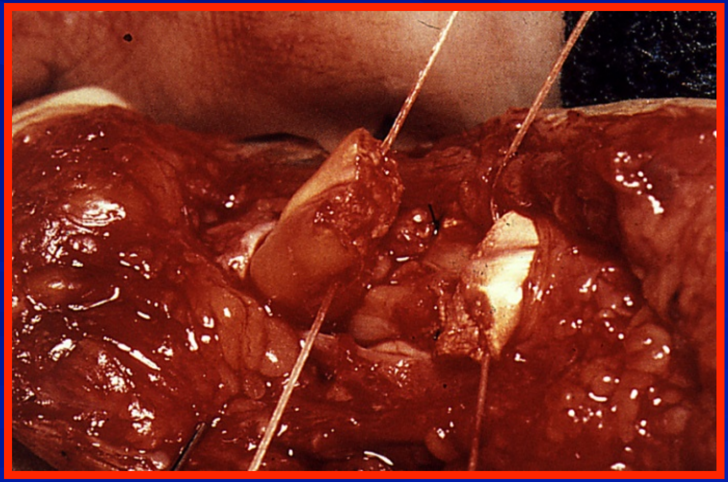
No conflicts with this presentation

Tendon Healing

- Tendon repair outcomes are variable
  - Re-rupture
  - Restrictive adhesions and scar
  - Thinner collagen fibril bundles
  - Reduced mechanical properties

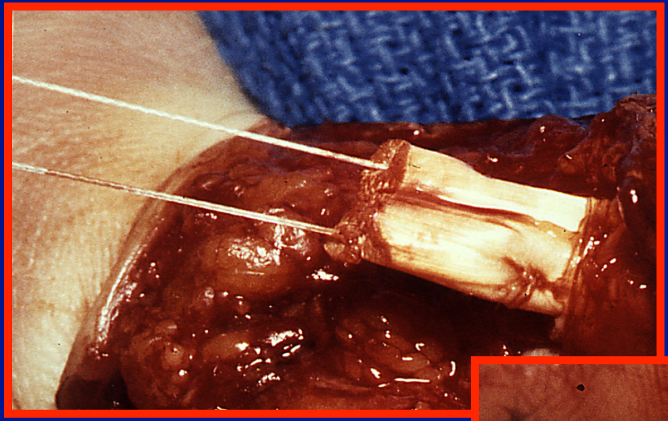
  (Morberg, et al. Scand J Med Sci Sports 1997)
  (Lilly, et al. JAAOS 2006)

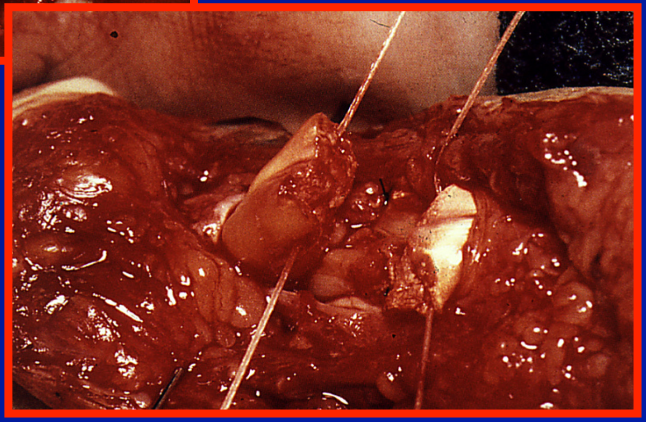


Repair Phase	Activity	Growth Factor
Inflammatory	Stimulates the recruitment of fibroblasts and inflammatory cells to the injury site	IGF-I
	Regulation of cell migration	TGF-β
	Expression of other growth factors (e.g. IGF-1)	PDGF
	Induction of angiogenesis	VEGF, bFGF
Proliferative	Cellular proliferation (DNA synthesis)	IGF-I & PDGF, TGF-β, bFGF, GDF-5, -6, & -7
	Stimulates synthesis of collagen and ECM components	IGF-I & PDGF, bFGF
	Stimulates cell-matrix interactions	TGF-β, bFGF
	Collagen Type III synthesis	TGF-β, GDF-5, -6, & -7
Remodeling	ECM remodeling	IGF-I
	Termination of cell proliferation	TGF-β
	Collagen Type I synthesis	TGF-β, GDF-5, -6, & -7

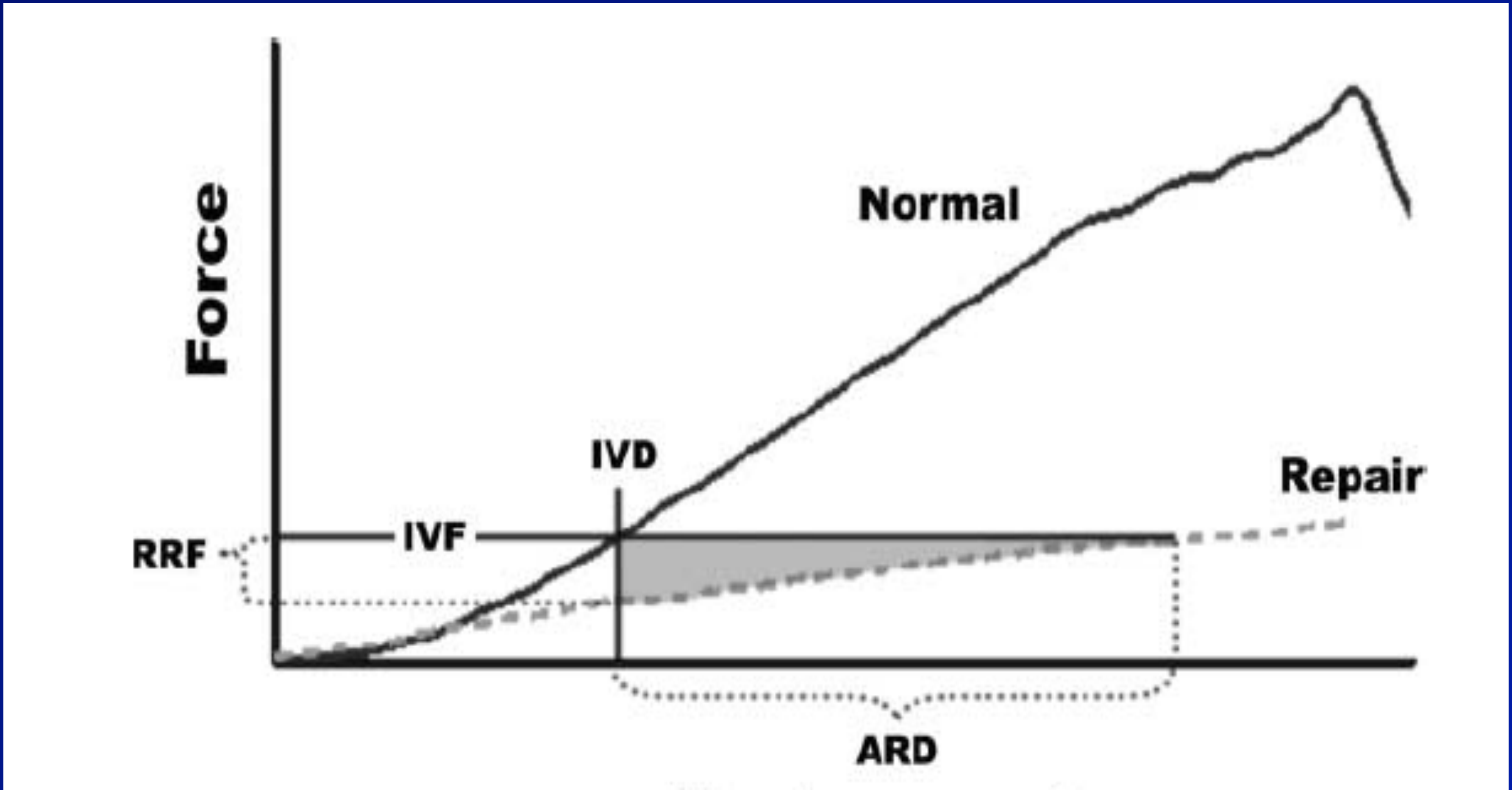
Normal Tendon Healing

- Haphazard w/ "scar" formation
- Always inferior to pre-injured tendon





Comparison of Normal and Repaired Tendon

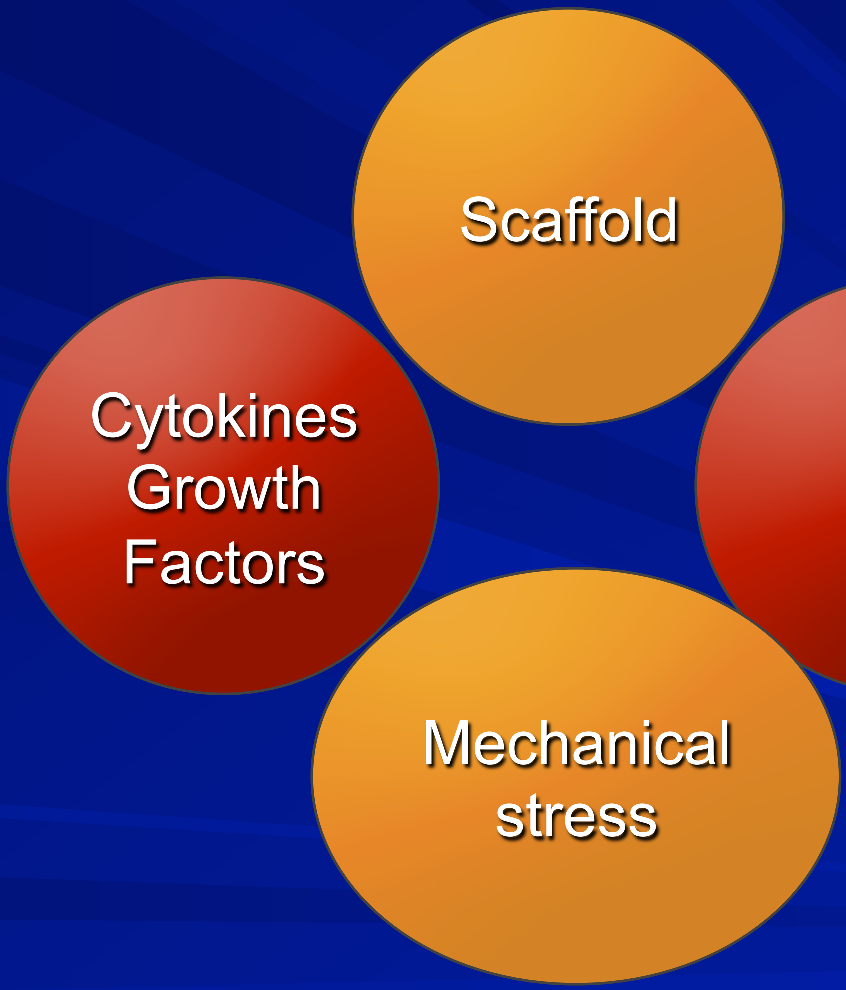


Butler et al., Ann Rev Biomed Eng., 2004; 6: 303

How Can We Improve Tendon Repair & Regeneration?

- Driving force: Inability of natural healing and current surgical techniques to truly regenerate native tendon

Tissue Engineering Solutions for Tendon Repair



Hogan, Katz, Chhabra

JAAOS 2011

Journal of the American Academy of Orthopaedic Surgeons

Review Article

Tissue Engineering Solutions for Tendon Repair

MaCalus V. Hogan, MD
Namory Bagayoko, MD
Roshan James, MS
Trevor Starnes, MD, PhD
Adam Katz, MD
A. Bobby Chhabra, MD

Abstract

Tendon injuries range from acute traumatic ruptures and lacerations to chronic overuse injuries, such as tendinosis. Even with improved nonsurgical, surgical, and rehabilitation techniques, outcomes following tendon repair are inconsistent. Primary repair remains the standard of care. However, repaired tendon tissue rarely achieves functionality equal to that of the preinjured state. Poor results have been linked to alterations in cellular organization

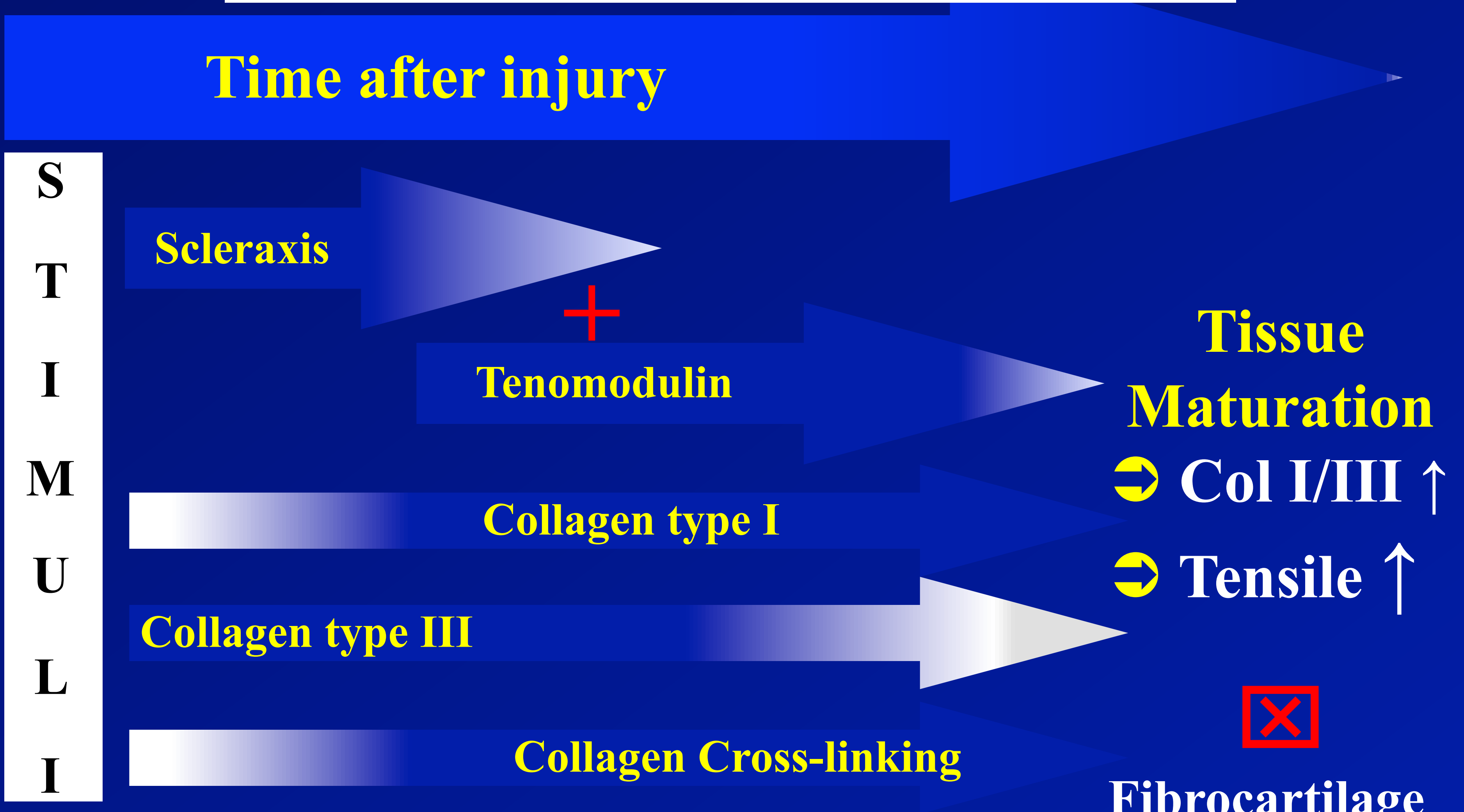
JAAOS 2011

REVIEW ARTICLE

Tendon: Biology, Biomechanics, Repair, Growth Factors, and Evolving Treatment Options

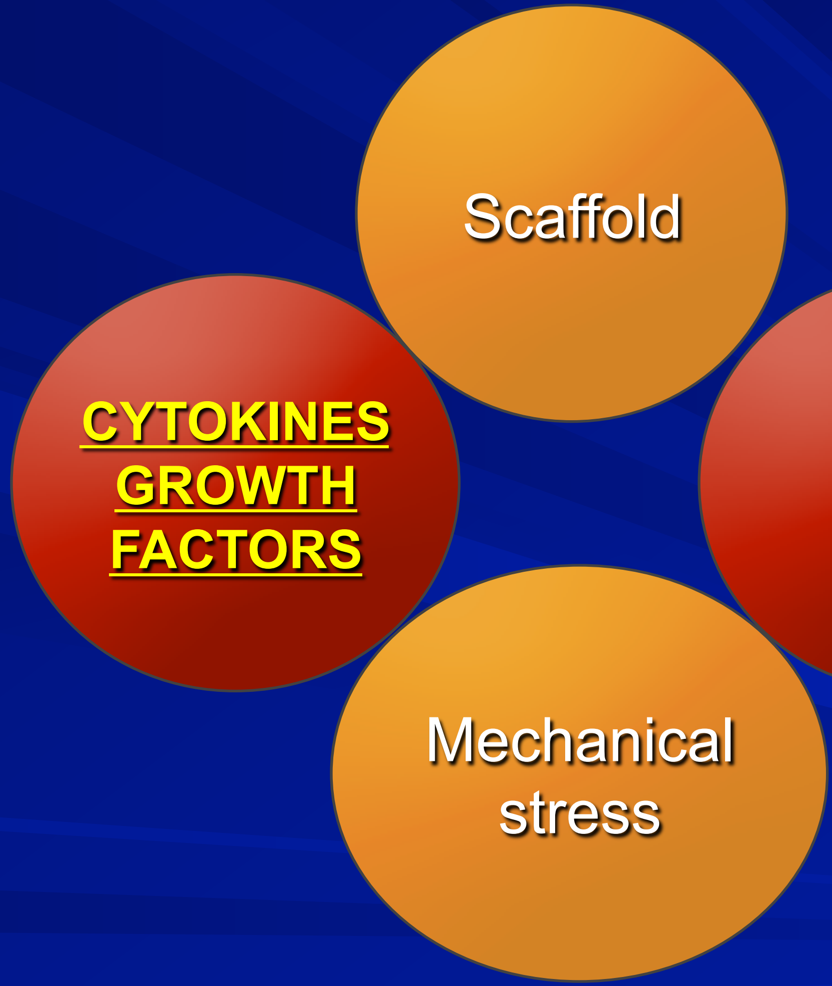
Roshan James, MS, Girish Kesturu, PhD, Gary Balian, PhD, A. Bobby Chhabra, MD

JHS 2008

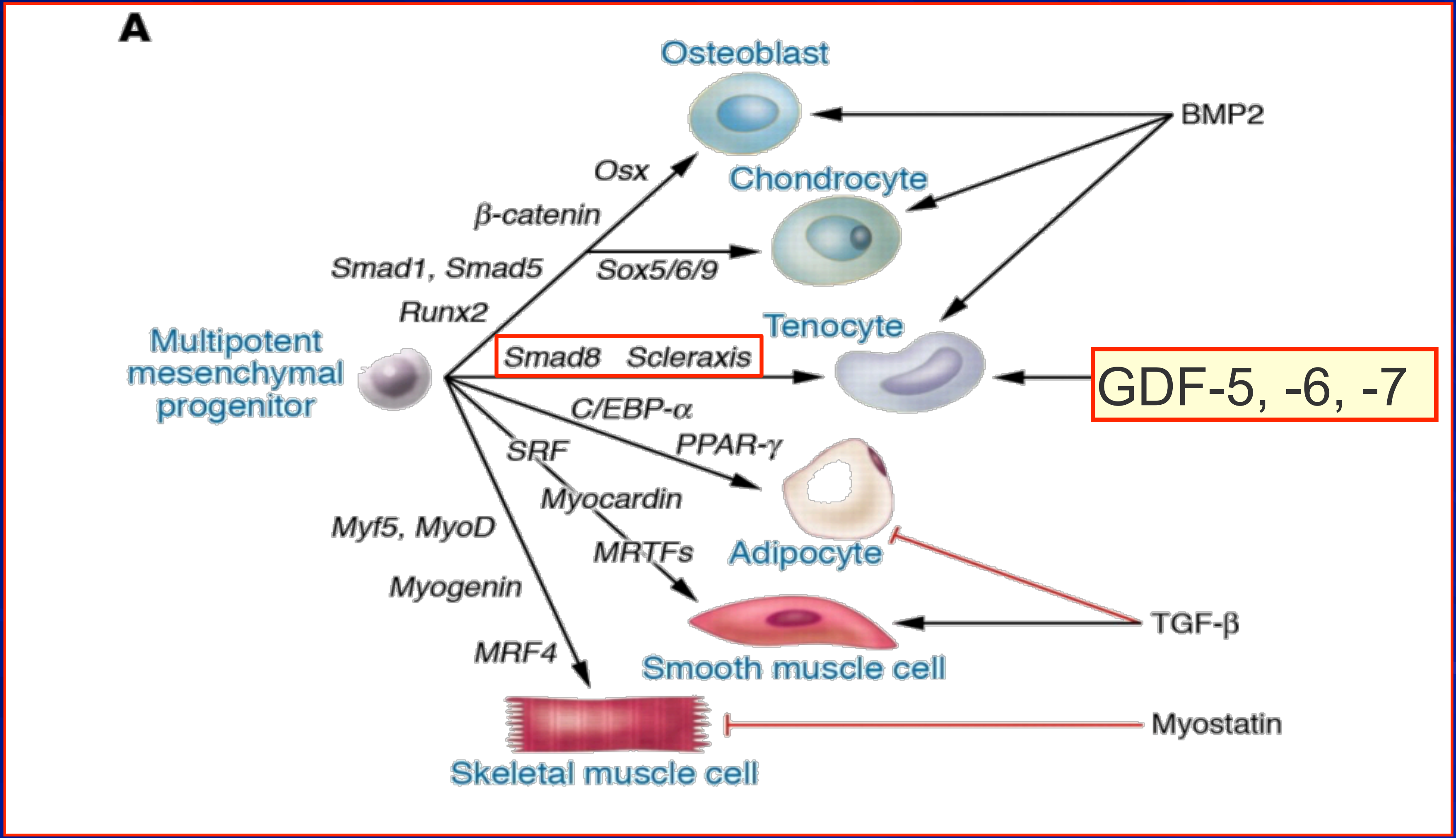


Published in:
James, R; Chhabra, A Journal of Hand Surgery, 2008 Jan; 33(1): 102-12

Tissue Engineering Solutions for Tendon Repair



GDF-5



A
Osteoblast
BMP2
Osx
Chondrocyte
β-catenin
Smad1, Smad5
Sox5/6/9
Runx2
Tenocyte
Multipotent mesenchymal progenitor
Smad8 Scleraxis
GDF-5, -6, -7
C/EBP-α
PPAR-γ
SRF
Myocardin
Myf5, MyoD
MRTFs
Adipocyte
Myogenin
TGF-β
MRF4
Smooth muscle cell
Myostatin
Skeletal muscle cell

JOURNAL OF TISSUE ENGINEERING AND REGENERATIVE MEDICINE
J Tissue Eng Regen Med 2011; **5**: 191–200.
Published online 23 July 2010 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/term.304

RESEARCH ARTICLE

Growth differentiation factor-5 regulation of extracellular matrix gene expression in murine tendon fibroblasts†

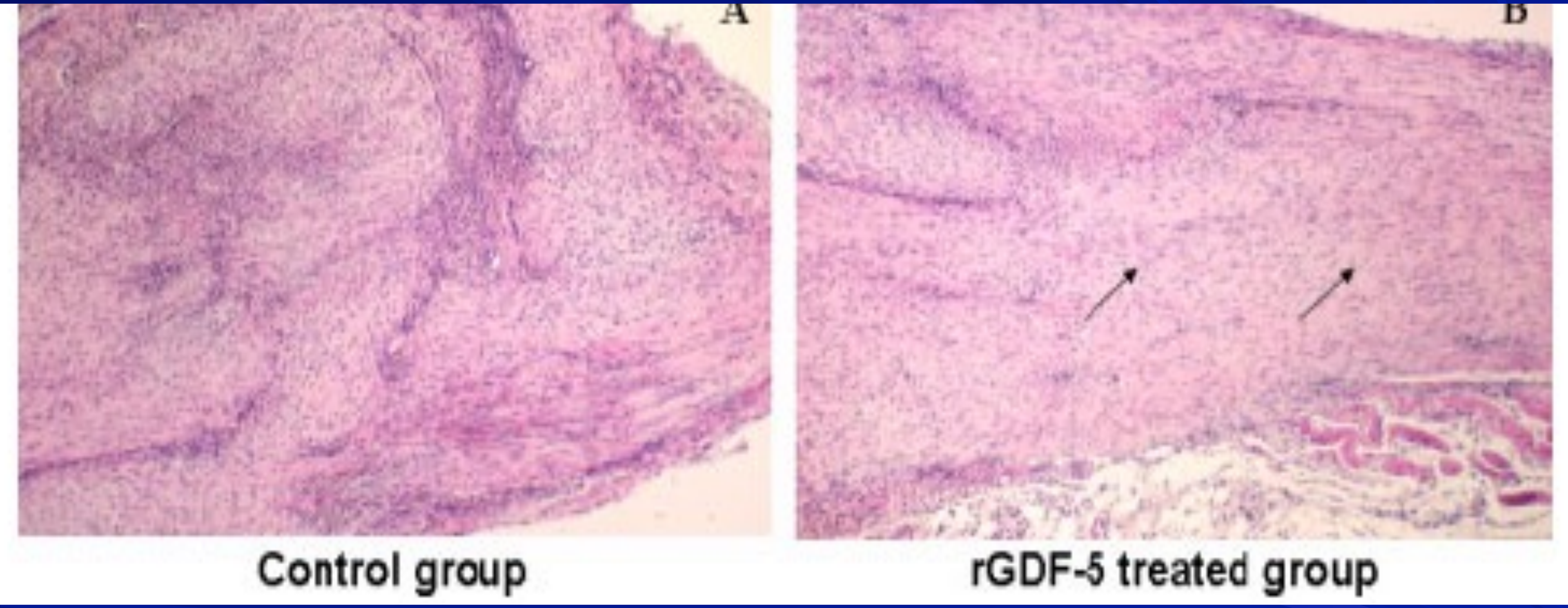
Macalus Hogan[1#], Kesturu Girish[1,2#], Roshan James[1,3], Gary Balian[1,4], Shepard Hurwitz[5] and A. B. Chhabra[1,6*]

- GDF-5 up-regulated relevant tendon healing genes early in the repair process (scleraxis, tenomodulin, Collagen type 1) – **CAN THIS ACCELERATE HEALING?**
- GDF-5 down-regulated pro-inflammatory genes – **CAN THIS DECREASE ADHESIONS ?**

Hogan, Chhabra et al.

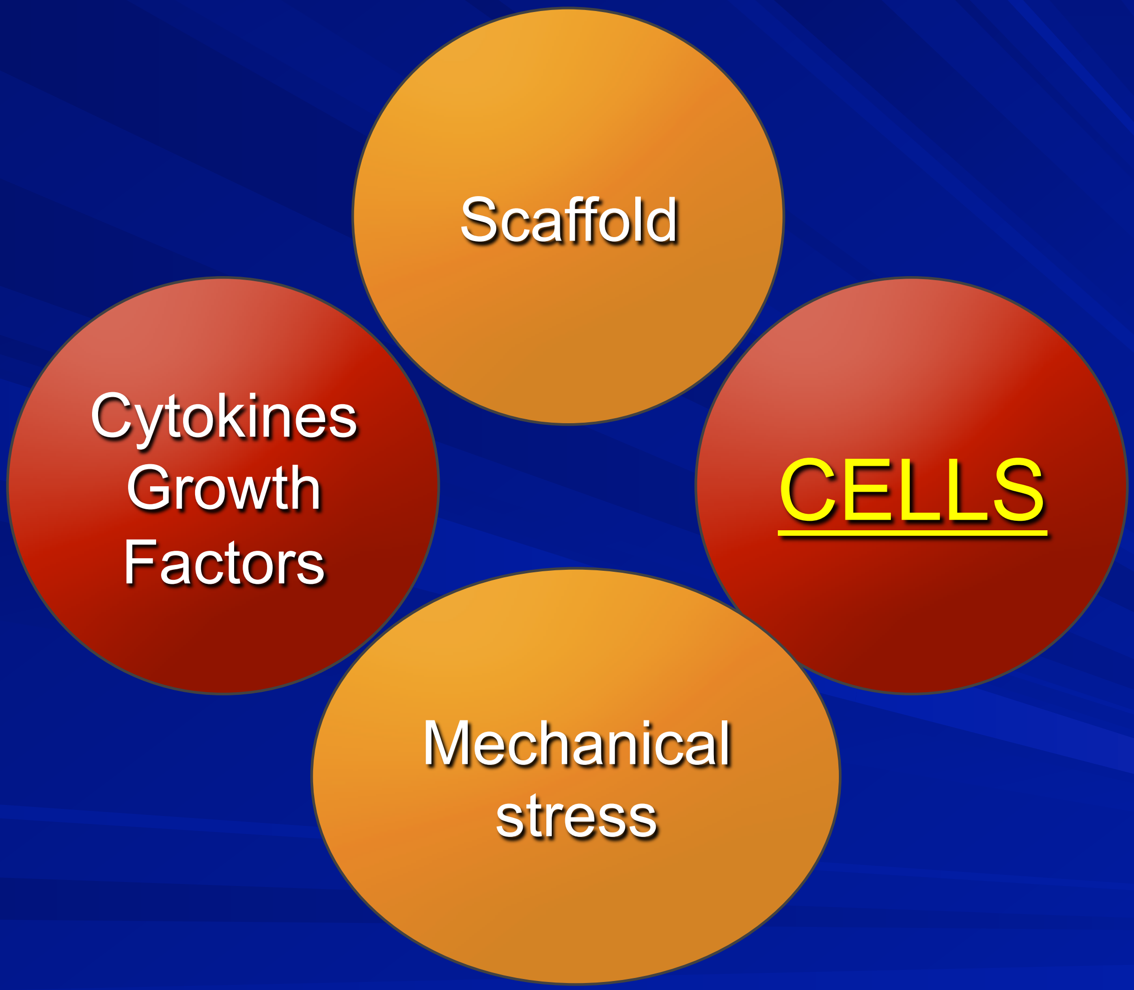
JTERM 2011

GDF-5



Hogan, Chhabra et al.
JTERM 2011

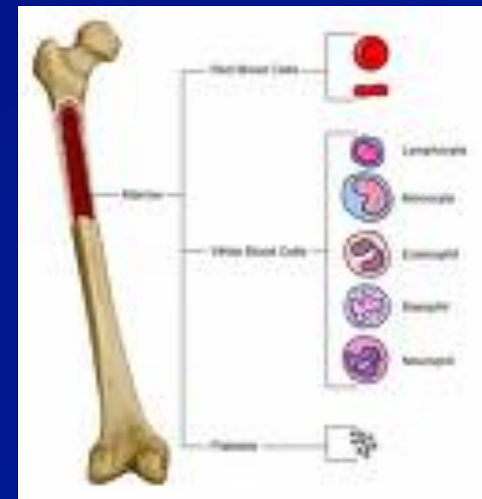
Tissue Engineering Solutions for Tendon Repair



Stem Cells and Tissue Engineering Hope or Hype?

Apligraf™-skin

BMT



Carticel ™

TISSUE ENGINEERING: Part A
Volume 16, Number 9, 2010

DOI: 10.1089/ten.tea.2009.0710

Adipose-Derived Mesenchymal Stem Cells Treated with Growth Differentiation Factor-5 Express Tendon-Specific Markers

Andrew Park, M.D.,[1,*] MaCalus V. Hogan, M.D.,[1,*] Girish S. Kesturu, Ph.D.,[2,*] Roshan James, M.S.,[1]
Gary Balian, Ph.D.,[1] and Abhinav Bobby Chhabra, M.D.[1]

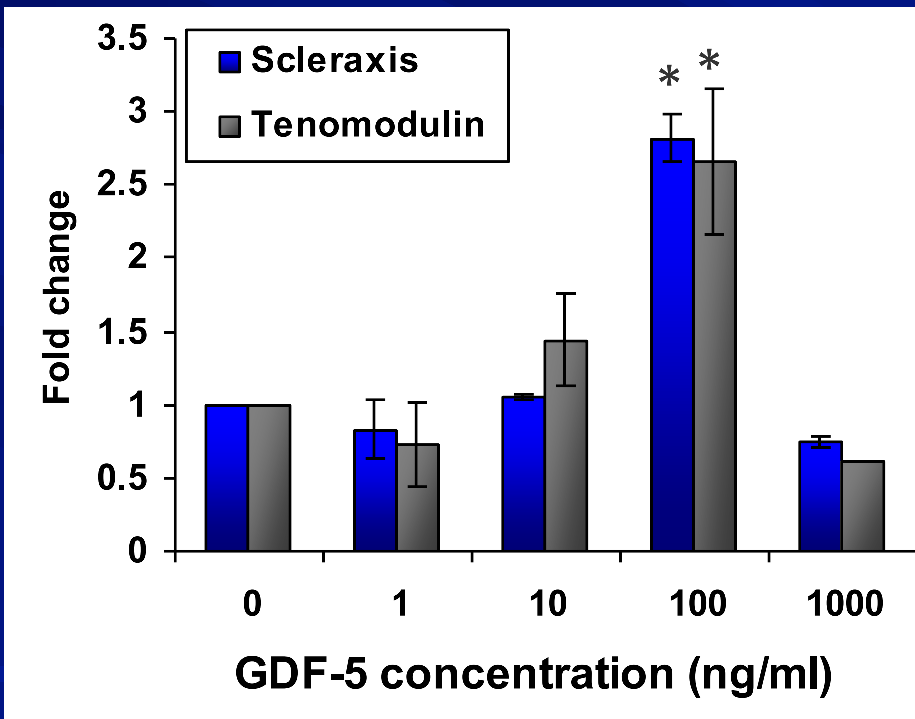
- ***Goal: Investigate the effects of GDF-5 on proliferation and tendinogenic gene expression of rat aMSCs.***

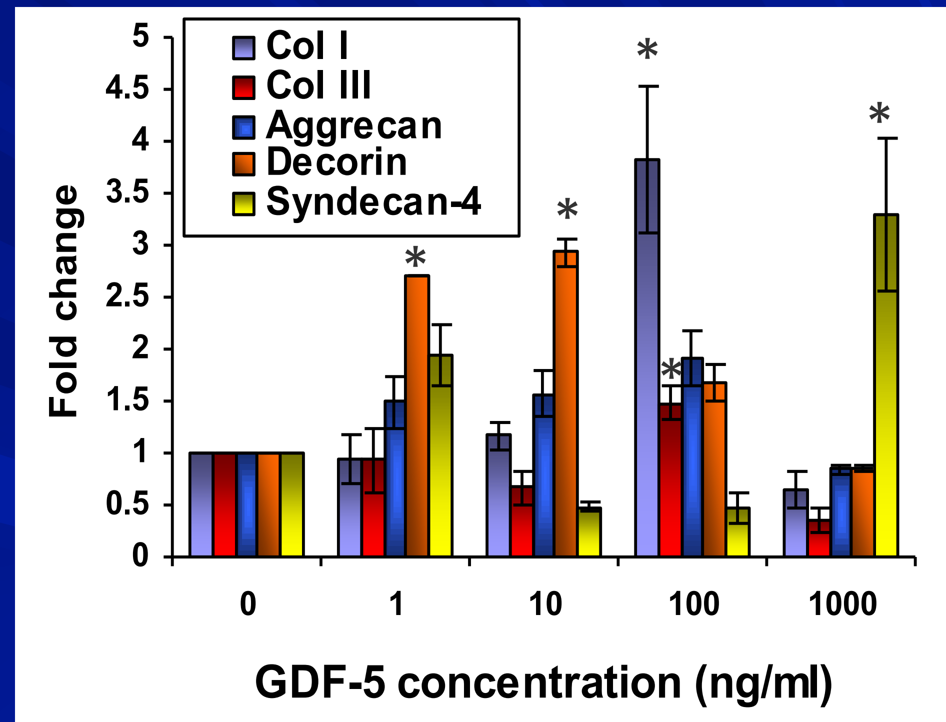
Park, Chhabra et al.

Tiss Eng 2010

aMSCs + GDF-5

Concentration Kinetics



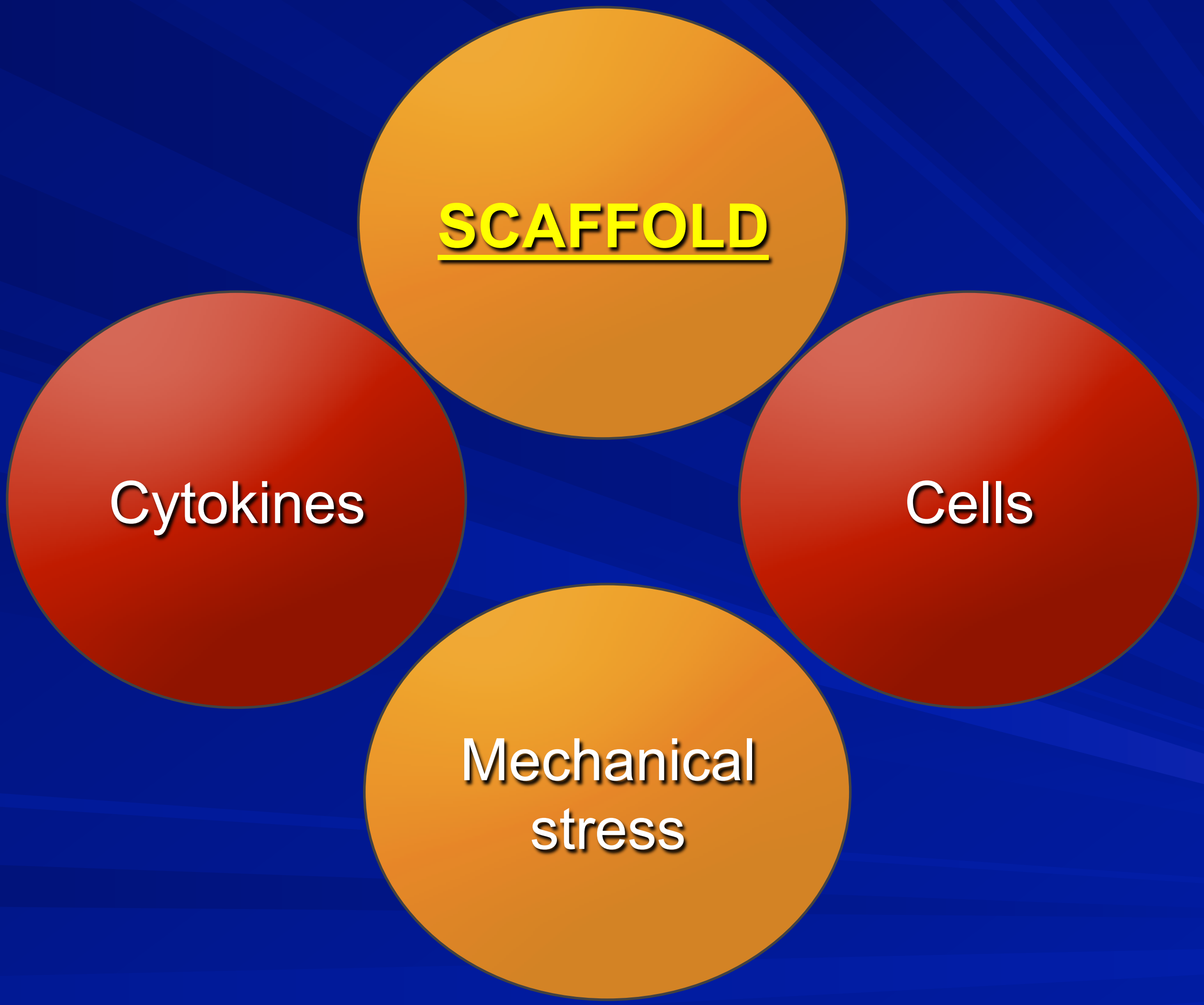


↑ Tenocyte Markers

↑ ECM & CAR

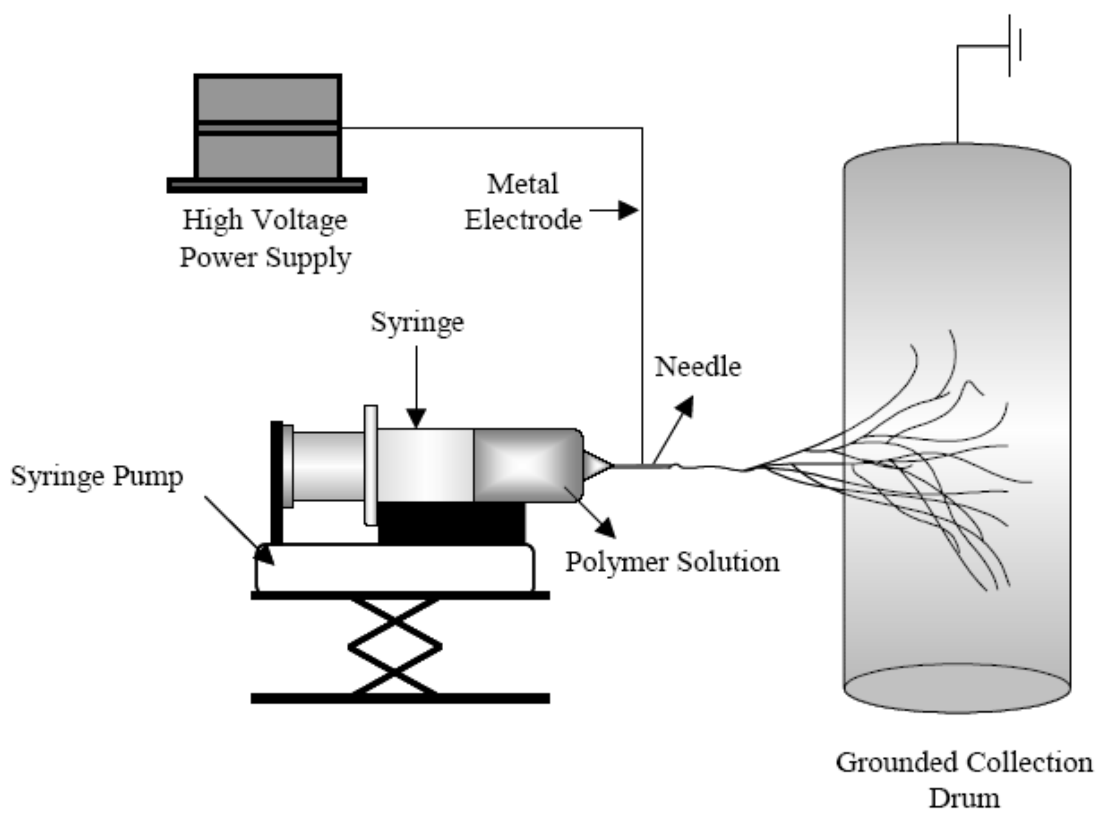
($p<0.05$)

Tissue Engineering Solutions for Tendon Repair

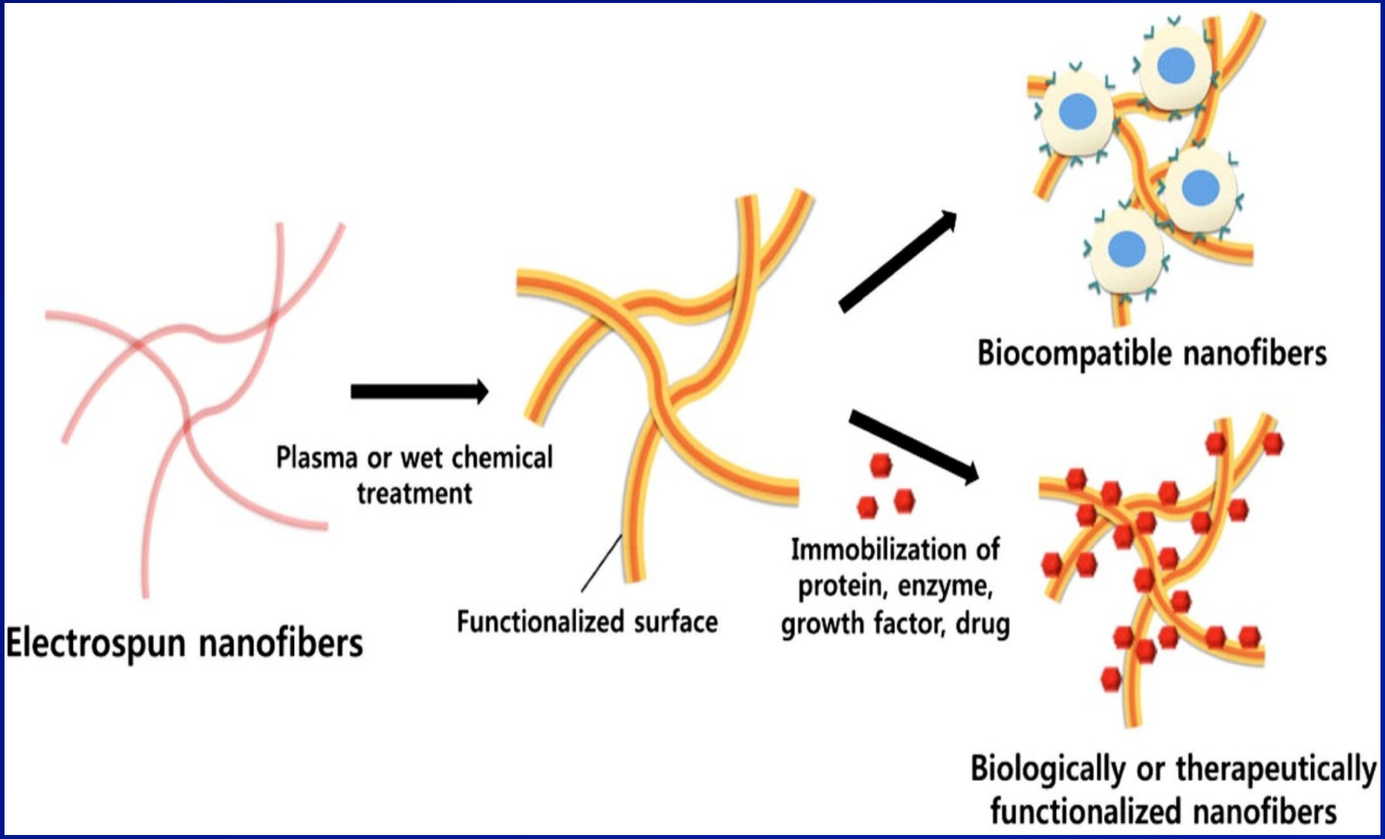


Tubular Electrospun Scaffold

- Setup for Fabrication of Tubular Scaffolds

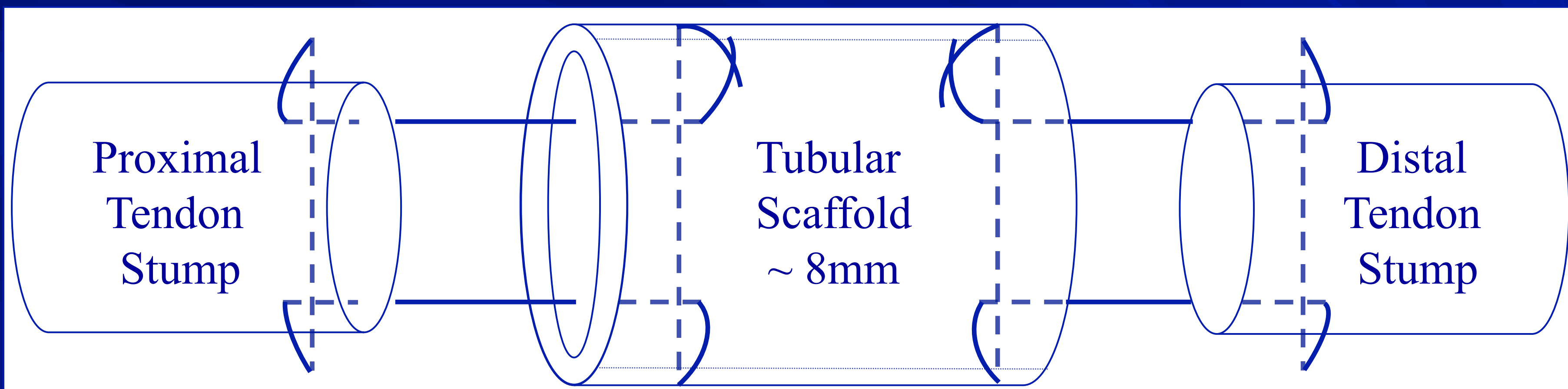


Functionally Active Scaffolds

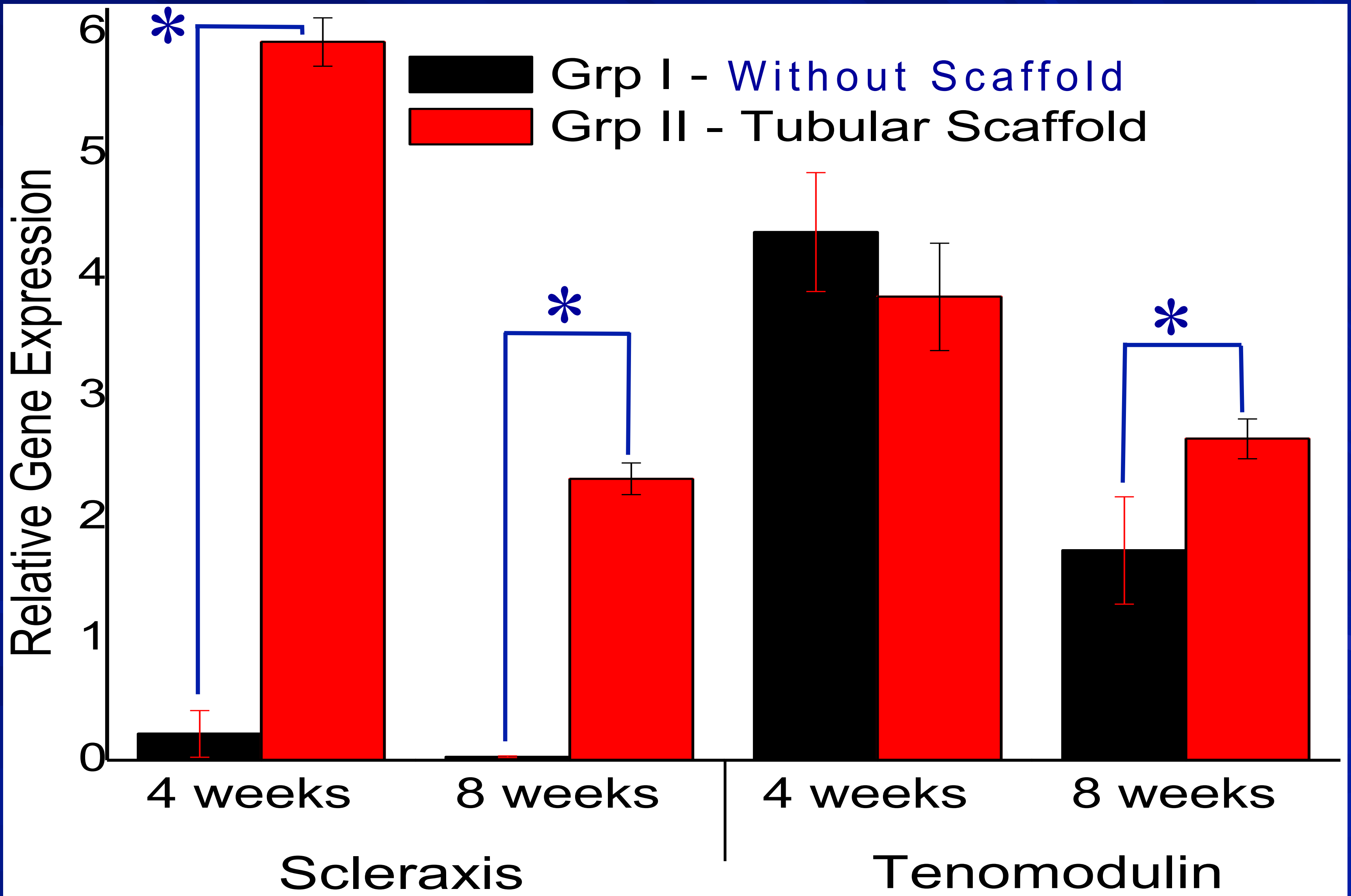


Rat Tendon Defect Model

- **Female Fischer 344 rat (8 week old)**
  - 8 mm Tubular Scaffold
  - Immobilization for 10 – 14 days

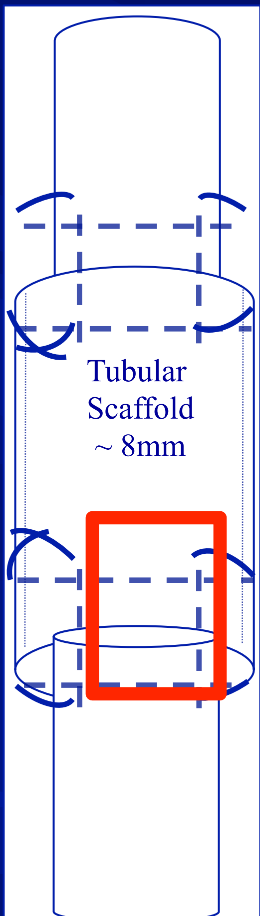


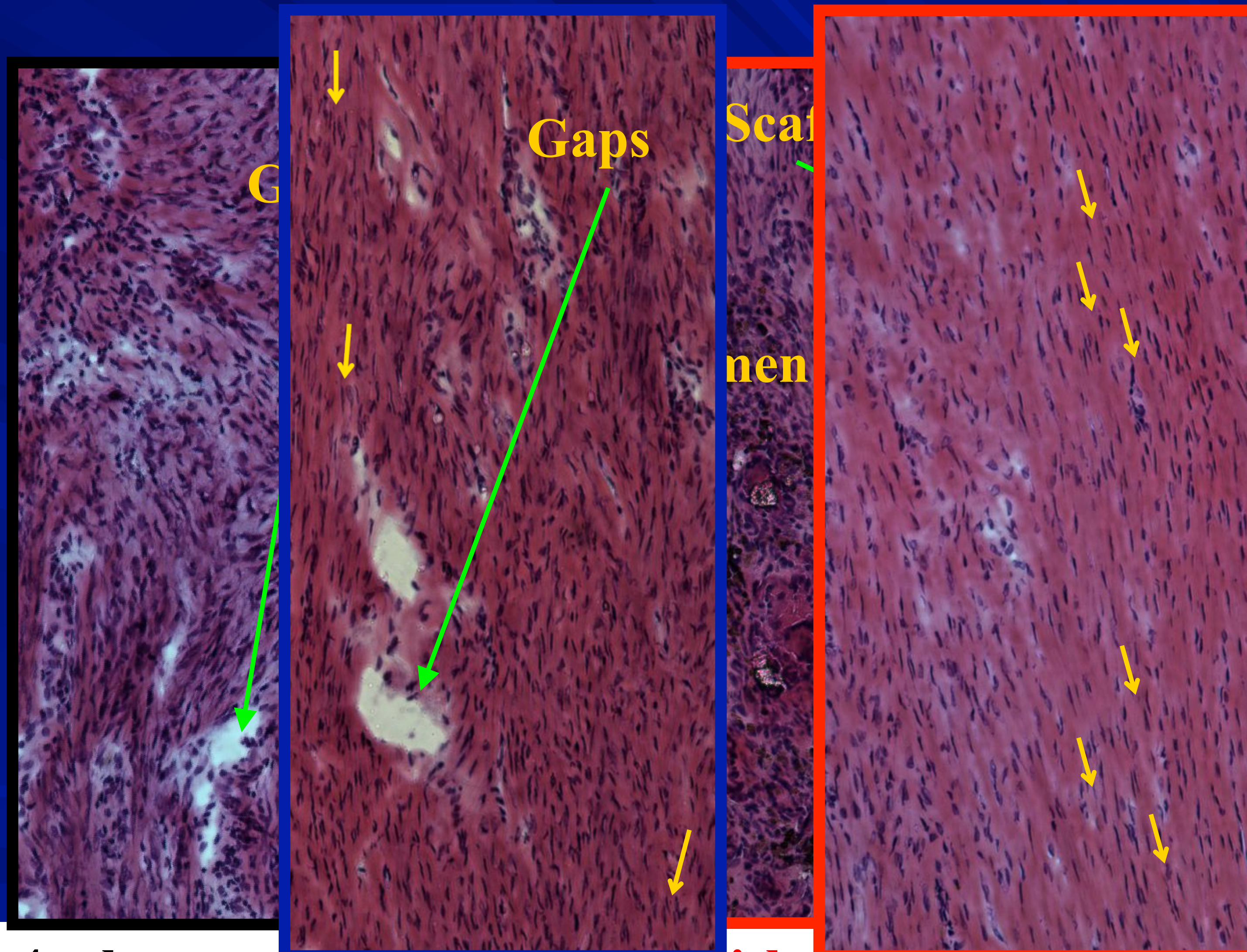
Increased Scx and Tnmd Expression



P < 0.05

Improved Orientation



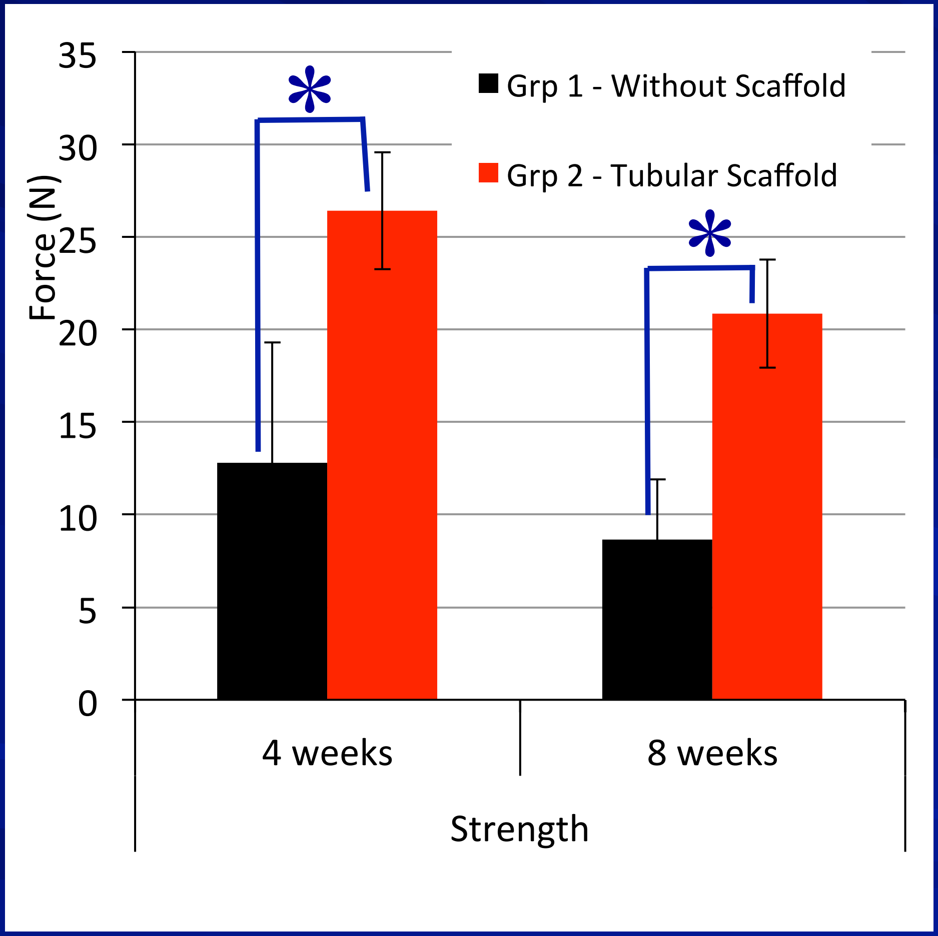


4 wks, no

8 wks, no scaffold

8 wks, with scaffold

Increased Strength of Repair

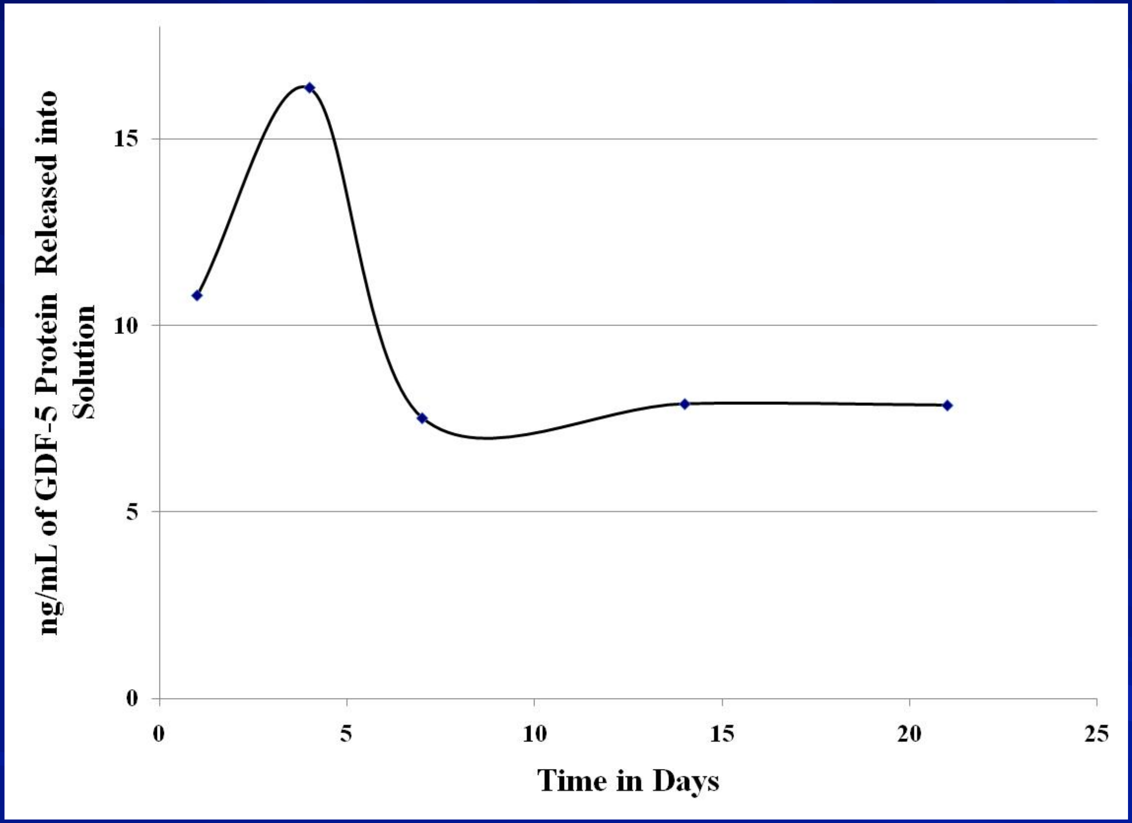


P < 0.05

- **Scaffold *In Vitro***
  - 16 – 22 N
- Increased Tensile Strength
- Native Rat Tendon
  - 30 – 70 N

Next Step: Drug-Scaffold

GDF-5 Protein Release



- GDF-5 covalently bonded to scaffold
- @ 2 weeks ~8ng/mL of GDF-5 is released
- Burst release profile is seen in the first 4 days.

Where We're Going

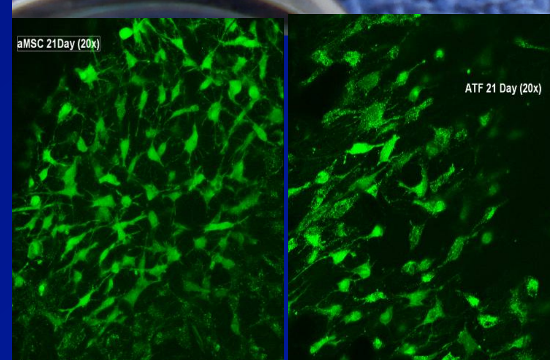
- MSC + PLAGA + GDF-5 construct optimization and *in vivo* application
- Manipulation of scaffold to minimize adhesions
- Mechanical stress of scaffold/cell/growth factor construct to enhance healing and improve biomechanical strength
- Translation to larger animal model

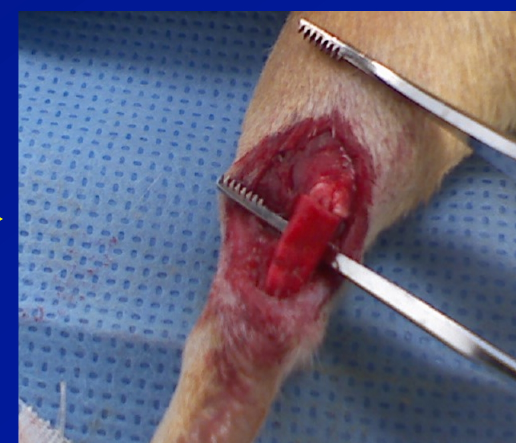
Conclusions

- Further study is needed to determine the ideal tissue engineered construct for tendon regeneration

+

GDF-5





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