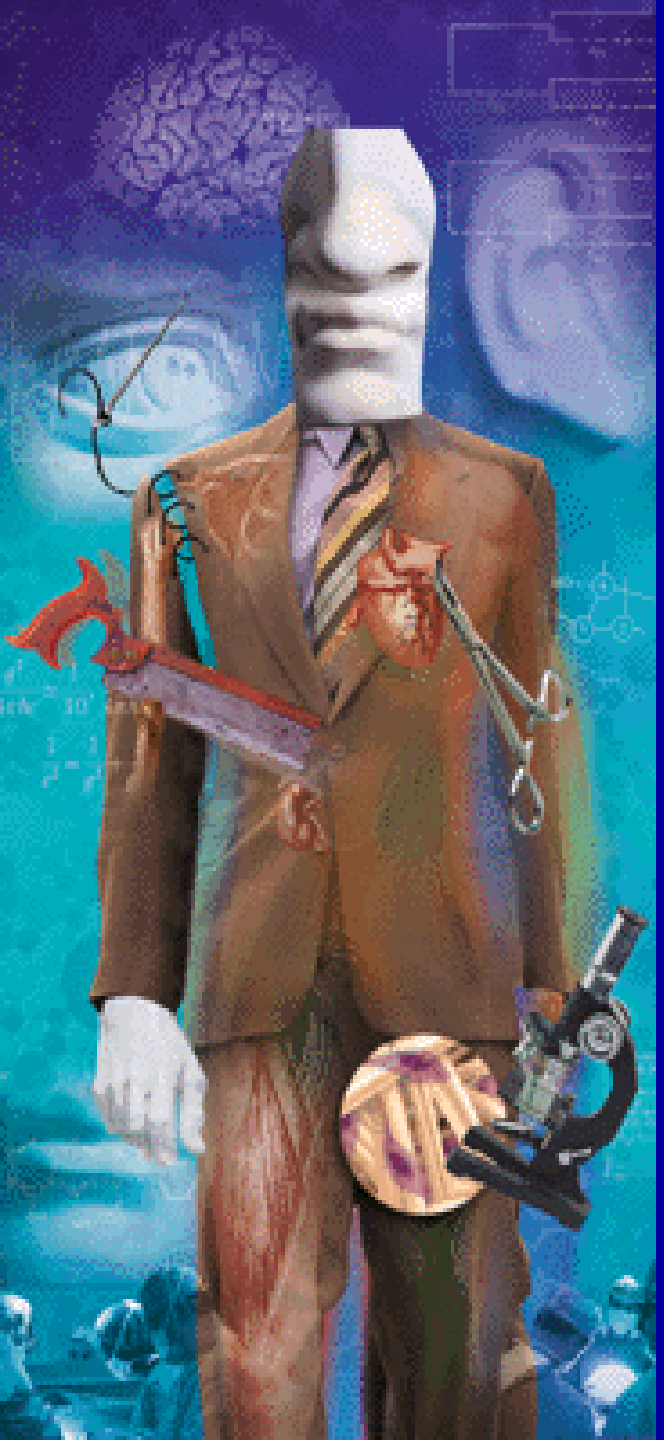


University of Miami Skin Disease Research Center

Tissue Engineering For Wound Healing: A Clinical Perspective

Robert S Kirsner, MD, PhD

Department of Dermatology & Cutaneous Surgery

Department of Epidemiology & Public Health

University of Miami Miller School of Medicine

Translational Wound Healing Research Program

Wound Healing Research Faculty
Department of Dermatology
at the University of Miami

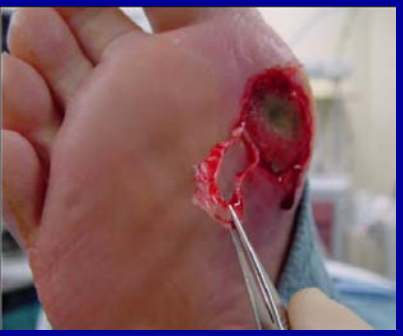
9 Federally Funded Wound Investigators

Dragana Adjac, PhD -Biofilms
Evangelos Badiavas, MD, PhD- Stem Cells
Tongyu Cao, PhD- Keratin Biology
Steve Davis- Animal Models
Robert S. Kirsner, MD PhD- Chronic Wounds
Jie Li, MD, PhD- Angiogenesis
Irena Pastar, PhD- MicroRNA
Olivera Stojadovanic, MD- Malignancy and Wounds
Marjana Tomic-Canic, PhD- Biomarkers

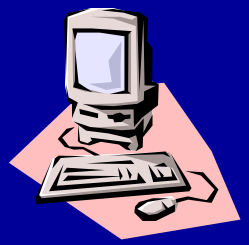
University of Miami Skin Disease Research Center

Translational Research: "Soup to Nuts"

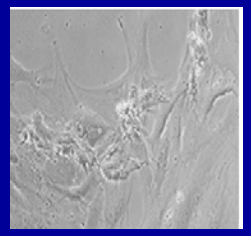
Study Patients



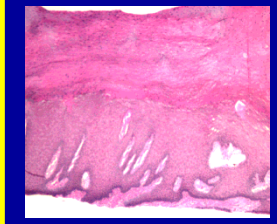
Analyze Tissue

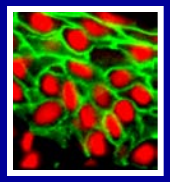


"Wound-omics"



Generate Primary Cells

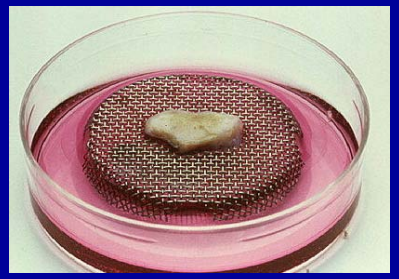




Histology & Immunohistochemistry

Develop Therapy

Animal Models



Reconstituted Skin

Test Therapy

Stem Cells
Tissue Therapy

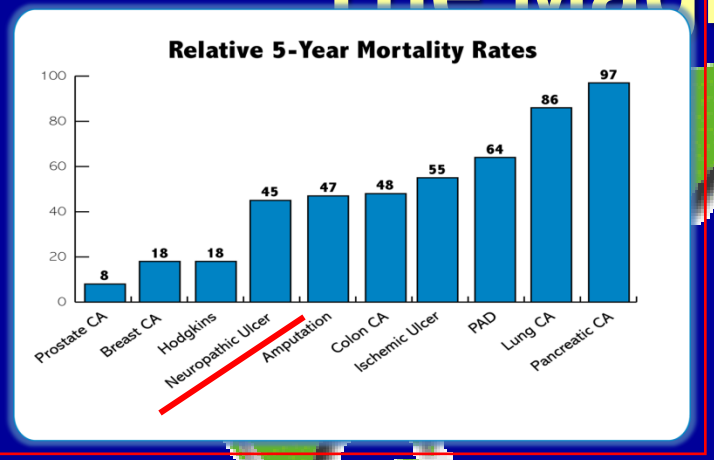
Outline

Improved Environment For Engineered Skin For Wound Healing

Greater Appreciation of Medical Need

Current and Future Perspective: The Magnitude of Wounds

DIABETES PANDEMIC: Projected 2025 (millions)



Worldwide
2025 = >500 million

1 in 4 will develop a foot ulcer

US
2025 = >50 million

HEALING OF CHRONIC WOUNDS

DFU

Clinical trials

12 weeks: 24%

20 weeks: 31%

Clinical Practice

32 weeks: 30-45%

Eurodial Registry

64%

VLU

Clinical Trial & Clinical Experience

6 months 30-75%

Standard of care 12-wk healing rates 20-40% in clinical trials

Current Standard of Care Inadequate for Some Patients

Commercially Available Tissue Engineered Therapies for Diabetic Foot and Venous Ulcers In US

Category	Product	Indication
Bilayered -Tissue Engineered Skin	Apligraf	VLU and DFU- Approved
Dermal -Tissue Engineered Skin	Dermagraft	DFU- Approved

Outline

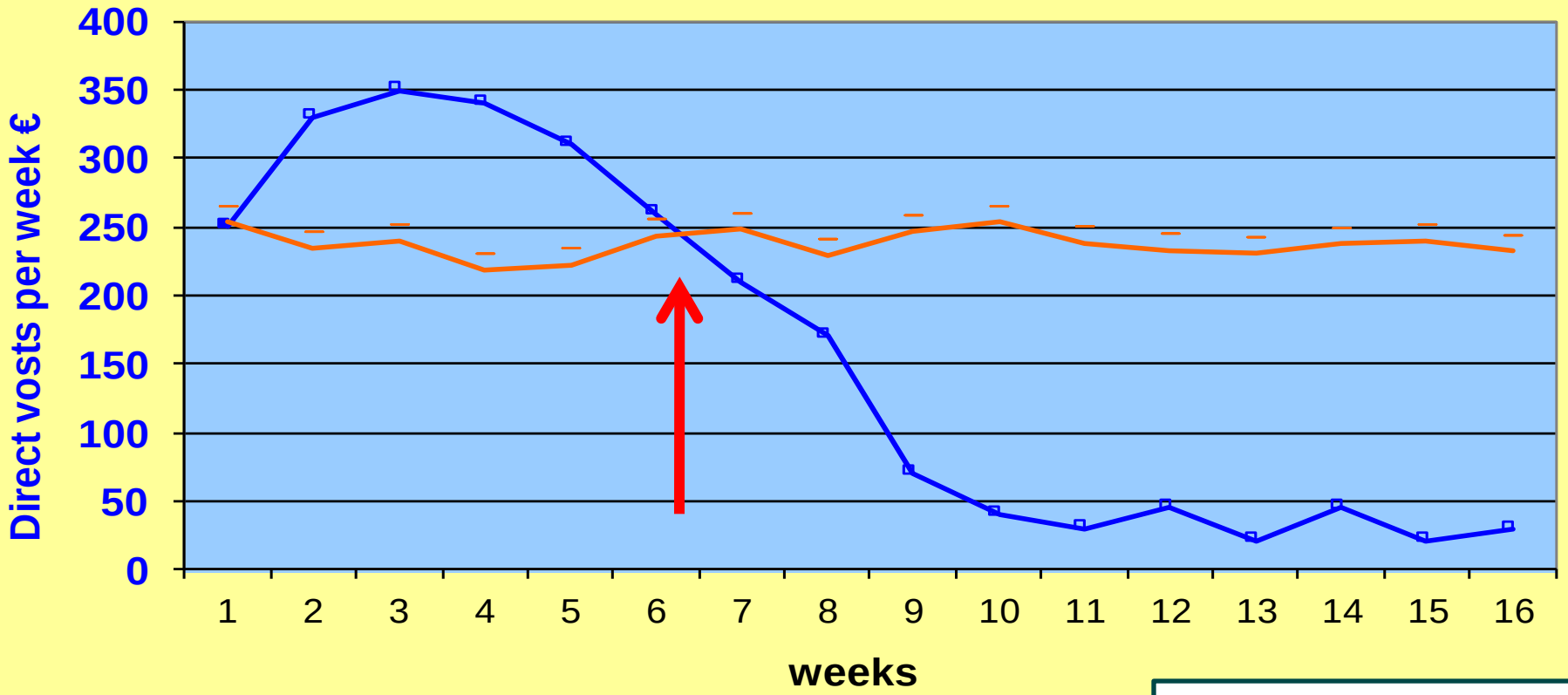
Improved Environment For Engineered Skin For Wound Healing

Greater Appreciation of Medical Need

Improved Understanding of When To Use

Advanced Wound Therapy:
Higher initial costs, but total costs reduced or benefits increased

„Traditional“ Wound Therapy:
Lower initial costs, but total costs increased or benefits reduced



Lancet In Press

Lack of 4 week wound size reduction-
Predictive of need for advanced therapies
and part of guidelines of care

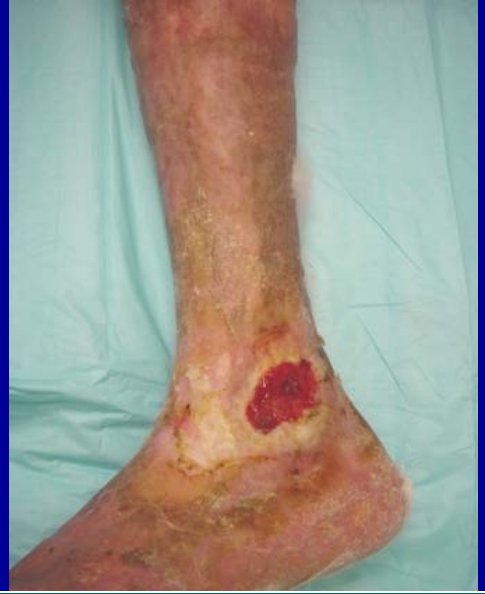
Outline

Improved Environment For Engineered Skin For Wound Healing

Greater Appreciation of Medical Need

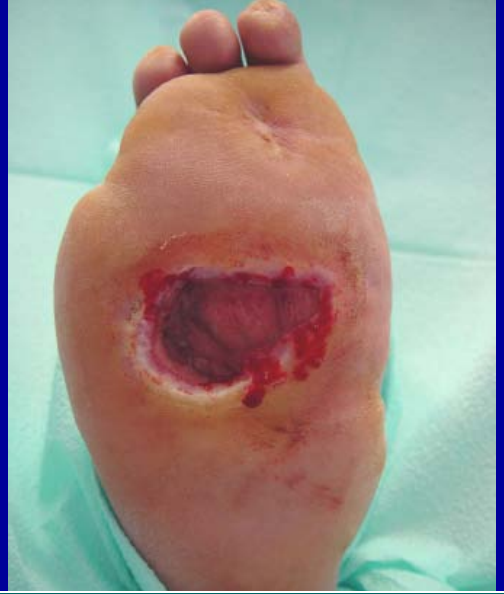
Improved Understanding of When To Use

Improved Access to Clinicians



Nurses

Therapists



Venous Ulcer

Diabetic Neuropathic Ulcer

Physicians/ Surgeons

Podiatrists

Wound Centers

Multi-Disciplinary Wound Healing Clinic
A Healogics Center

Robert Kirsner, MD, PhD- Dermatology*
Lee Goldstein, MD- Vascular Surgery
Arash Bornak, MD- Vascular Surgery
Seema Khurana, MD- Phys Med-Rehab
Magaly Rodriguez, MD- General Surgery
Alexis Powell, MD- Infectious Disease
Christopher Salgado, MD- Plastic Surgery
Haaris Mir, MD- Plastic Surgery
Tom Zwick, MD- Podiatry

Bertha Jimenez- Program Director
Monica Perez- Nurse Director
Adrian- Case Manager
Marlene- Case Manager
* Medical director

Healogics manages 540+ Wound Care Centers

188,000 New Patients Treated

Dedicated to Research

Outline

Improved Environment For Engineered Skin For Wound Healing

Greater Appreciation of Medical Need

Improved Understanding of When To Use

Improved Access to Clinicians

Better Appreciation of Mechanisms of Action Leading to Rational Study Designs, Dosing, and Reimbursement

Creating Skin Substitutes

The Biology of Skin Grafts

Skin Grafts as Pharmacologic Agents

Robert S. Kirsner, MD; Vincent Falanga, MD; William H. Eaglstein, MD

• *Background.*—Skin grafting is commonly used to treat nonhealing wounds. However, how skin grafts help to heal wounds is not entirely known. Why epithelium from grafted skin is able to migrate and cover these wounds, while epithelium at the edge of nonhealing wounds is unable to, is a long unanswered biologic question.

Observations.—The recent use of cultured epithelial allografts has rekindled interest in the biology of skin grafts. Replaced, even in chronic wounds, by recipient epithelium, cultured epithelial allografts appear to work by providing a potent stimulus to healing imparted by the graft itself. Based on this, we have reassessed how skin autografts help to heal wounds and hypothesize that, in a similar fashion, autografts may work not only by replacing tissue but also by providing a stimulus for healing.

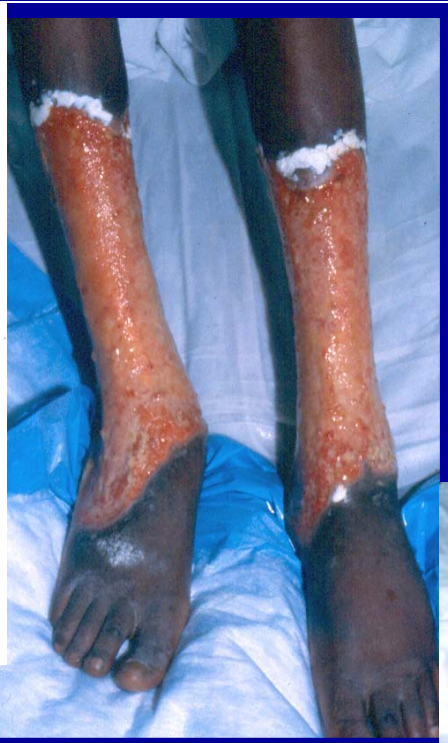
Conclusions.—We suggest that skin grafts may work not only as tissue replacement but as pharmacologic agents that provide a stimulus for healing. We believe that, someday, it may be possible to augment the stimulatory properties of donor skin to speed healing of the recipient wound.

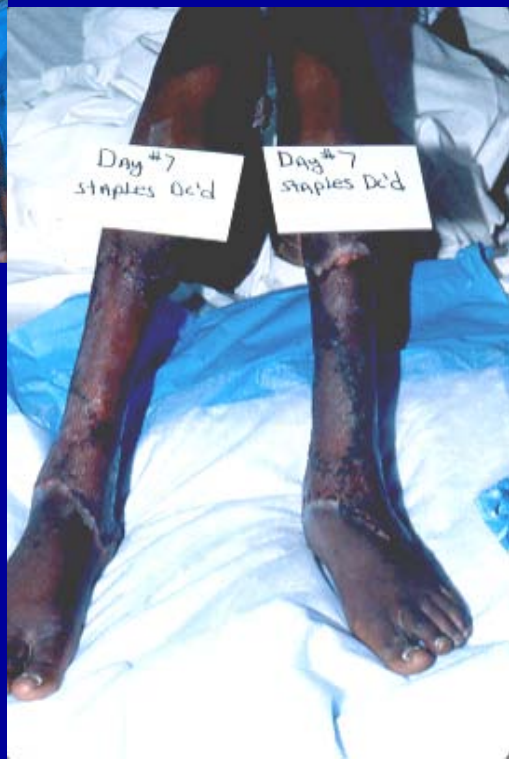
(*Arch Dermatol.* 1993;129:481-483)

partial-thickness grafts, is able to migrate and cover the same wounds is a long-standing unanswered biologic question.

Recently, information concerning the fate of cultured epithelial allografts has allowed us to hypothesize about how skin grafts work in healing chronic wounds. It has been learned that the success of cultured epithelial allografts appears to be due to a potent stimulus to healing provided by these grafts. We suggest, in a similar fashion, that autografts may work not only by replacing tissue but also as a pharmacologic agent stimulating wound closure.

Over the past decade, cells grown in the laboratory through tissue culture techniques have been used to treat acute and chronic wounds. In 1981, O'Conner et al[2] published the first data on the use of cultured expanded autologous (derived from self) epithelial cell sheets in the treatment of large wounds in burn patients. This event heralded the beginning of using cultured cells as skin grafts. However, the idea for using sheets of cultured cells for grafting may have begun

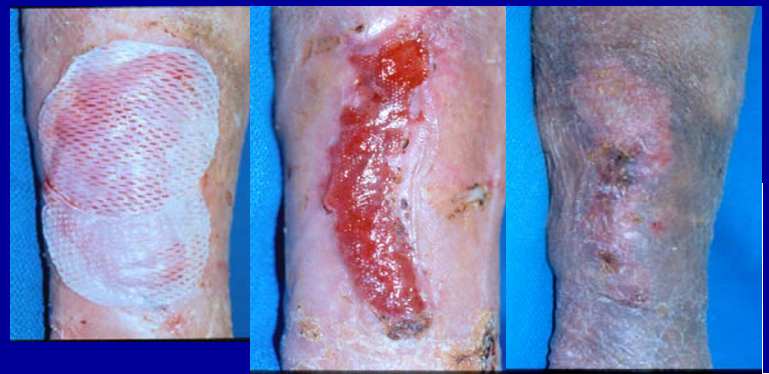




Kirsner RS, Falanga V, Eaglstein WH: Arch Dermatol 1993; 129: 481-483

Persistence of DNA from Tissue Engineered Skin

Study Protocol	Study Week			
	1	*2*	*4*	*6*
Venous ulcers	-	-	2/8	
EB wounds	-	-	-	2/11
Donor site wounds	2/7	1/6	1/7	

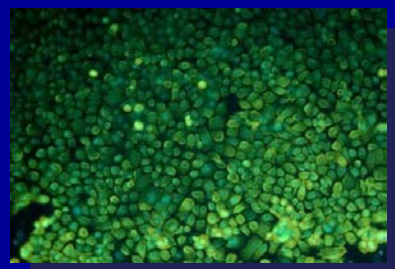


Hu et al: Wound Repair Regen 2006; 14:427-33.
Falabella et al: Arch Dermatol 2000;136:1225-30.
Phillips et al: Arch Dermatol 2002;138:1079-81.

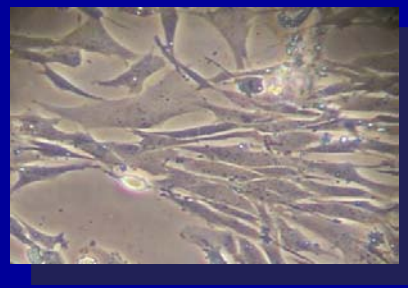
HP802-247

Allogeneic Living Cell Suspension

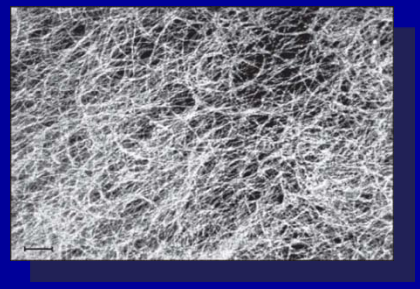
- First-in-Class Product
  - **Component 1:** Growth-arrested allogeneic keratinocytes and fibroblasts in a solution of thrombin and cryo-protectant
  - **Component 2:** Fibrinogen solution
- Cell Delivery
  - Components sprayed sequentially onto ulcer
  - Fibrinogen and thrombin form human fibrin provisional matrix



Keratinocytes (active)



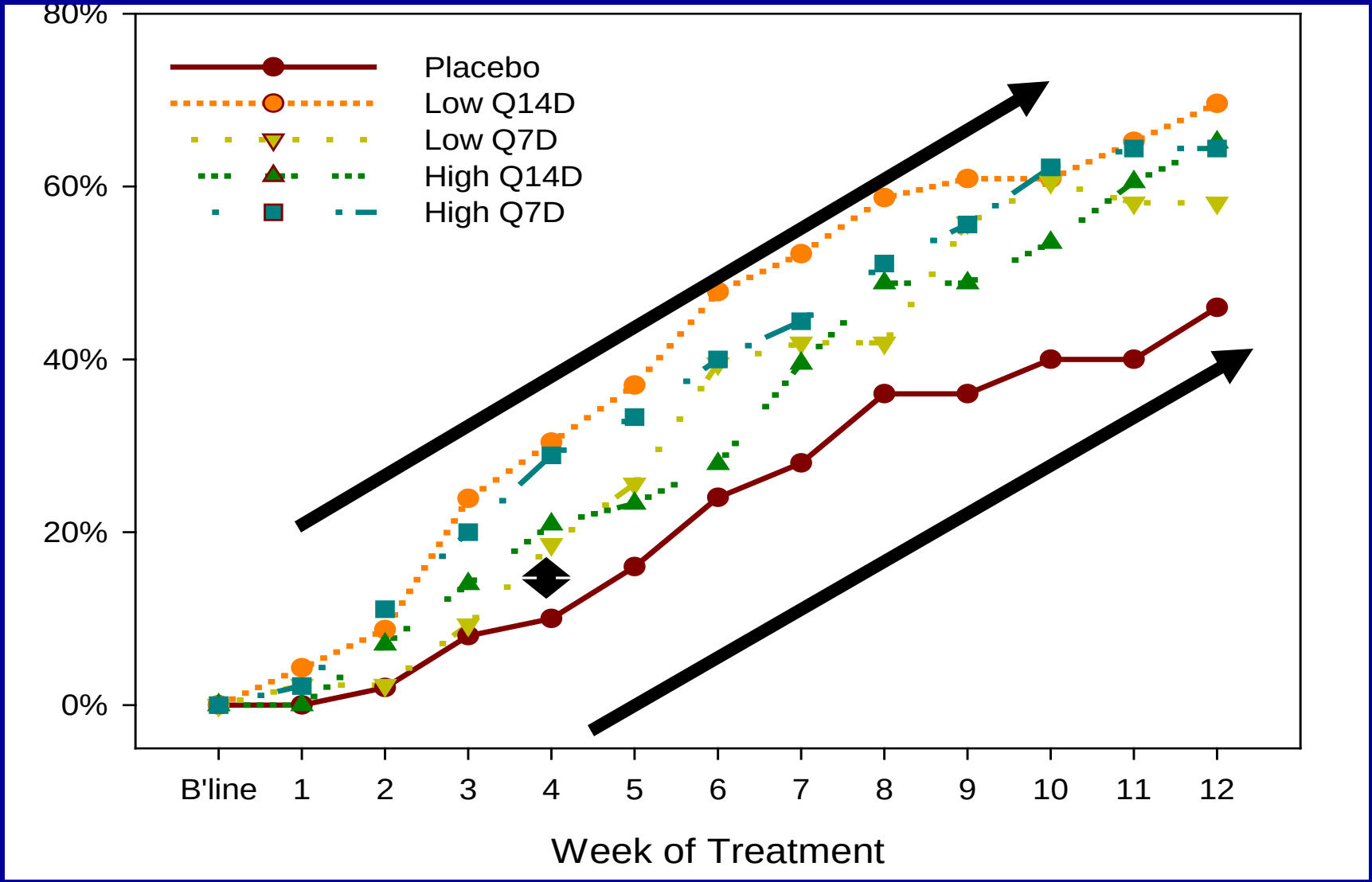
Fibroblasts (active)



Provisional Matrix

Cell Delivery Method

HP802-247 Phase II(b) Trial Results
% of Subjects with Complete Wound Closure by Visit



Q14d=every 14 days, Q7d=every 7 days; significant differences from fibrin control (P<.05) observed for one or more dose groups at all follow-up weeks except 1-3.

Kirsner et al: Lancet In Press.

Summary

Improved Environment For Engineered Skin For Wound Healing

Greater Appreciation of Medical Need

Improved Understanding of When To Use

Improved Access to Clinicians

Better Appreciation of Mechanisms of Action Leading to Rational Study Designs, Dosing, and Reimbursement

University of Miami