

# **Hypertrophic Scar: What We Know, What We Don't**

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# Hypertrophic Scar (HTS)

Abnormal healing after serious burn injury.

Excessive dermal fibrosis.

Persistent scar and contracture.

For most burn survivors, long term morbidity due to HTS, contracture and limited functional recovery.







# HYPERTROPHIC SCAR

Raised, Erythematous, Pruritic

Occur after significant (deep 2<sup>nd</sup>-3<sup>rd</sup>) injury

More common in locations with fixed skin and frequent motion

Begins weeks after injury, resolves years later

# Histologic Differences

|                   | <u>HTS</u>       | <u>Keloid</u>          |
|-------------------|------------------|------------------------|
| Connective tissue | ++               | ++                     |
| Collagen fibers   | Thin, in nodules | Thick, parallel arrays |
| Ground substance  | -                | ++                     |
| Myofibroblasts    | + +              | -                      |

# *$\alpha$* -SM Actin Expression in Fibroblastic Cells of Connective Tissues

| Tissue      | <i><math>\alpha</math></i> -SM Actin Expression |      |       |
|-------------|---|------|-------|
|             | -   | +/-  | +     |
| Dermis      | 13/13   | 0    | 0     |
| Normal Scar | 7/7   | 0    | 0     |
| Keloid      | 15/17   | 2/17 | 0     |
| HTS         | 0   | 4/17 | 18/22 |

# What is HTS and How is it Different Than Scar and Keloid?

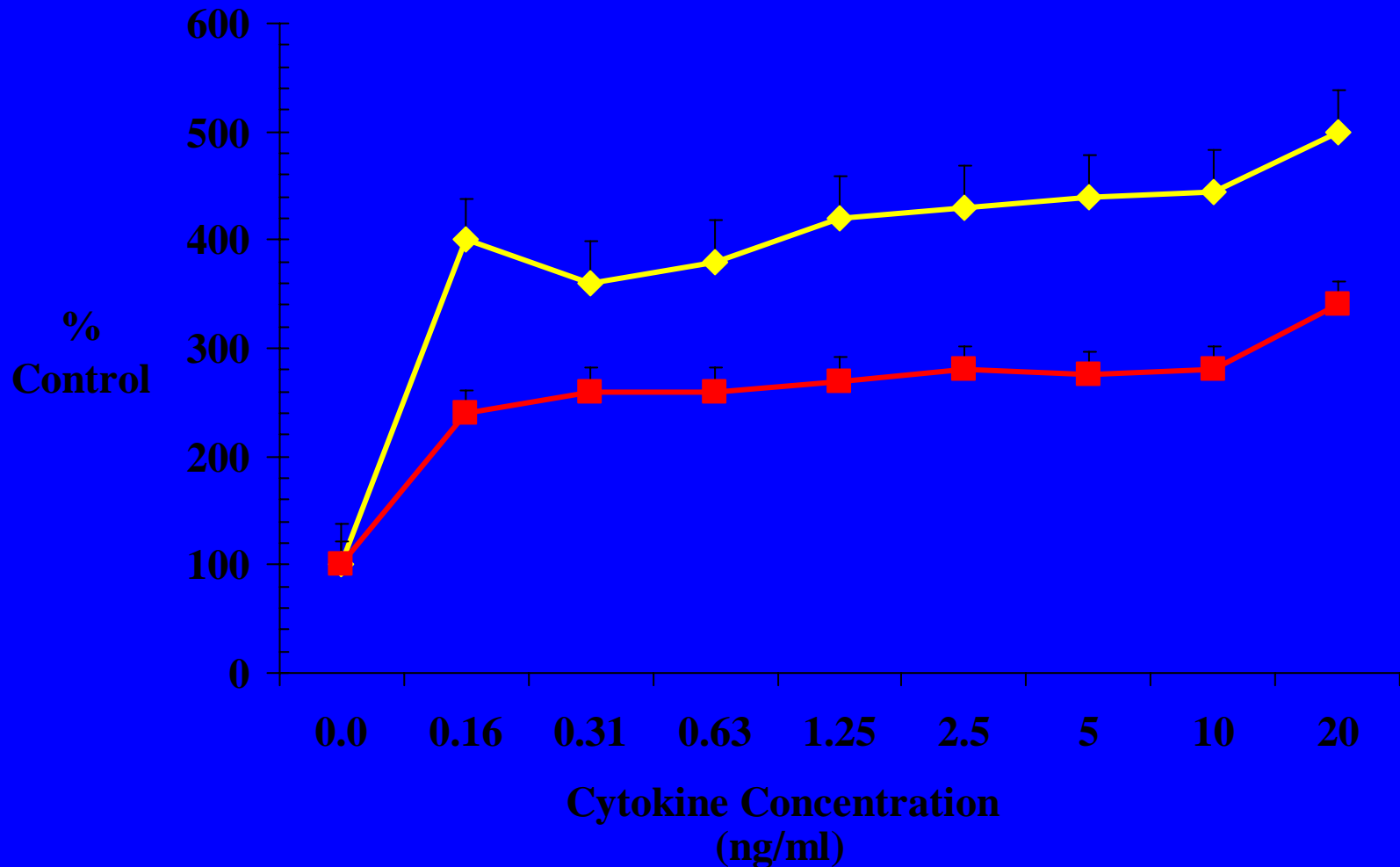
- What are accurate and specific characteristics of HTS?
- Are there specific blood or tissue markers for HTS?
- How can we best educate clinicians about the clinically defined characteristics of HTS?
- Who should be targeted for such educational programs?

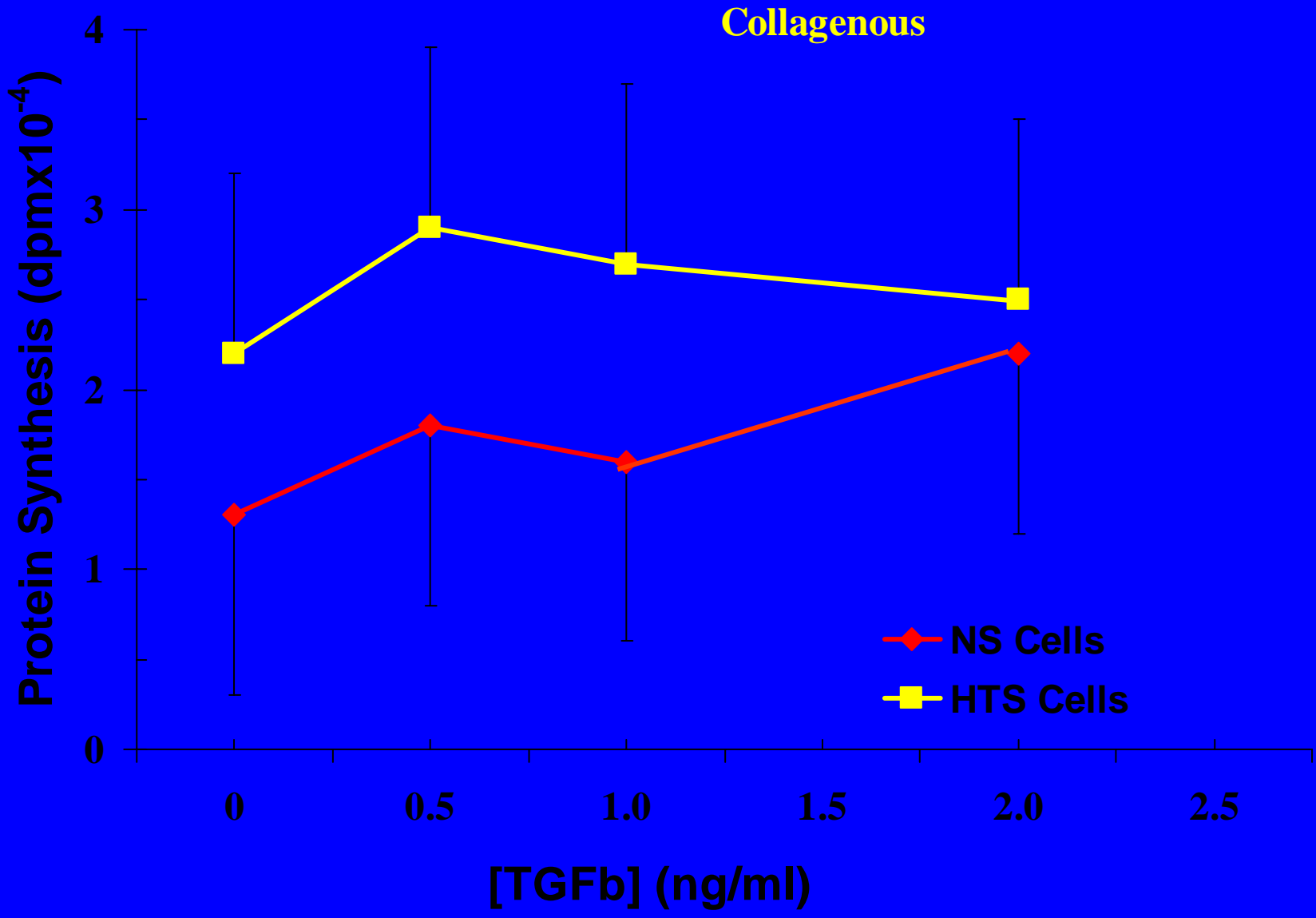
# What Do We Study to Understand Excess Scar after Burns?

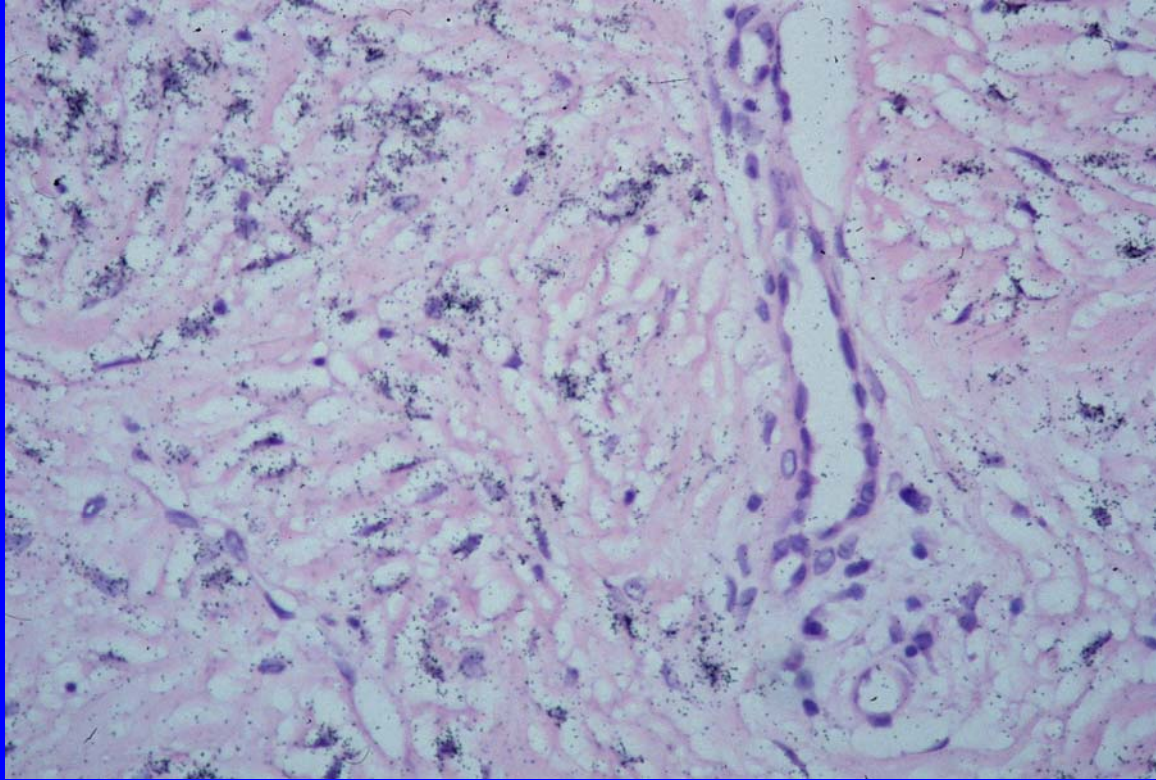
No relevant animal models  
Must biopsy patients

Continuously changing scar  
Operative interventions when scars are in late stages

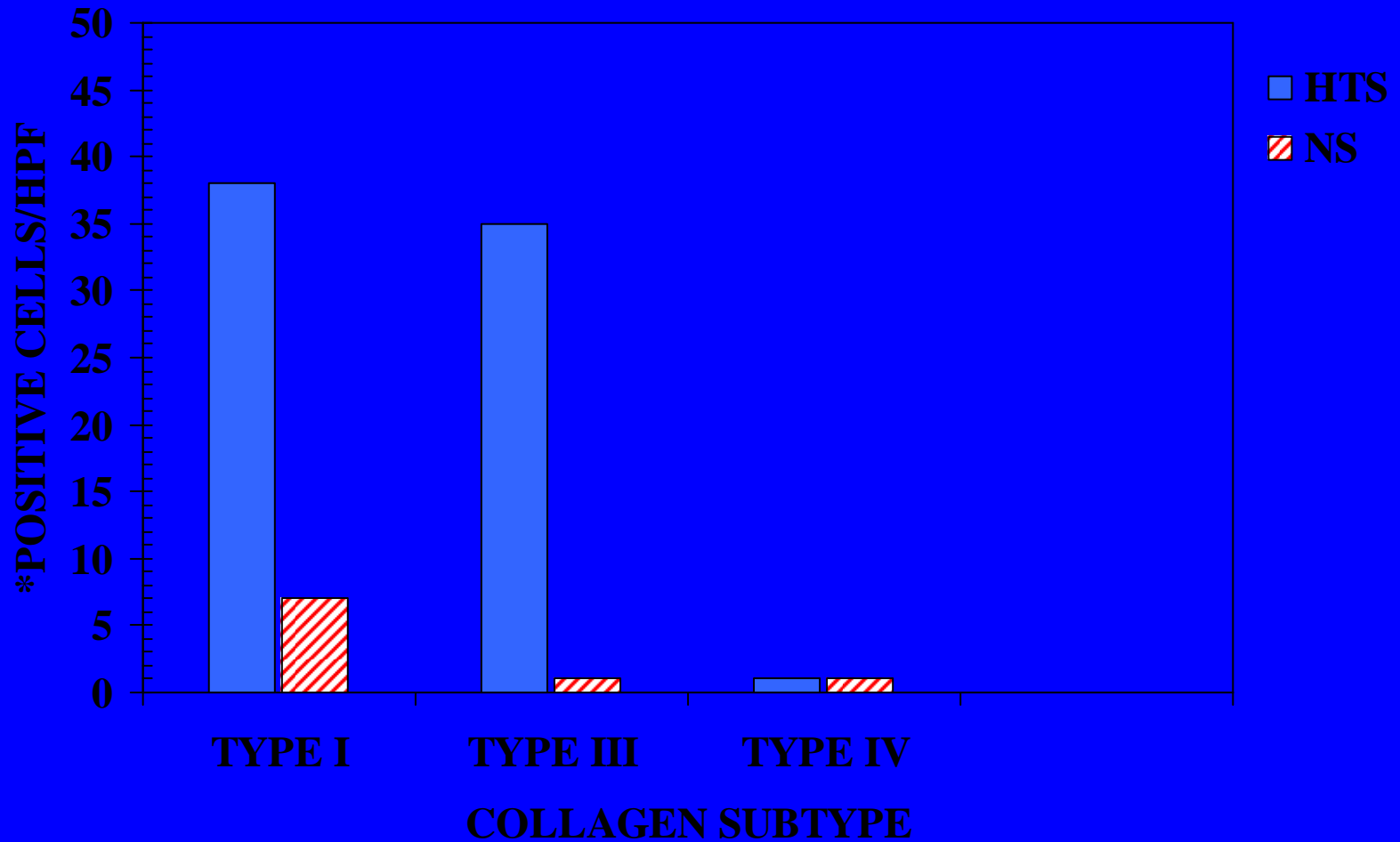
# Mitogenic Response to TNF- $\alpha$





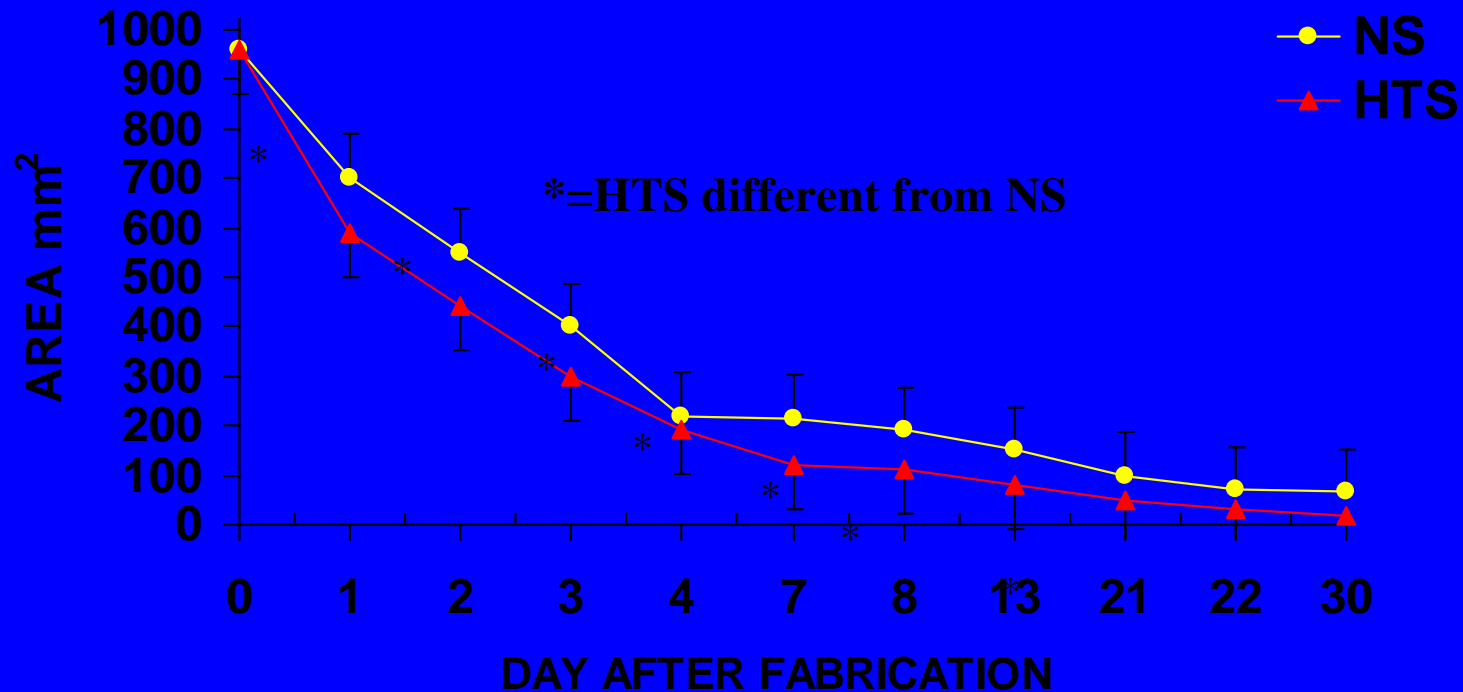


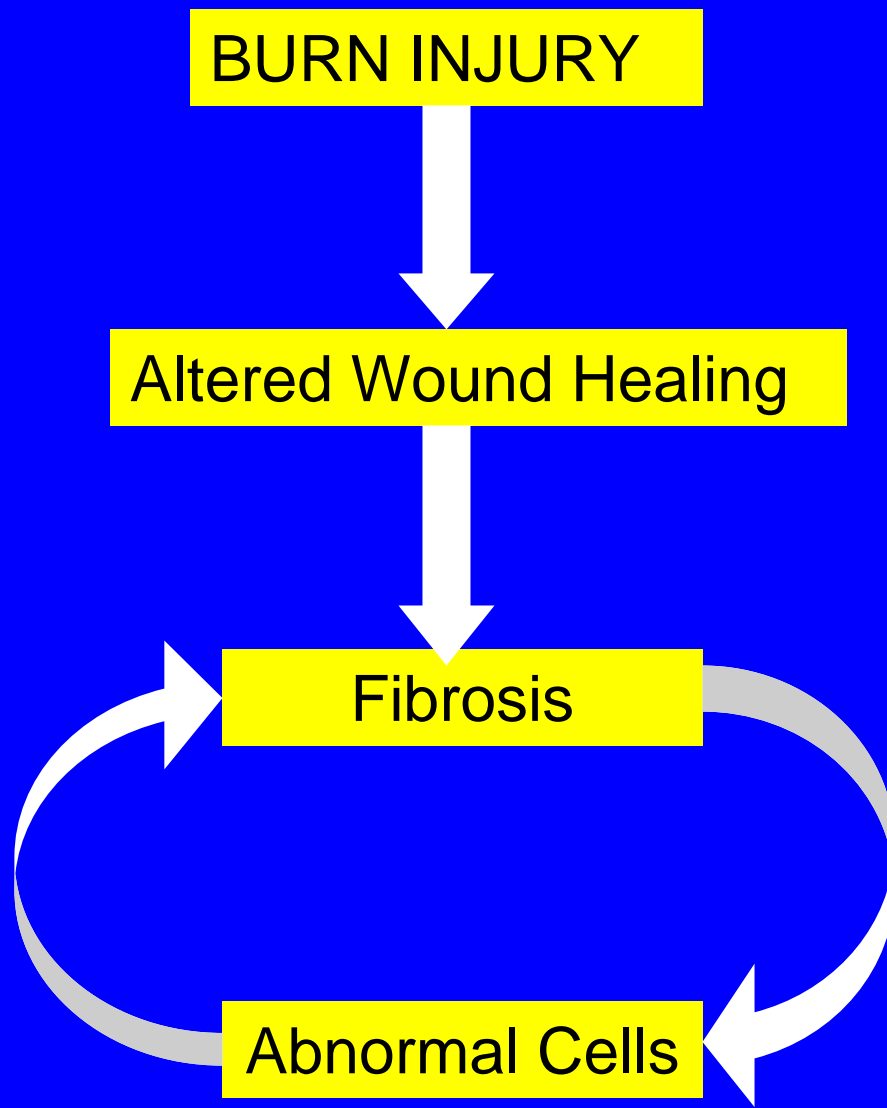
# QUANTITATION OF IN SITU HYBRIDIZATION HTS vs NORMAL SKIN





# CONTRACTION RATES





# CELL PHENOTYPE CHANGES

## WHAT WE DO NOT KNOW

- What changes cell phenotype?
  - Epigenetic, altered signaling systems, microenvironment
- HTS **SLOWLY** resolves. Why slow and are those events controllable?
- What are the specific inducers for excess collagen synthesis and matrix contraction?

# Pathophysiology of HTS

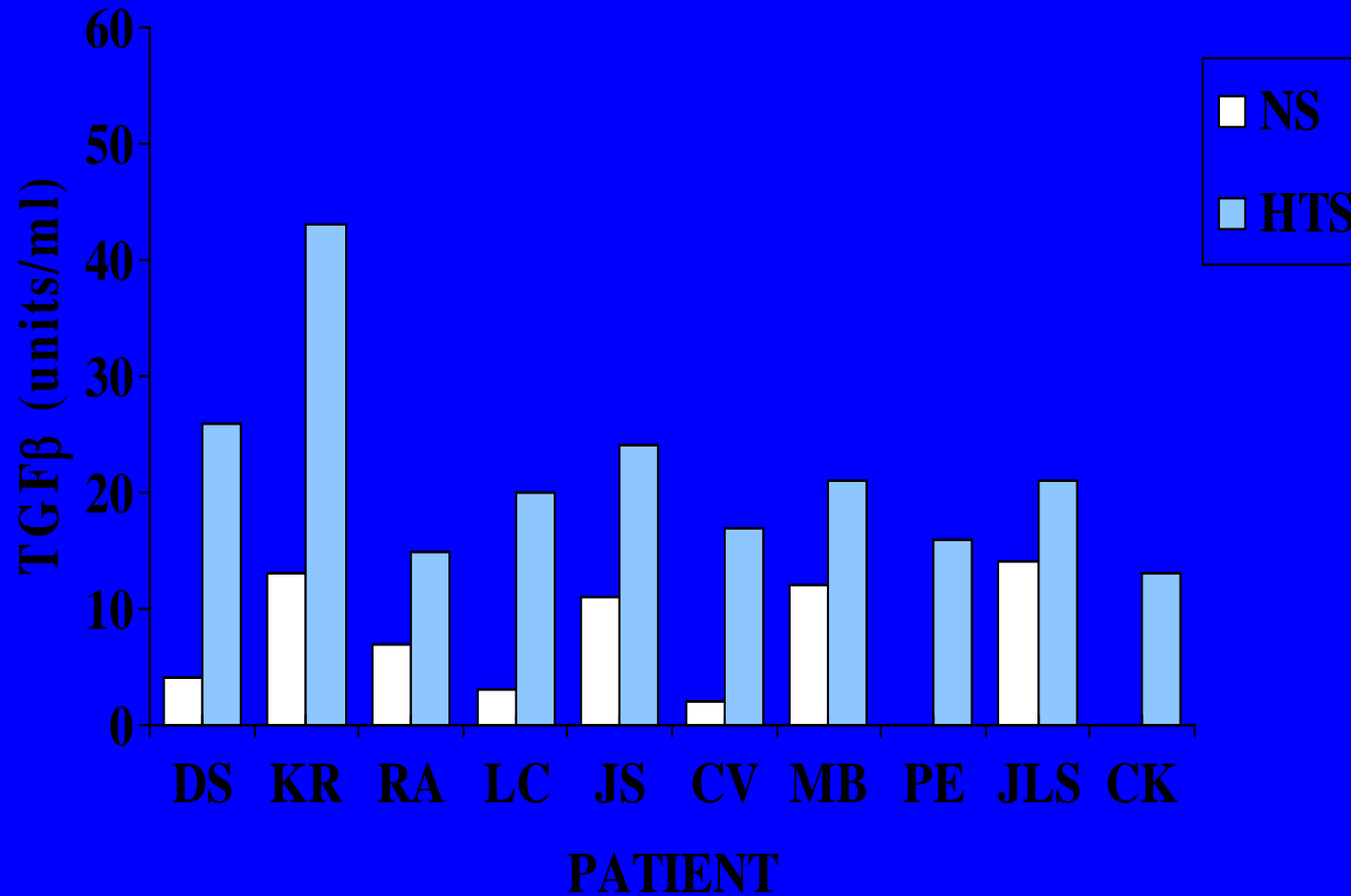
Increased collagen

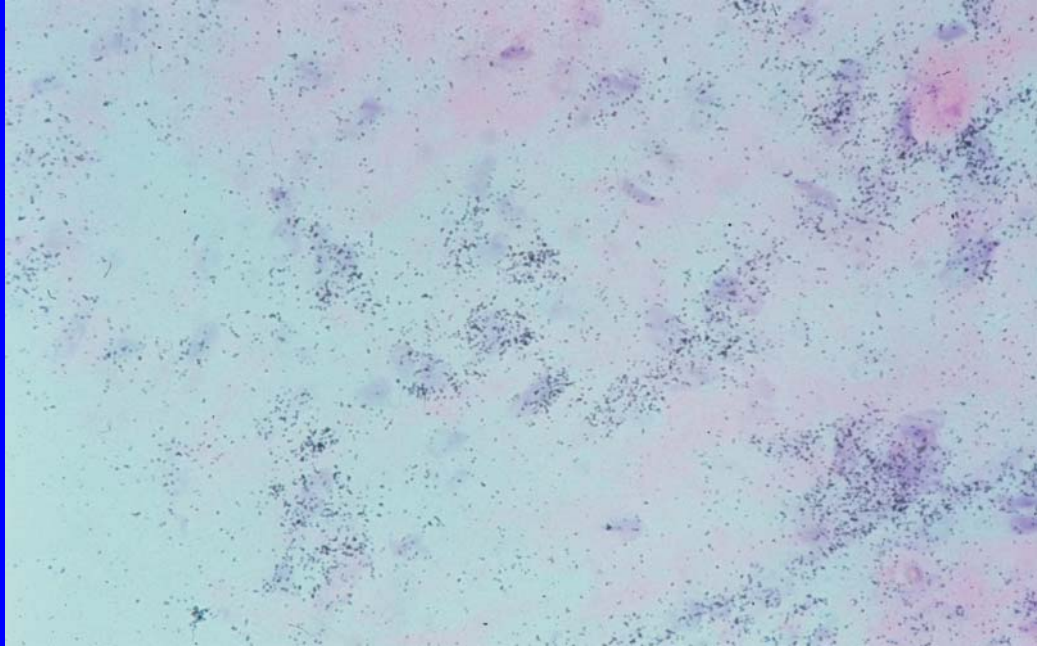
Increased matrix contraction

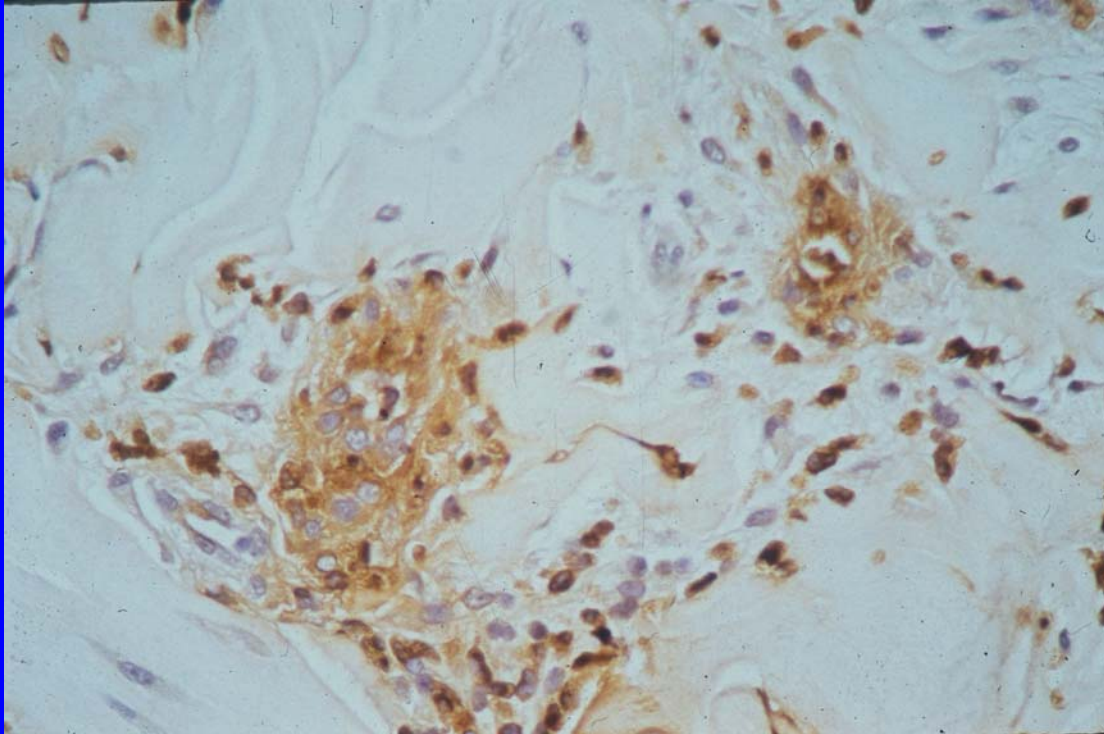
Decreased replication

TGF- $\beta$

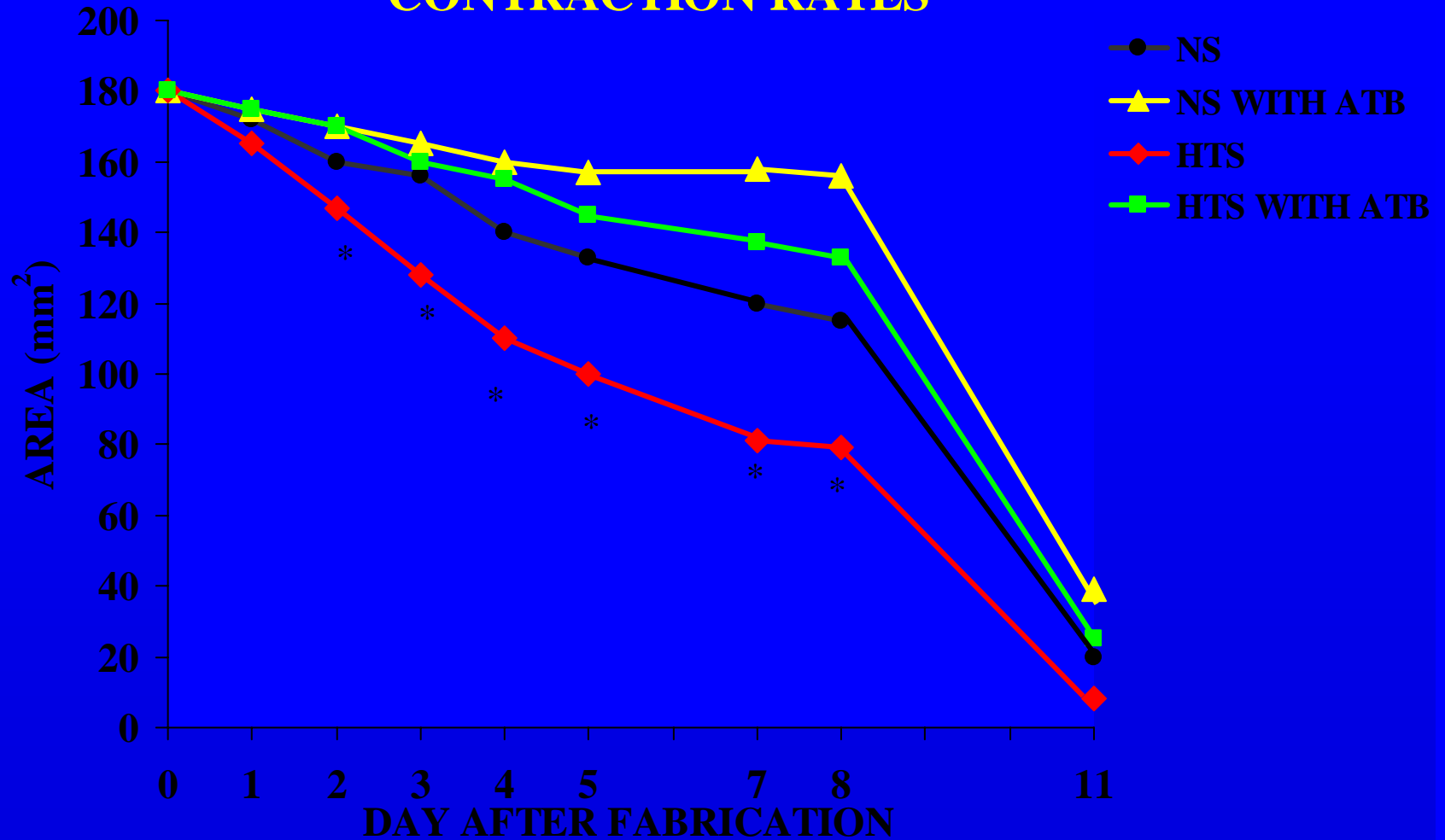
# TGF $\beta$ ACTIVITY FROM SKIN BIOPIES







# CONTRACTION RATES



\* = SIGNIFICANT DIFFERENCE BETWEEN HTS AND HTS+ATBD

† = SIGNIFICANT DIFFERENCE BETWEEN NS AND NS+ATB

NO DIFFERENCE BETWEEN CELL TYPES AFTER ATB TREATMENT

# TGFb UPREGULATION

## What researchers do not know

- What causes TGFb upregulation, increased signal or altered responses?
- What specific signals for increased TGFb are increased?
- Is there a breakdown of normal TGFb regulation
- Are TGFb regulatory proteins present?  
Functional? Relevant?
- Are there other inducers of matrix and contraction?

# TGF $\beta$ UPREGULATION

## What clinicians want to know

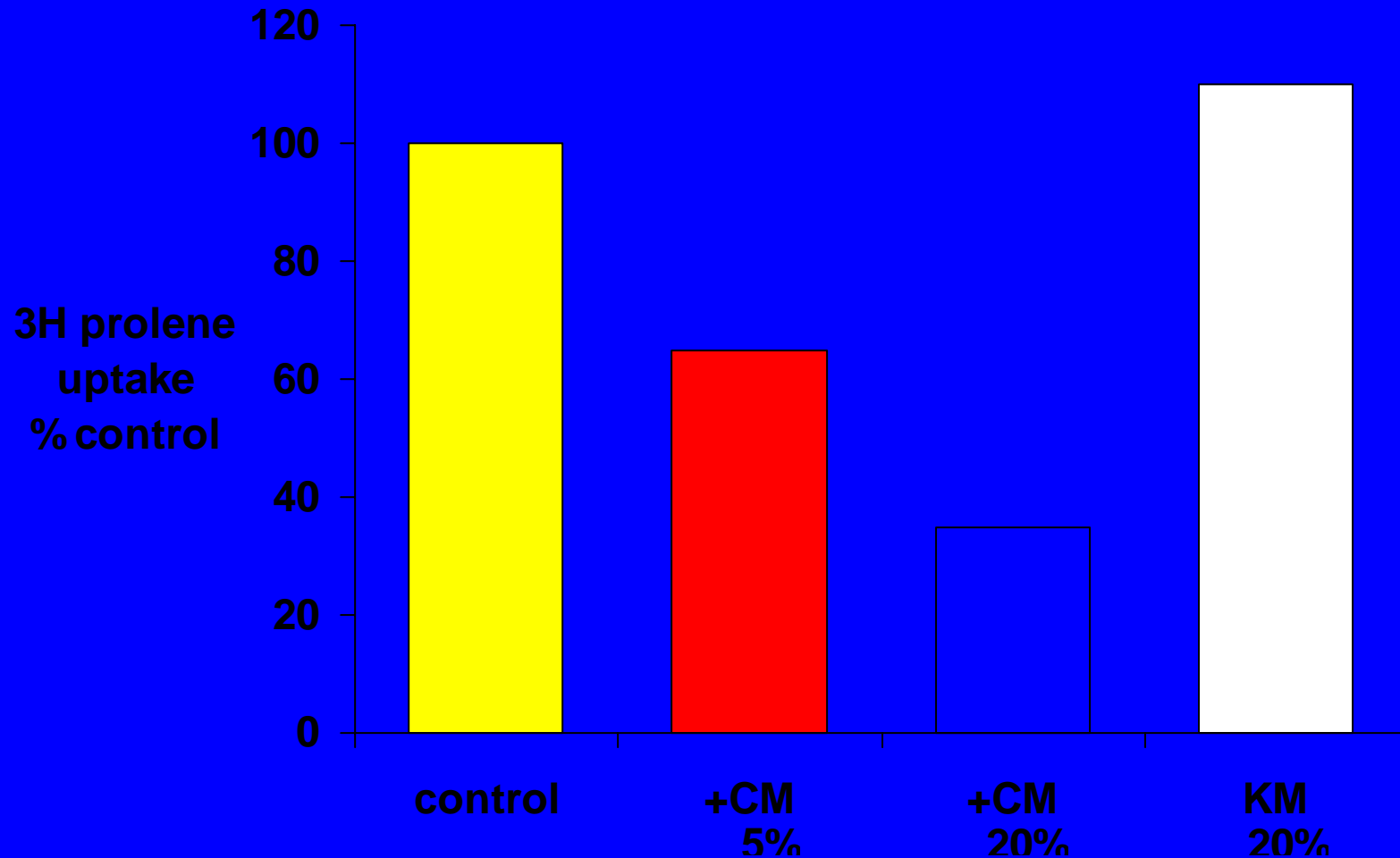
- How to inhibit, scavenge, prevent synthesis, block, minimize, oppose TGF $\beta$  actions
- Same problem for all fibrotic diseases, pulmonary and kidney fibrosis, scleroderma



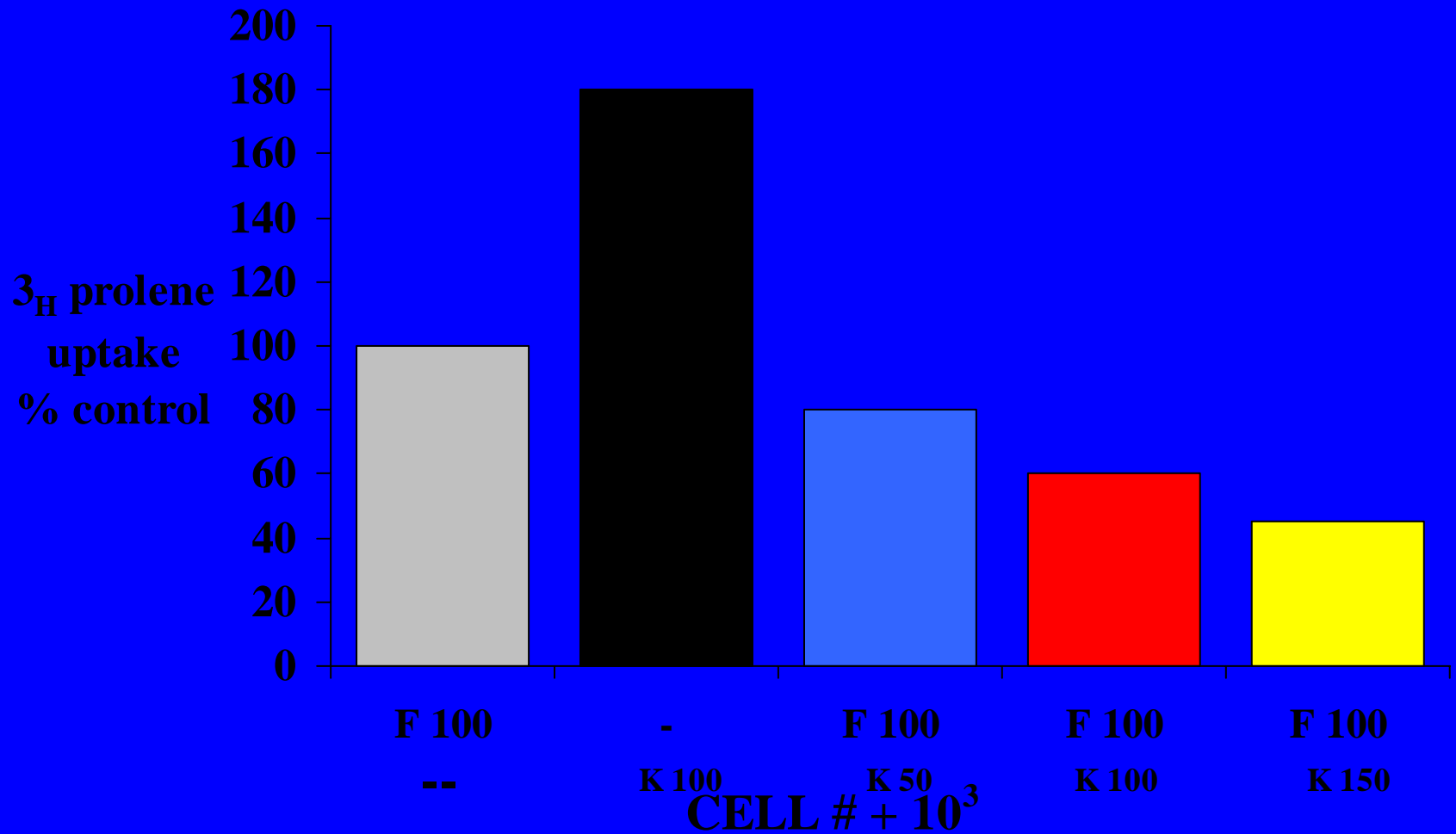




# Fibroblast Collagen Synthesis Effects of Keratinocyte CM



# Co-culture – Normal Fibroblasts and Keratinocytes



# WHAT WE DO NOT KNOW

- What can epithelial cells produce that regulates collagen synthesis?
- Can this product independently limit scar symptoms?
- Are proteases part of HTS regulation?
- Are differentiation or barrier effects important?



# Anisotropy in the Skin of the Arm

| Type of Site                                | No. of Patients Measured | No. of Measurement Locations | Mean SVD Value(M/S) X-Direction | Mean SVD Value(M/S) Y-Direction | p-value (paired t-test) |
|---|--------------------------|------------------------------|---------------------------------|---------------------------------|-------------------------|
| Site Matched Uninjured Skin on Opposite Arm | 5                        | 9                            | 37.4                            | 47.9                            | 0.005                   |
| HTS   | 10                       | 17                           | 59.8                            | 85.4                            | p<0.0001                |
| Adjacent Uninjured Skin                     | 6                        | 8                            | 45.6                            | 46.0                            | 0.45                    |

# WHAT WE DO NOT KNOW

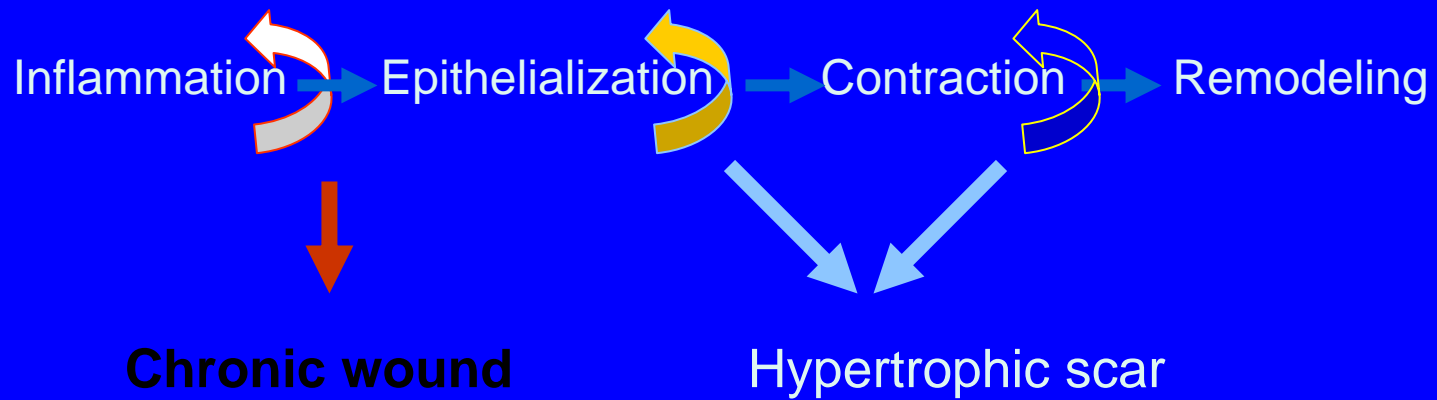
- What regulated the remodeling of tissue within and adjacent to the burn wound?
- What are the mechanical signals that regulate tissue performance?
- How is the micro-structure of burn scar different than normal skin and scar?
- Does an altered microenvironment cause changes in cell function, TGFb and the rest?

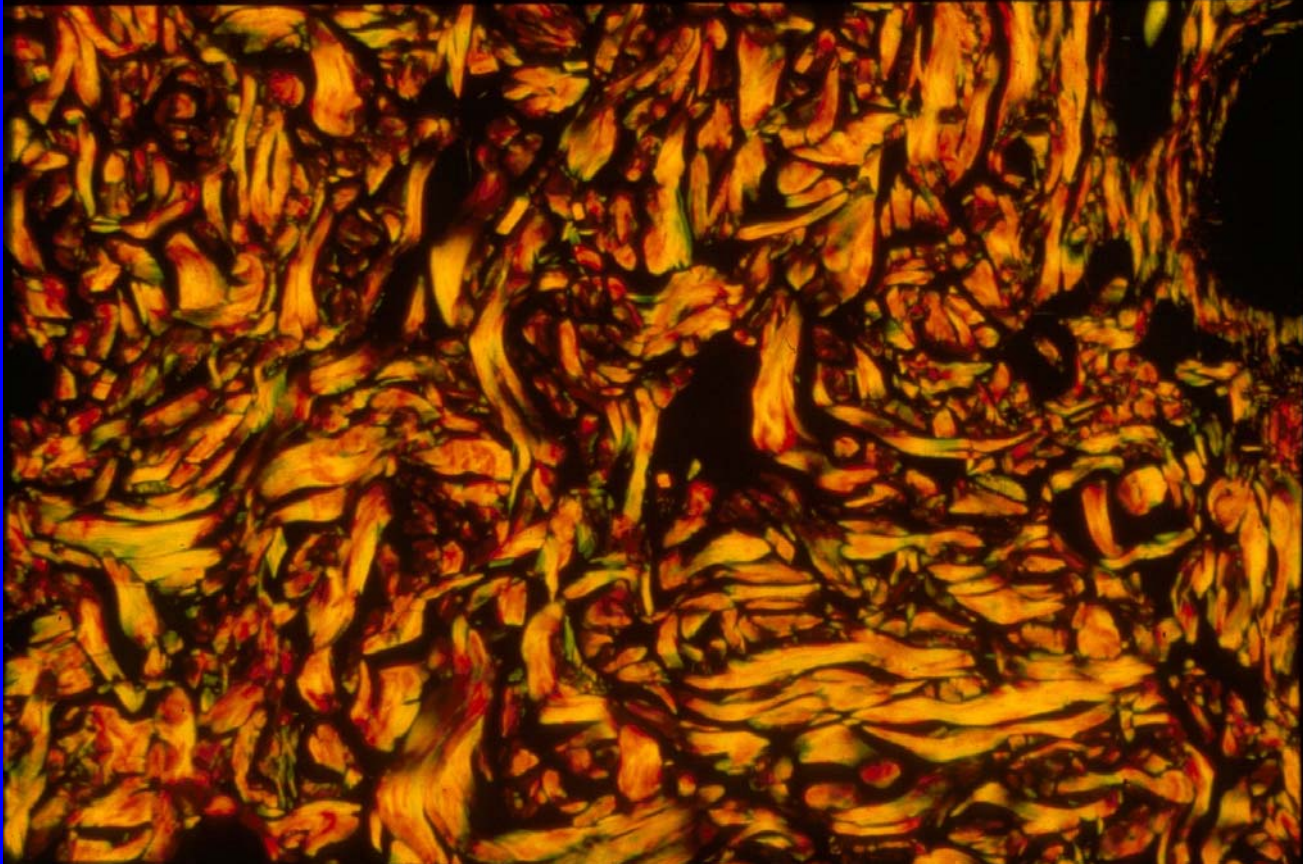
# WHAT WE NEED TO DO NOW

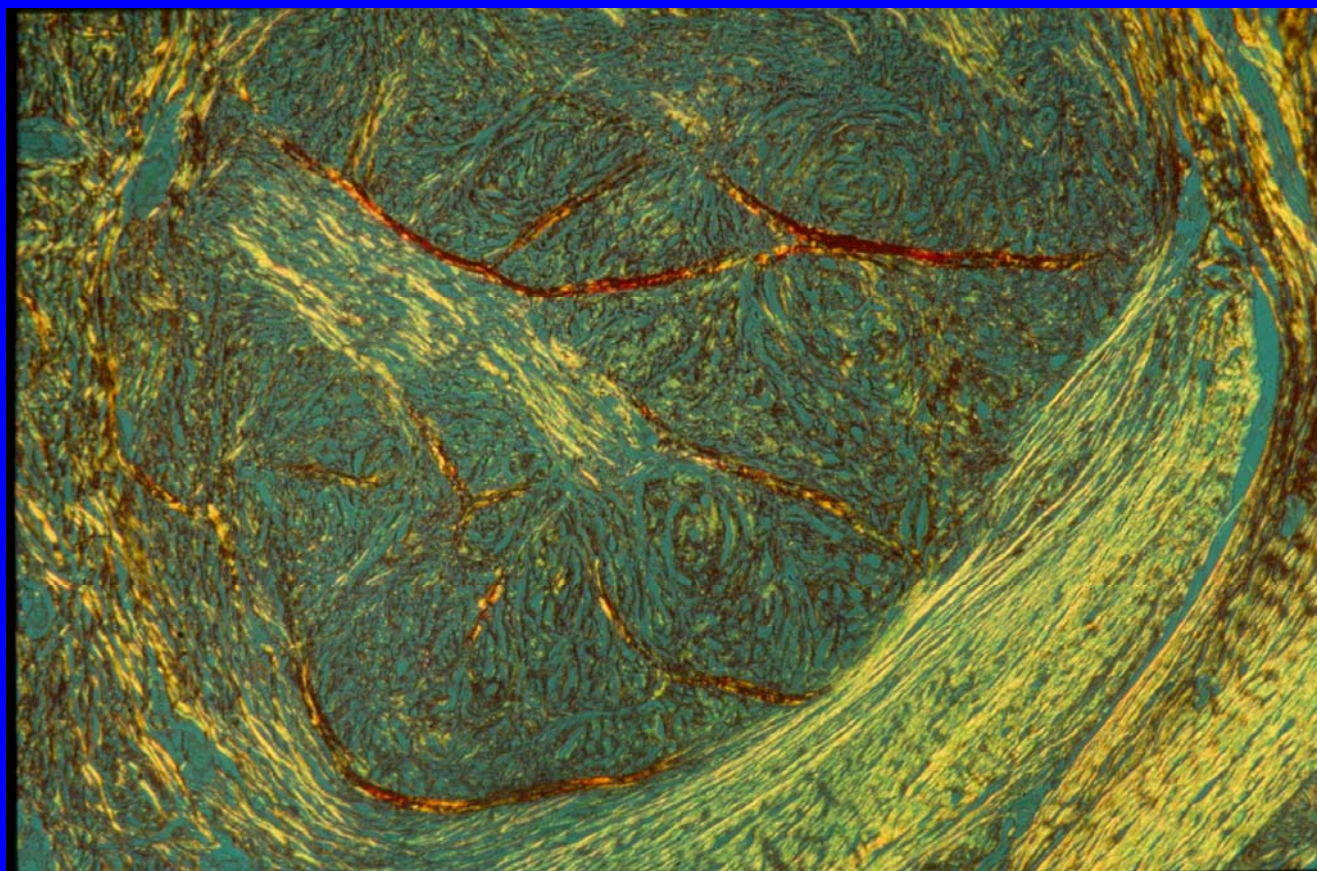
- Many fundamental questions about scar physiology can be defined.
- How can these results be translated into clinically useful interventions?
- How to fund research into high impact, but low frequency treatments?

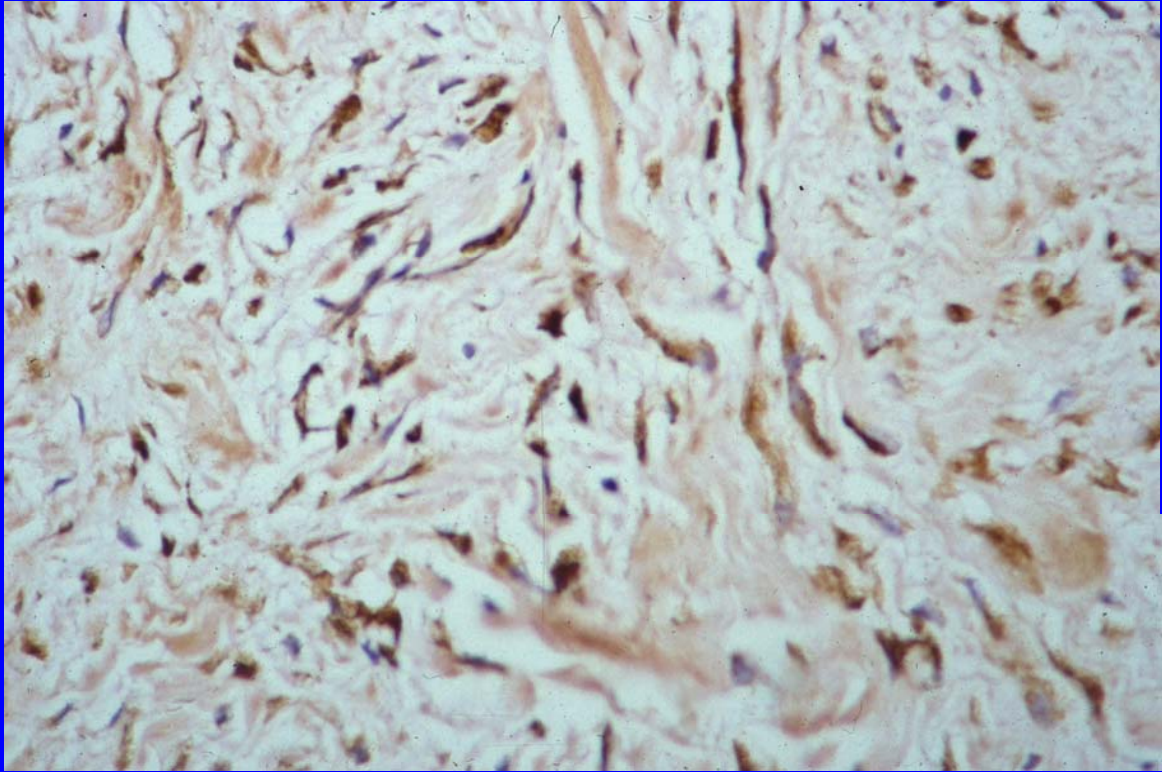
THANK YOU

# ABNORMAL WOUND HEALING



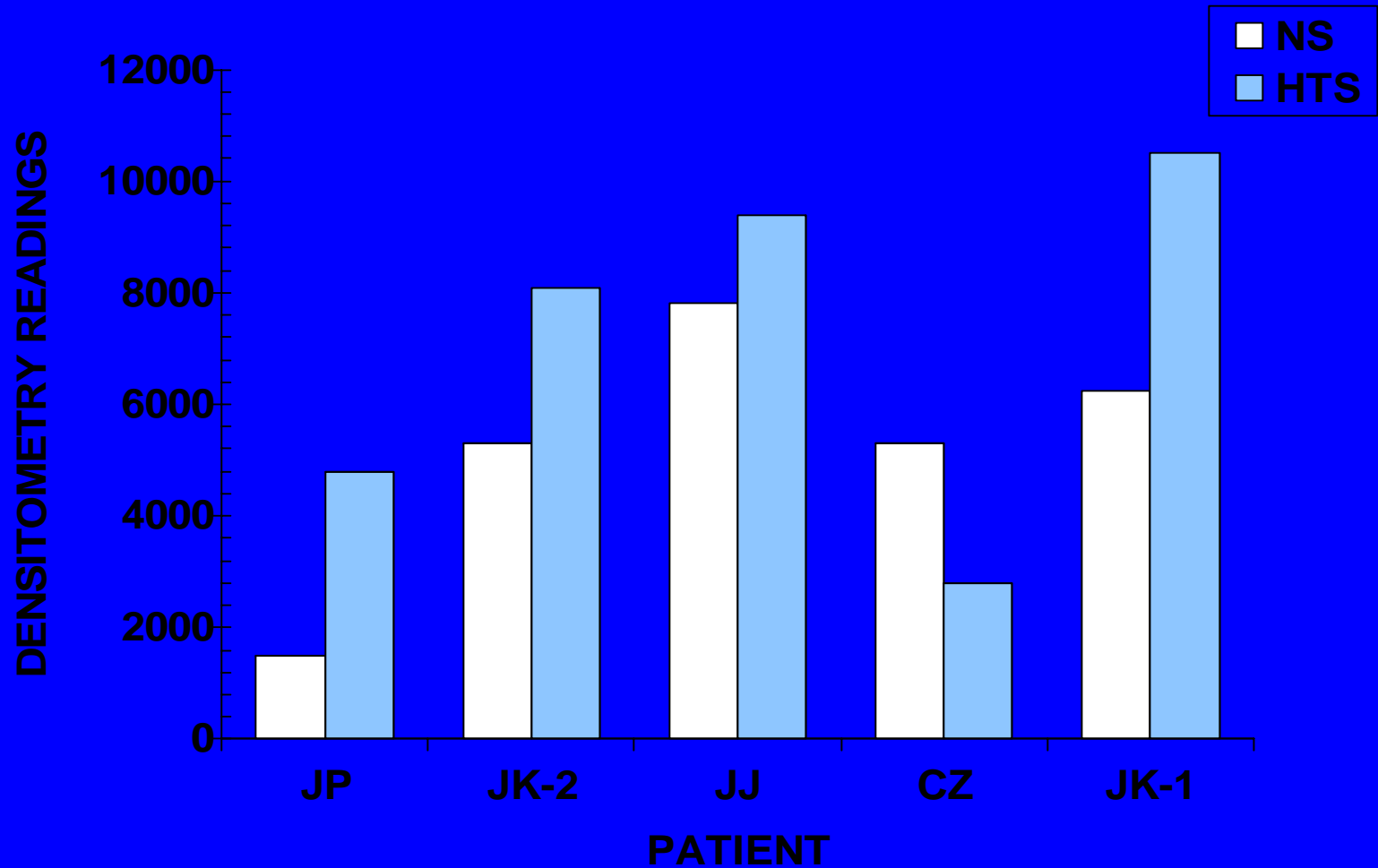








# TGFb Synthesis by Scar Cells

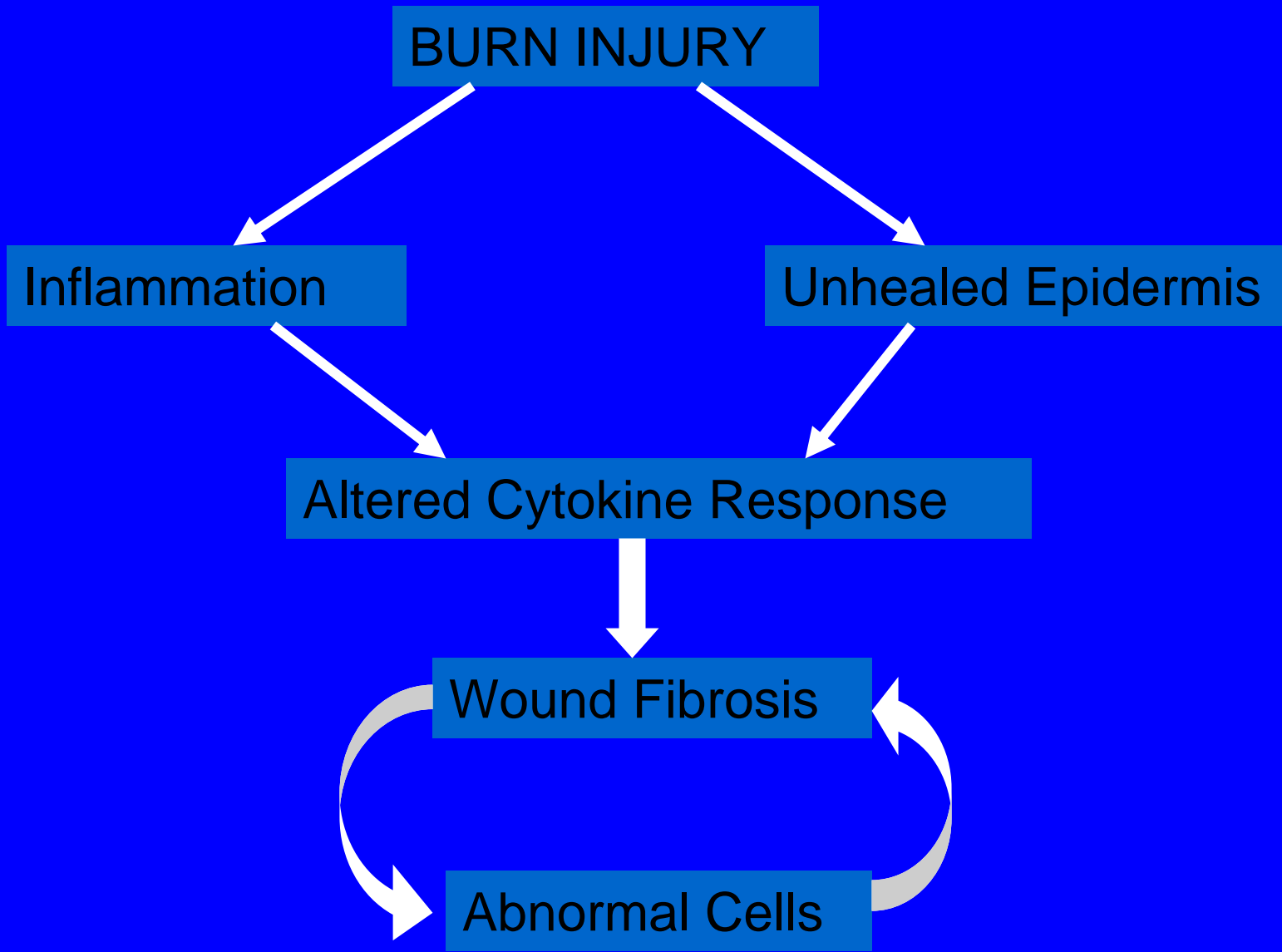


# Results

Conditioned media from keratinocytes decreased fibroblast collagen synthesis ( $p,0.001$ ) and increased cell replication ( $p=0.004$ )

Neither fibroblast conditioned media nor unconditioned media had this effect

Co-culture of fibroblasts with keratinocytes decreases collagen synthesis when the cells are in direct contact or separated by a 0.2 micron filter



# Hypothesis

Epidermal cells regulate fibroblast  
matrix synthesis

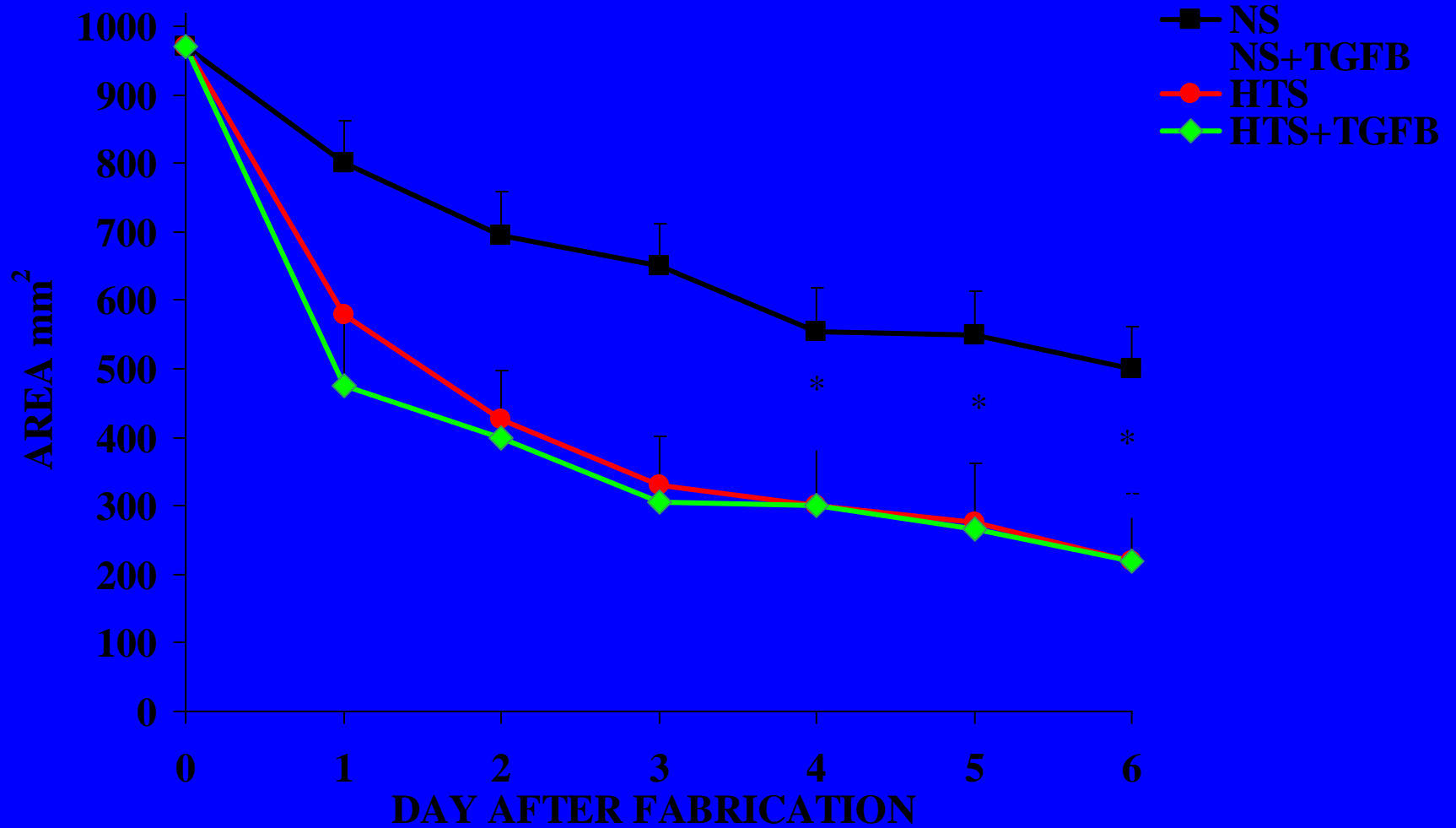
# WHAT WE DO NOT KNOW

- What are the specific inducers for excess collagen synthesis and matrix contraction?
- Is TGF $\beta$  the only important HTS inducer?
- Are TGF $\beta$  regulatory proteins present?, Functional?, Relevant?

# Comparison of Shear Wave Propagation Velocity Between Uninjured Skin and Normally Healed Skin

| Comparison Sites               | No. of Measurement Locations | Mean (m/s) | p-value (t-test) |
|--------------------------------|------------------------------|------------|------------------|
| Distant Uninjured              | 182                          | 48.4       | .175             |
| Adjacent Uninjured             | 67                           | 50.2       |                  |
| Distant and Adjacent Uninjured | 249                          | 48.9       | .018             |
| Adjacent Normally Healed       | 21                           | 54.6       |                  |

# CONTRACTION RATES



\* + significant difference between NS and NS+TGFB  
and no difference between NS + TGFB and HTS