Developing Small Molecule Therapeutics for Overhealing and Underhealing Wounds

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Banner University Medicine

THE UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE TUCSON
Surgery

Disclosures

- I have an equity interest in in these companies that will be mentioned in my talk
- Only published peer-reviewed data will be presented
- No off-label indications will be discussed

TAUTONA GROUP

Patient Story: Panfacial Burn

17 yo boy, working as “electrician’s helper”, no prior medical history

Cleaning transformer with wire brush

Suffered flash burn to face only, primarily deep partial thickness injury

Transferred to Boston Shriner’s Burn Center

Multiple operations over 6 week admission

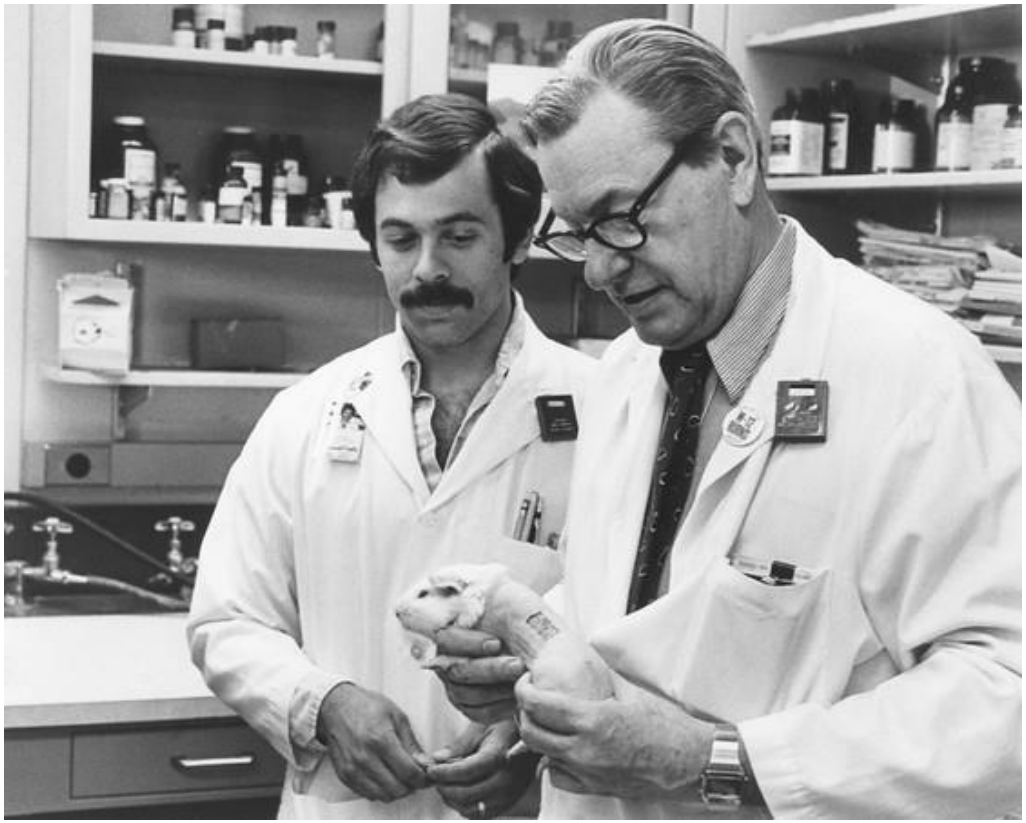
Shriners Hospitals for Children®

HARVARD MEDICAL SCHOOL

Shriners Children's Provides Care for Families Regardless of Financial Circumstances

At Shriners Children's all care and services are provided regardless of the families' ability to pay or insurance status.

Artificial Skin: John F Burke, MD



Wound Tissue Can Utilize a Polymeric Template to Synthesize a Functional Extension of Skin

Abstract. *Prompt and long-term closure of full-thickness skin wounds in guinea pigs and humans is achieved by applying a bilayer polymeric membrane. The membrane comprises a top layer of a silicone elastomer and a bottom layer of a porous cross-linked network of collagen and glycosaminoglycan. The bottom layer can be seeded with a small number of autologous basal cells before grafting. No immunosuppression is used and infection, exudation, and rejection are absent. Host tissue utilizes the sterile membrane as a culture medium to synthesize neoepidermal and neodermal tissue. A functional extension of skin over the entire wound area is formed in about 4 weeks.*

Excessive fluid loss and massive infection are two major problems immediately threatening the life of an individual who has suffered extensive skin loss. This is the case, for example, with victims of deep burns extending over more than 50 percent of the body. Current treatment emphasizes fluid resuscitation and prompt closure of wounds with autografts, cadaver skin, or pig skin following the excision of dead tissue (*1*). Failure to achieve closure of burn wounds within 3 to 7 days after injury significantly increases the probability that the patient will die (*1*).

We have developed a bilayer polymeric membrane that promptly and aseptically closes skin wounds in animals and humans while serving as a template for the construction of a functional extension of the skin. Our design has evolved over the past 11 years from studies of guinea pigs (*2*). The top layer of the membrane is a silicone elastomer and the bottom layer is a highly porous, covalently cross-linked network of bovine hide collagen and glycosaminoglycan (GAG) (Fig. 1) (*3*). We have achieved reproducible conditions under which autologous basal cells, seeded into the

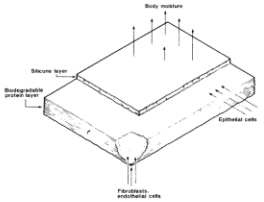


Fig. 1. Schematic representation of a standard version of the noncellular bilayer polymeric membrane (stage 1). The moisture flux through the layers ranges from 1 to 10 mg/cm² per hour. Fibroblasts and endothelial cells migrate into the bottom layer while epithelial cell sheets advance from the wound edge in the plane of the membrane, between the two layers. The top layer is a conventional medical-grade silicone which undergoes cross-linking at room temperature following exposure to ambient moisture. The bottom layer is a cross-linked network of collagen and chondroitin 6-sulfate, a GAG (bound GAG content 8.2 ± 0.8 percent by weight, average molecular weight between cross-links 12,750 ± 3,300, pore volume fraction 96 ± 2 percent, mean pore size 50 ± 20 μm). The collagen-GAG layer undergoes biodegradation at a controlled rate and is replaced by neodermal tissue while the silicone layer is spontaneously ejected following formation of a confluent neoepidermal layer under it. Stage 2 membranes are identical except that autologous epidermal (basal) cells are seeded into the membranes before grafting.

Science, 1982

Artificial Skin for Burn Victims Is Reported Developed in Boston

By LAWRENCE K. ALTMAN

Artificial skin made from cowhide, shark cartilage and plastic has been successfully used by doctors at the Massachusetts General Hospital in Boston to replace skin destroyed by burns, the doctors reported yesterday. They said that the new skin successfully performed many of the functions of real skin.

Unlike other substances that are used temporarily to cover the skin of burned patients, they said, the newly developed skin avoids the need for drugs that suppress the body's immune system when skin is taken from relatives and other people for skin grafts. Accordingly, the new skin does not increase the burn patient's chances of getting a fatal infection. Infections are a common cause of death among burn patients.

A total of 10 burn patients were treated with the new skin at the Massachusetts General Hospital and the adjacent Shriner's Burns Institute. Three of the 10 "probably would have died" without it, Dr. John F. Burke, the surgeon who headed the Boston team, reported at a meeting of the American Surgical Association in Chicago.

The artificial skin, which is still experimental, is made in small amounts in a laboratory, Dr. Burke said in an interview. He said that it was available now only at the hospital and the institute.

"We can make only a very small proportion of what we need," he said. "We have to treat one patient at a time because we can't make it quick enough for others."

Accordingly, it has been used only for patients with extensive burns. However, he said that prospects for commercial application were very good and that ultimately it could be stockpiled in hospitals for immediate use.

"The manufacturing process is relatively simple," he said.

It was not immediately clear whether approval by the Food and Drug Administ-

Continued on Page A20, Column 3

INSIDE

Exxon Earnings Fall 16.0%

The Exxon Corporation reported a 16.0 percent decline in earnings, a confirmation of the current oil glut. Gulf Oil had a 22 percent decline. Page D1.

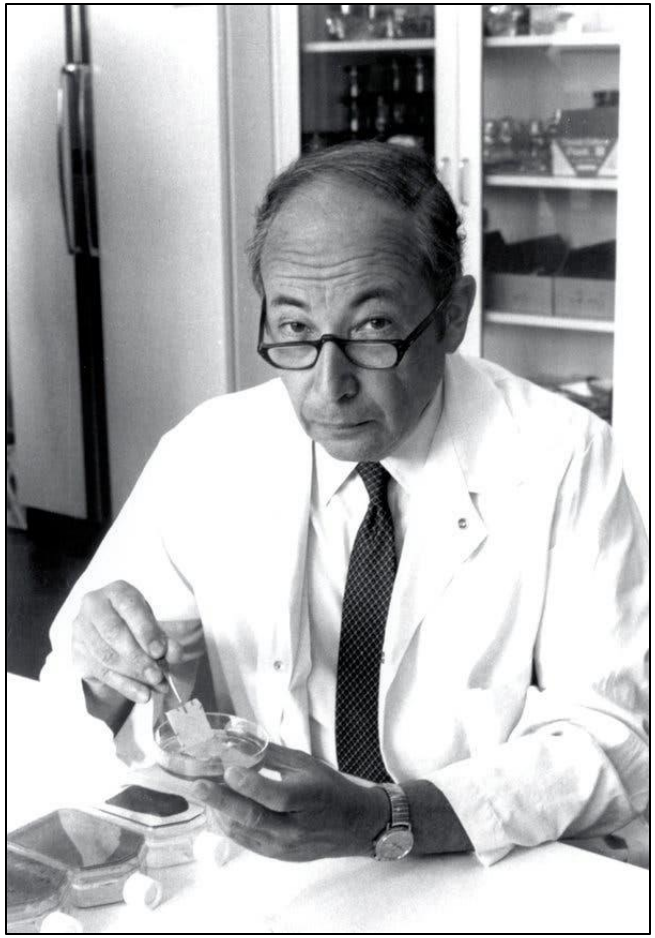
Suslov in Warsaw for Talks

Mikhail A. Suslov, a top member of the Soviet Politburo and a symbol of Kremlin orthodoxy, is meeting with Polish Communist leaders. Page A8.

News Summary and Index, Page B1

NY Times, 1982

Cultured Keratinocytes: Lab Grown Skin



Howard Green, MD

MEDICAL INTELLIGENCE

PERMANENT COVERAGE OF LARGE BURN WOUNDS WITH AUTOLOGOUS CULTURED HUMAN EPITHELIUM

G. Gregory Gallico, III, M.D.,
Nicholas E. O'Connor, M.D.,
Carolyn C. Compton, M.D.,
Olaniyi Kehinde, B.A., and Howard Green, M.D.

WHEN burns are so extensive that skin grafts obtainable from remaining donor sites are insufficient to provide wound coverage, a new source of autograft must be found. Human epidermal cells from a small skin-biopsy sample can be cultured to produce coherent epithelial sheets sufficient to cover the entire body surface.[1,2] When this epithelium was applied to wounds on athymic mice it generated a human epidermis.[3] Autologous cultured epithelium placed on small burn wounds in adults[4] and children[5] adhered and generated a permanent epidermis similar to that resulting from split-thickness skin grafts. We report here that in two children who sustained burns on more than 95 per cent of their bodies, half or more of the body surface was successfully covered with cultured epithelial autografts.

From the Departments of Surgery, Division of Plastic Surgery, Shriners Burns Institute, Massachusetts General Hospital, and Brigham and Women's Hospital, Boston; the Department of Pathology, University of Massachusetts, Worcester; and the Department of Physiology and Biophysics, Harvard Medical School, Boston. Address reprint requests to Dr. Gallico at Massachusetts General Hospital, Boston, MA 02114.

Supported in part by grants from the Shriners Burns Institute and the National Cancer Institute and by a gift from Johnson and Johnson.

Methods

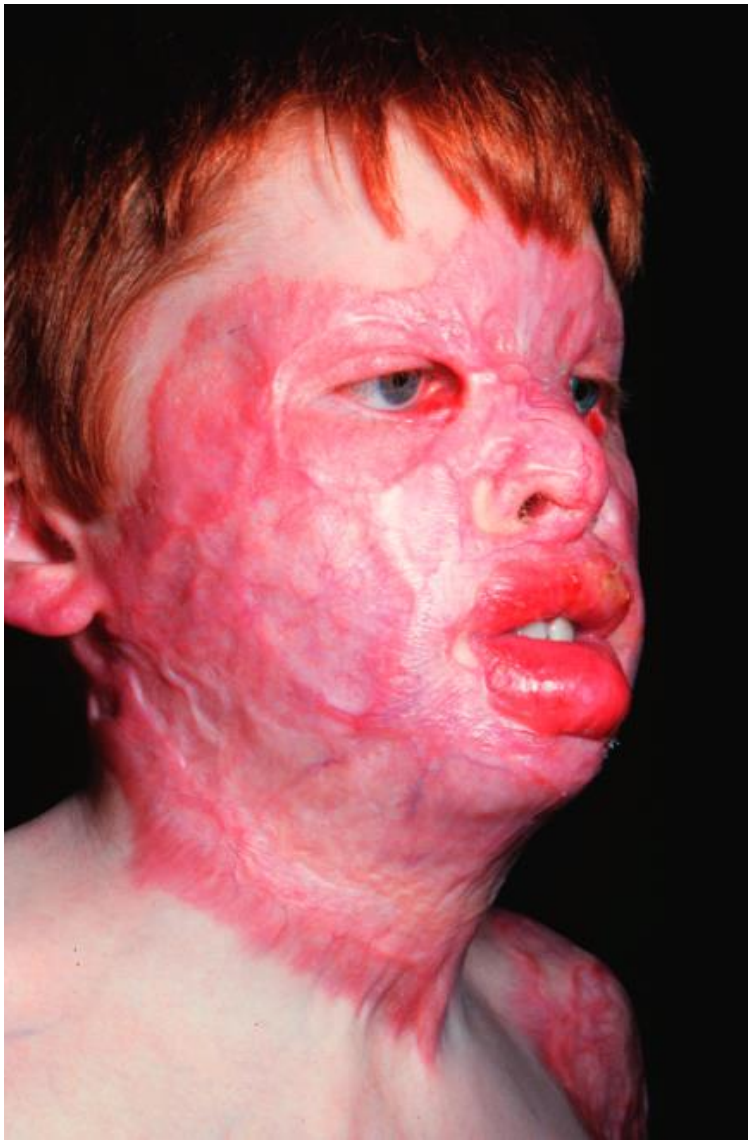
On admission, full-thickness biopsy specimens of skin (2 cm^2) were removed from an axilla in each patient. The skin was minced and trypsinized to produce a single-cell suspension. Aliquots of 2×10^6 cells were frozen and stored or cultured in flasks with a surface area of 75 cm^2, as described previously.[5] When the colonies became confluent at 10 days, the cultures were trypsinized, and 3×10^5 cells were inoculated to make secondary and tertiary cultures for grafting.

To prepare grafts, the cultured sheets of cells were released from the flasks with Dispase,[1] washed with medium, and clipped to petrolatum gauze cut to 4.5 by 6 cm.[5] The cultured grafts with their gauze backing were placed on prepared wound surfaces, sutured in place, and dressed with dry gauze. The petrolatum gauze was removed 7 to 10 days later.

Except for the cultured epithelial grafts, both patients received the same therapy given to other pediatric patients with major burns. They were nursed individually in enclosed directional-air-flow units with controlled temperature and humidity. Occlusive dressings

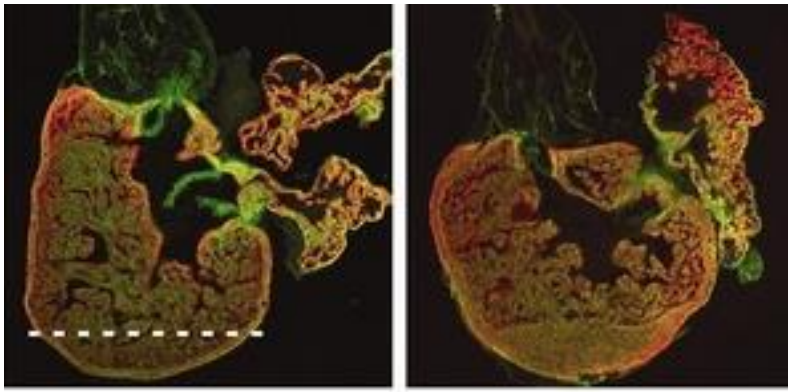
New England Journal of Medicine, 1989

Long Term Follow Up



Scarless Repair and Regeneration in Nature

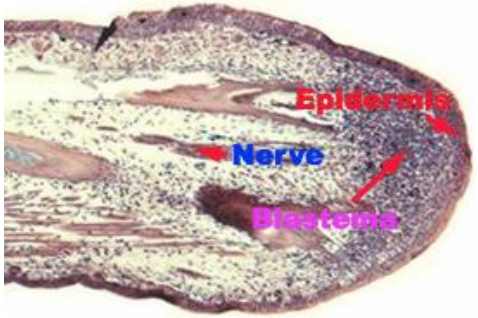
Zebrafish



Pre-amputation heart

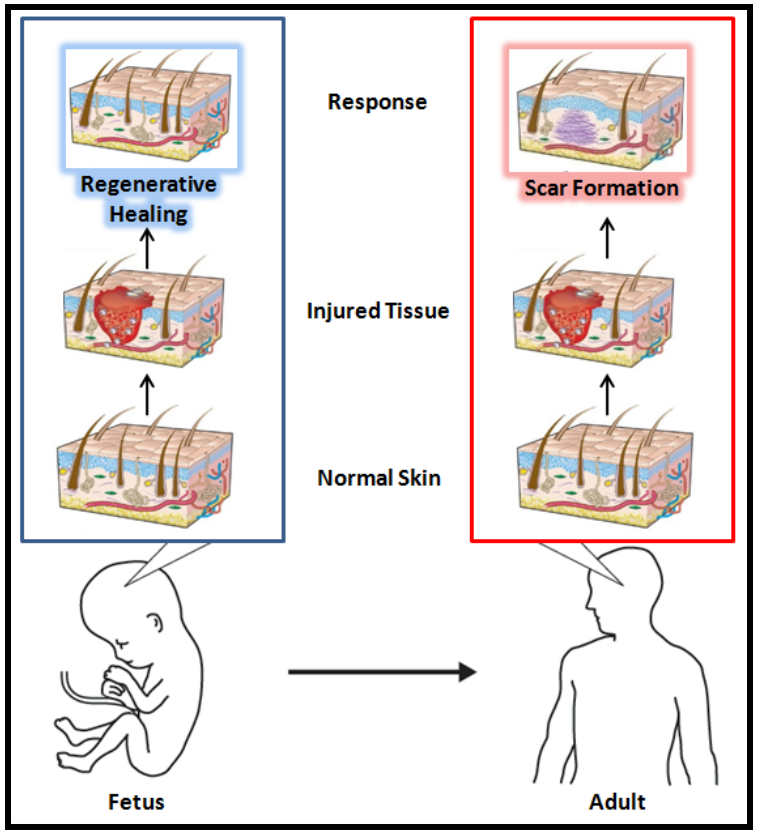
Regenerated heart at 60 days

Salamander



Limb Regeneration

Human Skin Regeneration

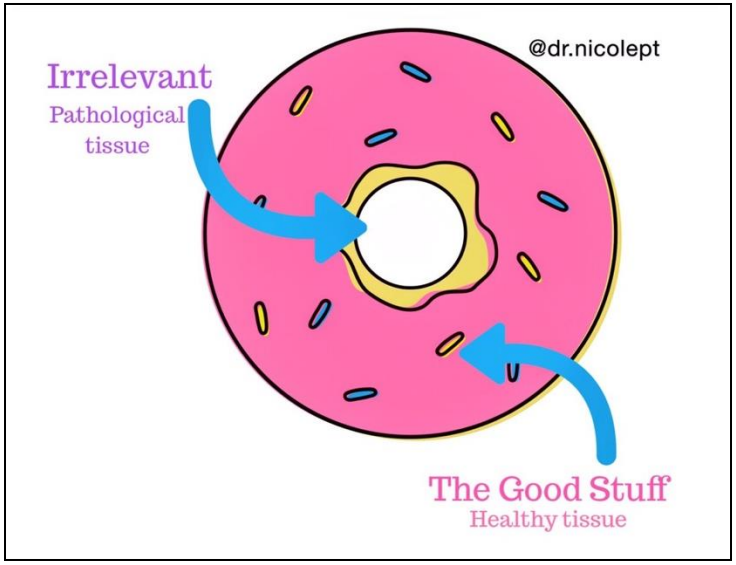


Scarless Fetal Healing

Need New Approaches

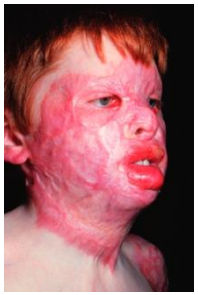
- There are ***unique*** challenges in the surgical wound environment (proteases, bacteria)
- Small molecules (i.e., drugs) can withstand these challenges
- Ideally, would deliver therapeutics to surrounding healthy ***intact skin***
- Small molecules have low cost manufacturing which is well-understood by pharma

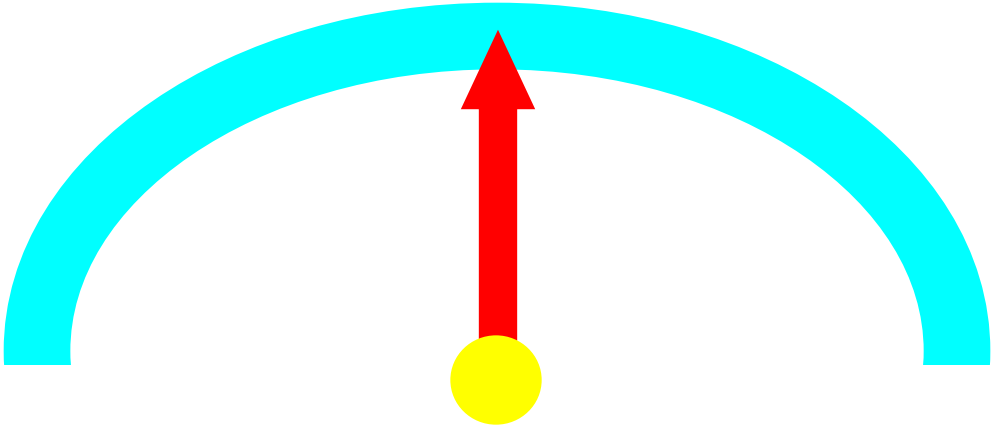
"Treat the donut, not the hole"



Developing New Drugs for Burns and Skin Injuries

Normal Adult Wound Healing



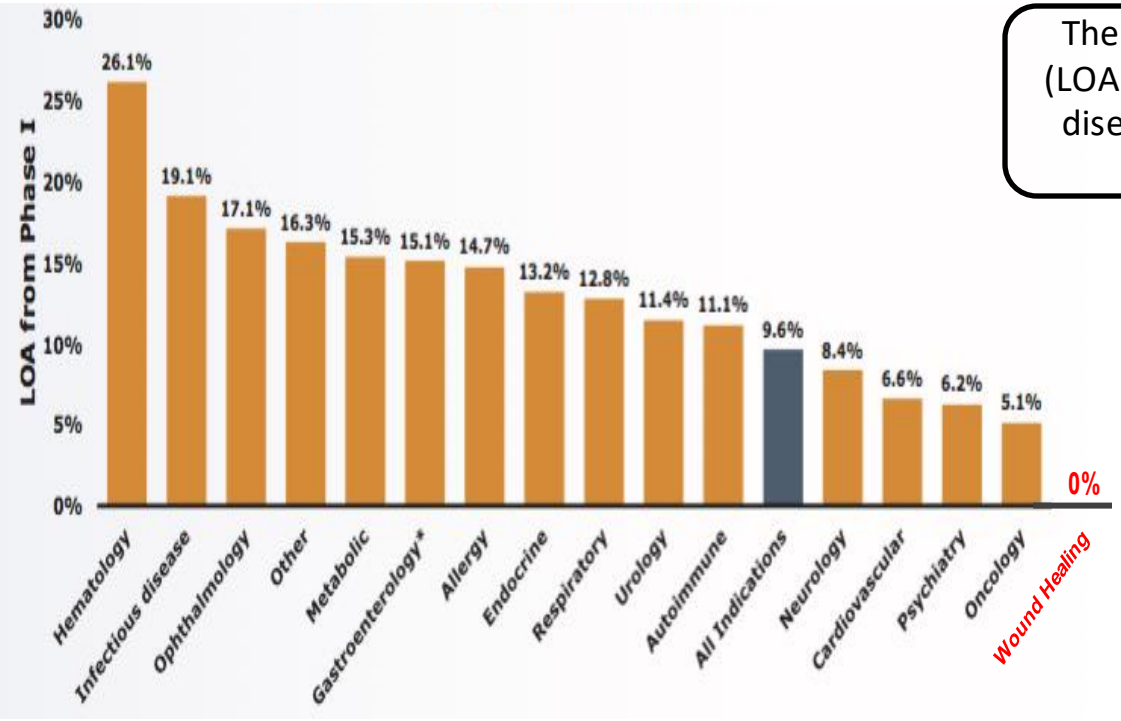


Burns

Chronic Wounds

Largest medical vertical without a single small molecule drug

No FDA Drug Approval for Skin Injury in 25 Years



The Likelihood for Approval (LOA) for drugs across various disease categories between 2006 and 2015

- The last investigational drug approved by FDA for healing chronic wounds was rhPDGF-BB (regranex) approved in 1997 for DFUs

- No small molecule has ***EVER*** been approved for wound healing

Pharma Has Misfired in this Space

Unique Challenges of Skin Injury

- Unlike other medical conditions, skin injury has procedural components (debridement, offloading) making trials difficult to standardize and enroll
- Diabetes has been the focus for pharma but it is the most challenging area for clinical trials
- Low tolerance for off-target side effects, requires local (vs. systemic) formulations typically not developed for early trials by Pharma

As a Consequence, Medical Device Companies Dominate by Selling Modestly Effective, Lightly Regulated Products

We are going to have to do this on our own…

Will Require Entrepreneurship

- What is entrepreneurship?
- Widely misunderstood
- Not about money, “start-ups” or Silicon Valley
- Entrepreneurial thinking guides strategy

What is Entrepreneurship?

"Pursuit of opportunity beyond the resources you currently control"

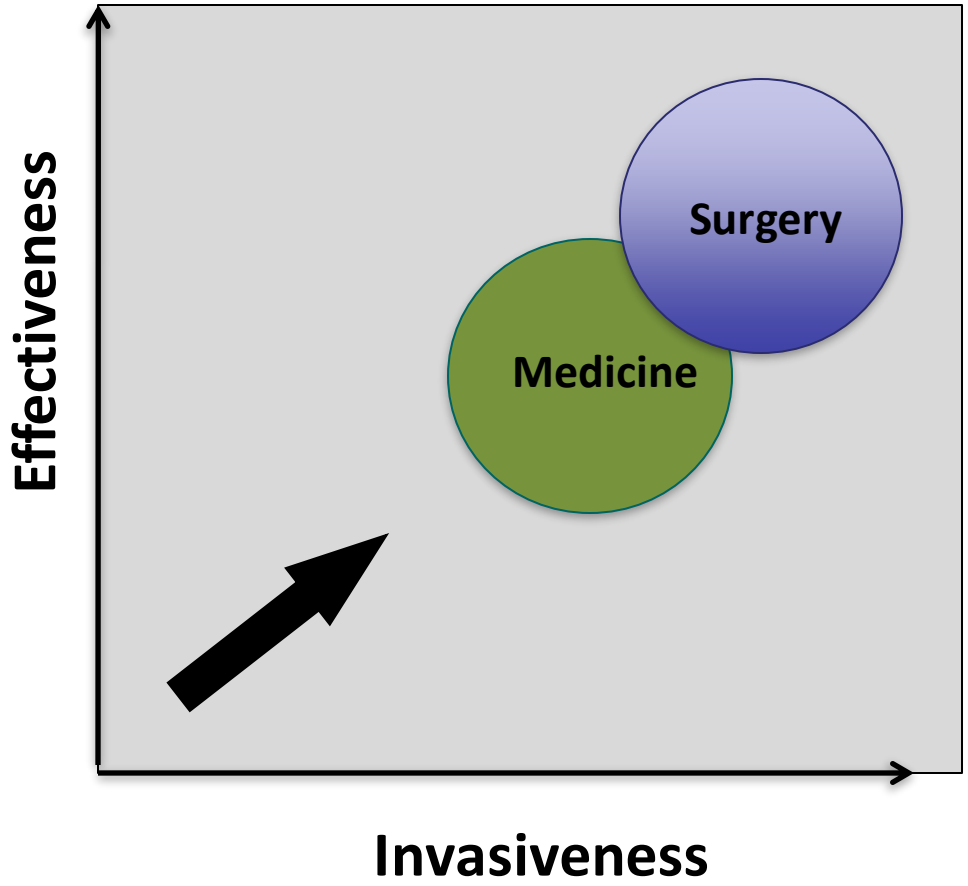
Howard Stevenson, HBS

Pursuit of Opportunity… a singular, relentless focus to solve a problem or fill a need (not primarily financial)

…Beyond Resources Controlled: without the needed resources guaranteed

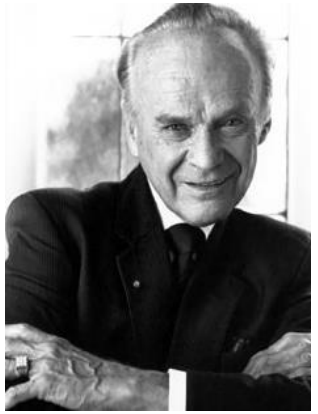
Howard Stevenson, father of entrepreneurship studies at Harvard Business School

Throughout history, surgeons have been driven innovation in medicine through bench to bedside research



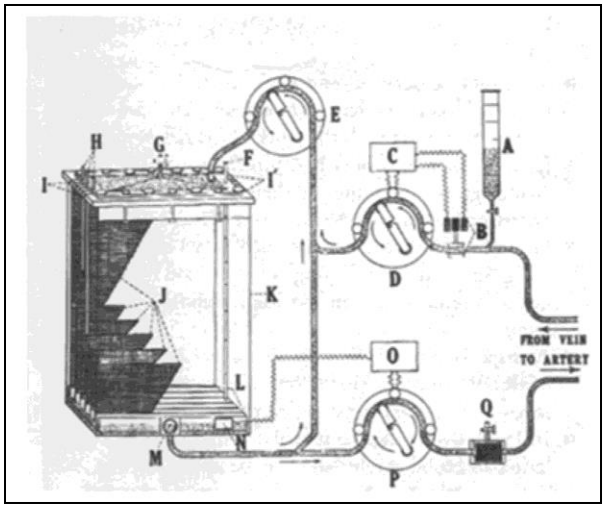
Many Examples of Bedside-to-Bench-to-Bedside Innovation

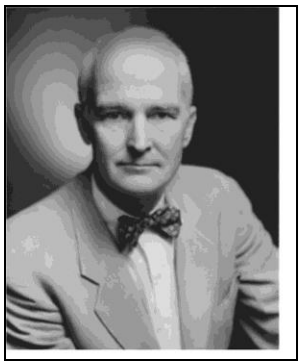
- Solid tumors
- Cardiac therapy
  - Bypasses to stents
  - Valve replacement to TAVR
- Transplantation
- Immunotherapy and Hormonal Therapy for Cancer
- Parenteral Nutrition
- Critical Care

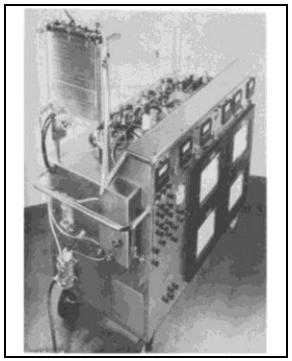


Going from “Bench to Beside” is Getting Harder

- Increasing regulations (FDA)
- Decreasing risk tolerance
- Opportunity cost for surgeons
- Increasing overall expense of getting products to market

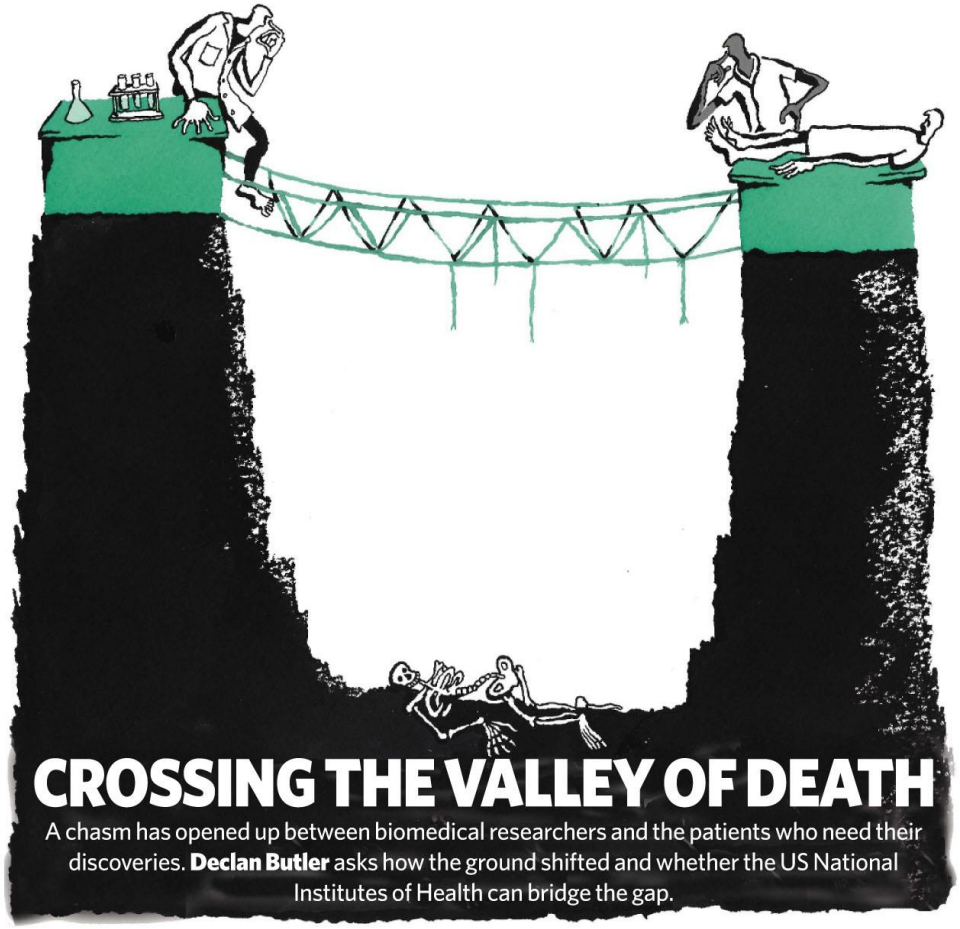






Cardiopulmonary Bypass Machine
John H. Gibbon, Jr

The ”Valley of Death”



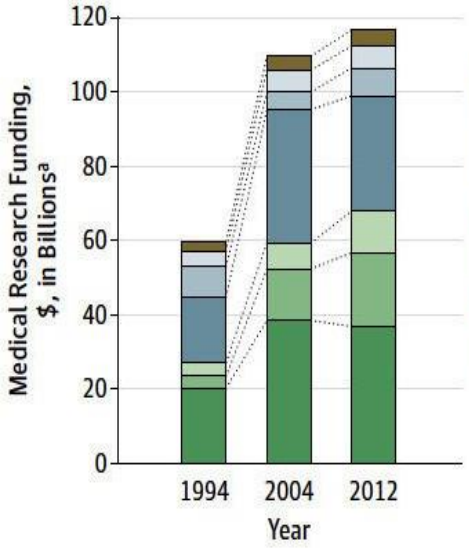
The Cost of Bringing Scientific Advances to Patients is Significant

- To bring a new medical **device** to market costs between $31 million (510k) to $94 million (PMA)

- To bring a new **drug** to market costs from $800 million to $2 billion

Where Do You Find the Money?

1. Federal Grants: NIH, NSF, DoD
2. Industry
3. Foundations/Philanthropy

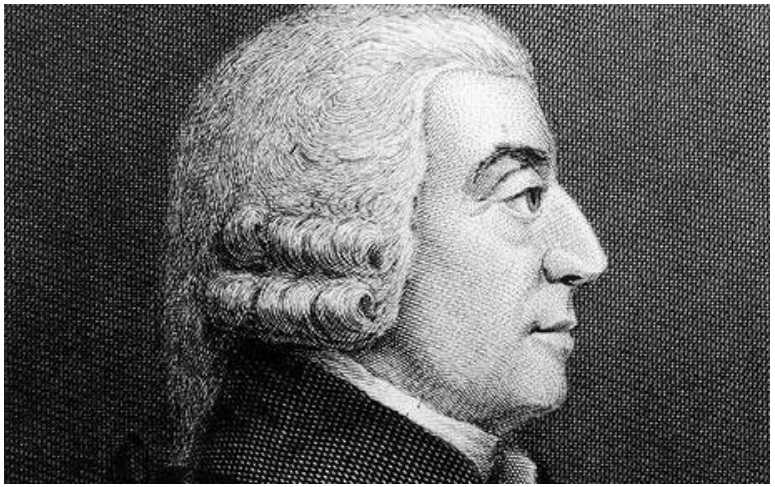


Funding Source	Medical Research Funding, $ (%), in Billions[a] 1994	2004	2012	Compound Annual Growth Rate, %[b] 1994-2004	2004-2012
Foundations, charities, other private	2.6 (4)	3.9 (4)	4.2 (4)	4.2	1.0
State and local government	3.9 (7)	5.9 (5)	6.3 (5)	4.1	0.9
Other federal	8.0 (13)	4.8 (4)	7.1 (6)	-4.9	5.0
National Institutes of Health	17.6 (29)	35.6 (33)	30.9 (27)	7.3	-1.8
Medical device firms	3.8 (6)	7.1 (6)	11.5 (10)	6.6	6.2
Biotechnology firms	3.7 (6)	13.7 (12)	19.6 (17)	14.1	4.6
Pharmaceutical firms	20.0 (34)	38.6 (35)	36.8 (32)	6.8	-0.6
Overall	59.5	109.7	116.5	6.3	0.8

But, none of these funders have the money or interest to take your idea “all the way”…

…eventually you are going to need to more resources than can be obtained from grants or philanthropy

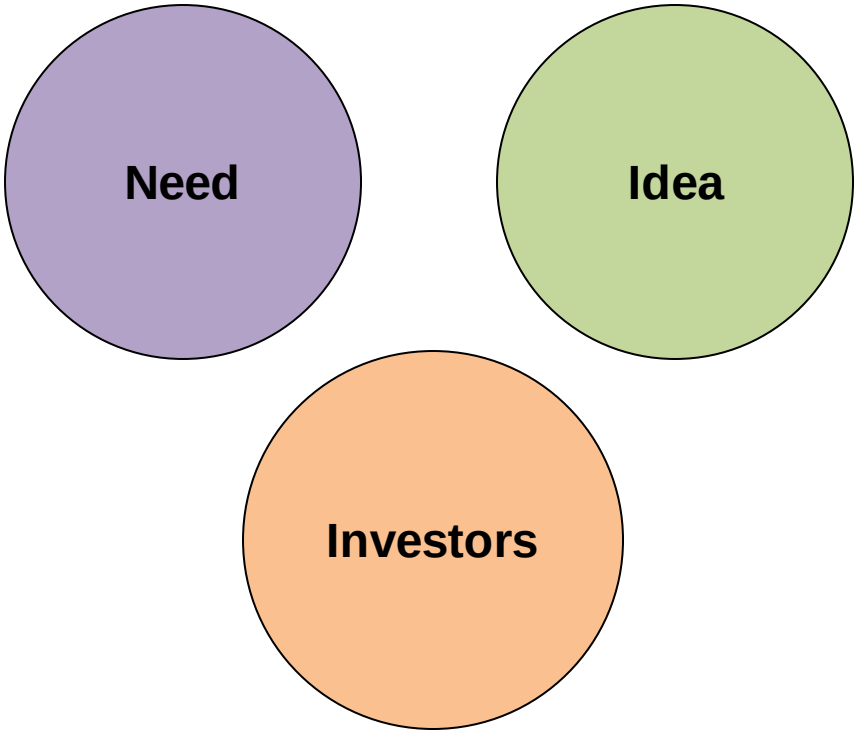
1. Harness the ”genius” of capitalism
2. Need to understand the difference between a good idea and a good business
3. Understand the psychology of professional Investors



Adam Smith
(1700-1986),
Father of Economics

…Usually this takes the form of starting a company and attracting investors

1. Clinical need
2. Idea for a technologic solution
3. Professional investors who believe in the value proposition



Starting a Company is a Building a Team

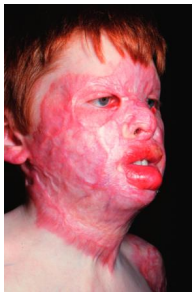
1. Need to find colleagues with complementary skill sets (engineer, MBA, legal, etc.)

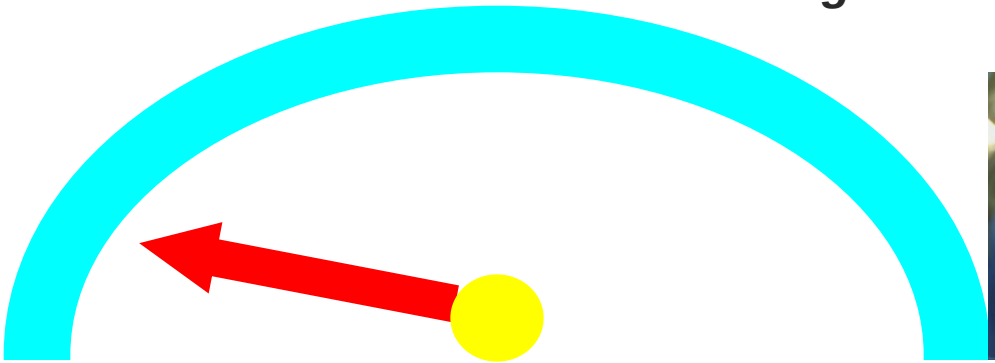
2. Participation on the team gives each member some ownership of the company in the form of equity or options

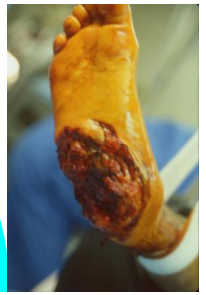
3. Need to create value faster than your “burn rate”

Developing Drugs for Burns and Skin Injuries

Normal Adult Wound Healing







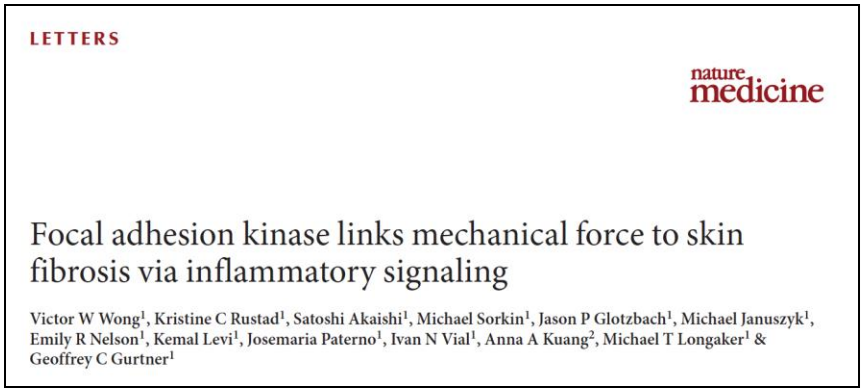
Burns
Hypertrophic Scars
Keloids

Chronic Wounds

Small Molecule Drug Based on an FDA Approved Device that has Treated Over 250,000 Patients

Matthias B. Donelan, MD
Chief of Staff, Boston Shriners Hospital

"Scar Forms Where There is Tension"



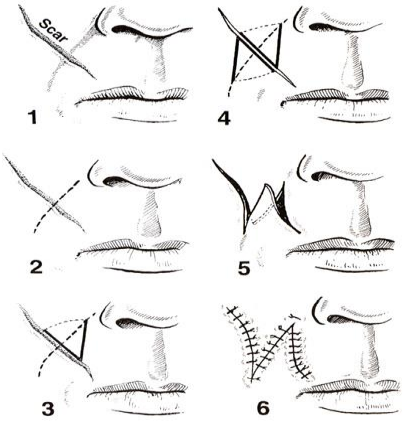
LETTERS

nature medicine

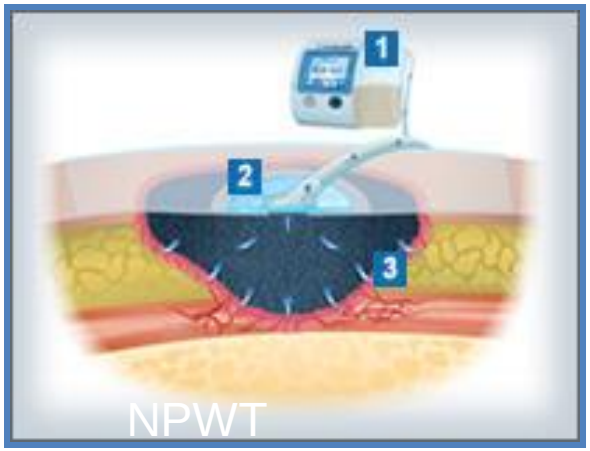
Focal adhesion kinase links mechanical force to skin fibrosis via inflammatory signaling

Victor W Wong[1], Kristine C Rustad[1], Satoshi Akaishi[1], Michael Sorkin[1], Jason P Glotzbach[1], Michael Januszyk[1], Emily R Nelson[1], Kemal Levi[1], Josemaria Paterno[1], Ivan N Vial[1], Anna A Kuang[2], Michael T Longaker[1] & Geoffrey C Gurtner[1]

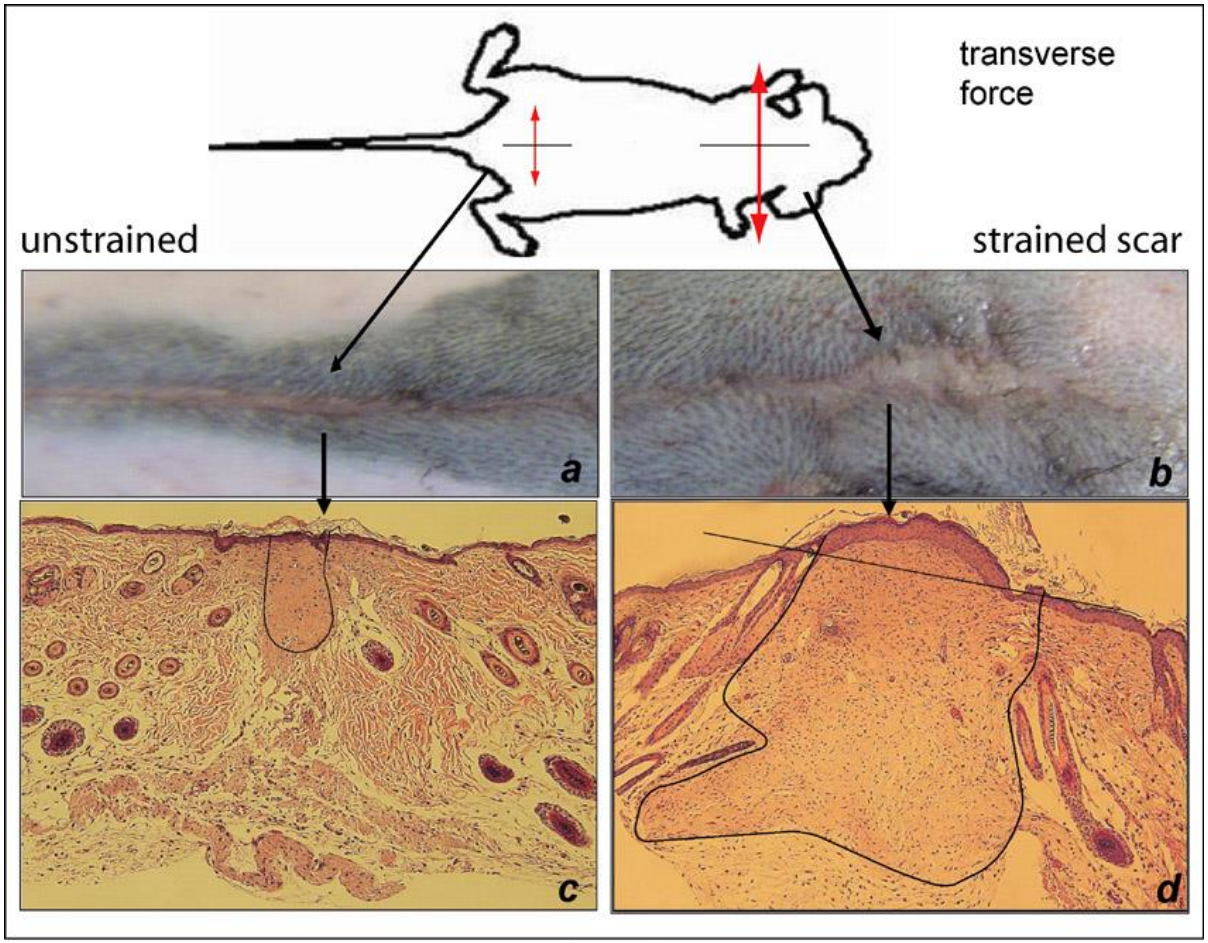
Mechanical Forces and Wound Healing



Scar Revision

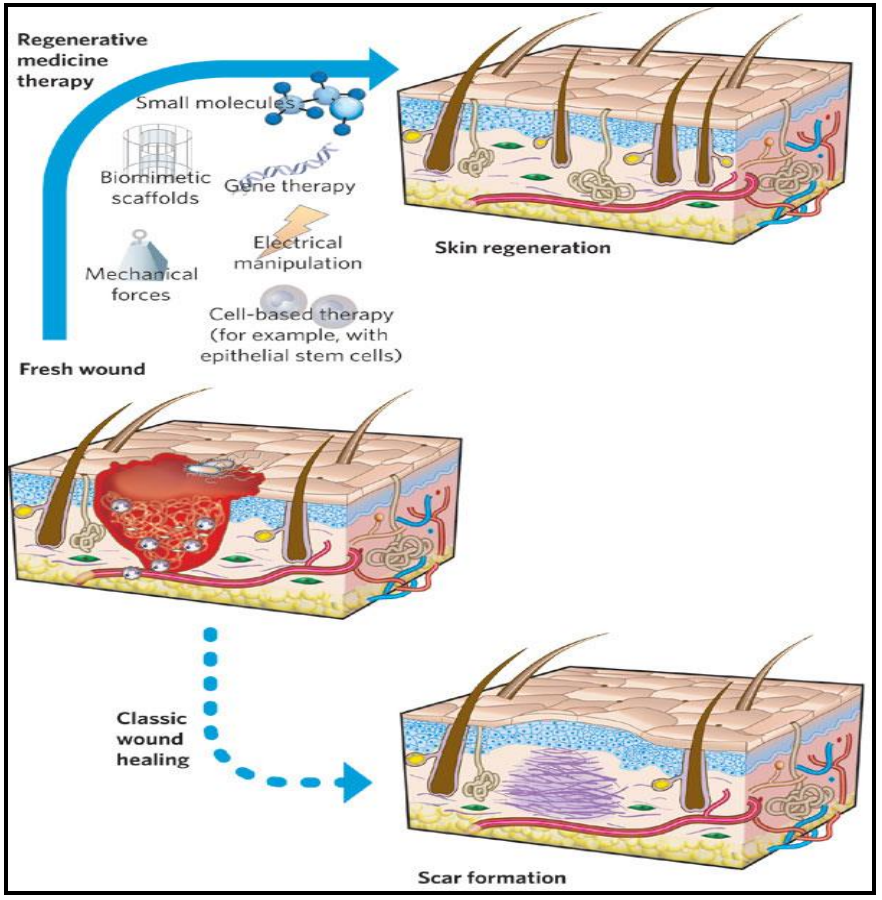


Human Levels of Mechanical Stress Produce “Human-like” Fibrosis and Scar Formation



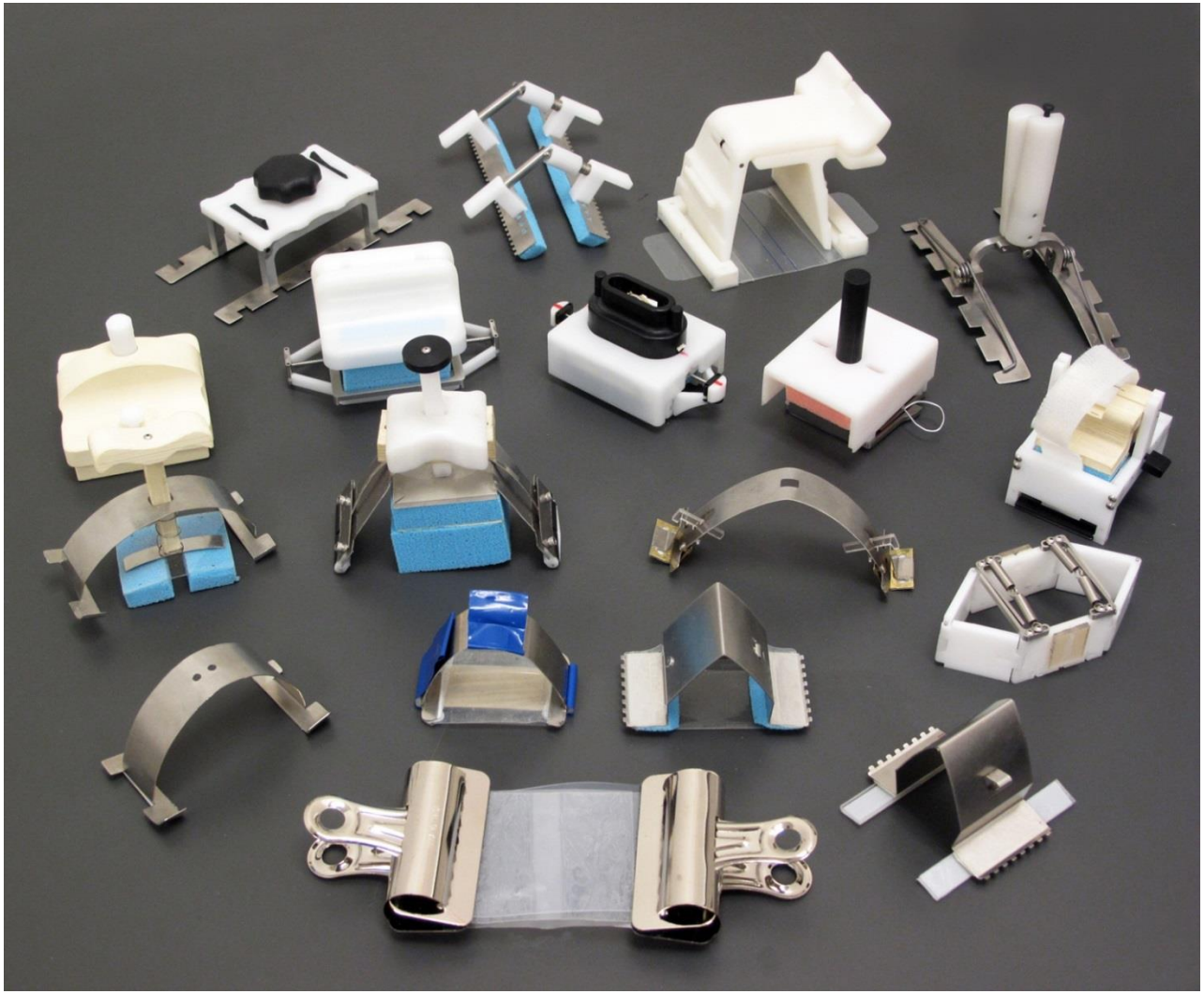
Aarabi, FASEB J 2007

Can we reverse this in humans?



Gurtner, Nature 2008

How to do this…..?



Dynamic Stress Shielding Device

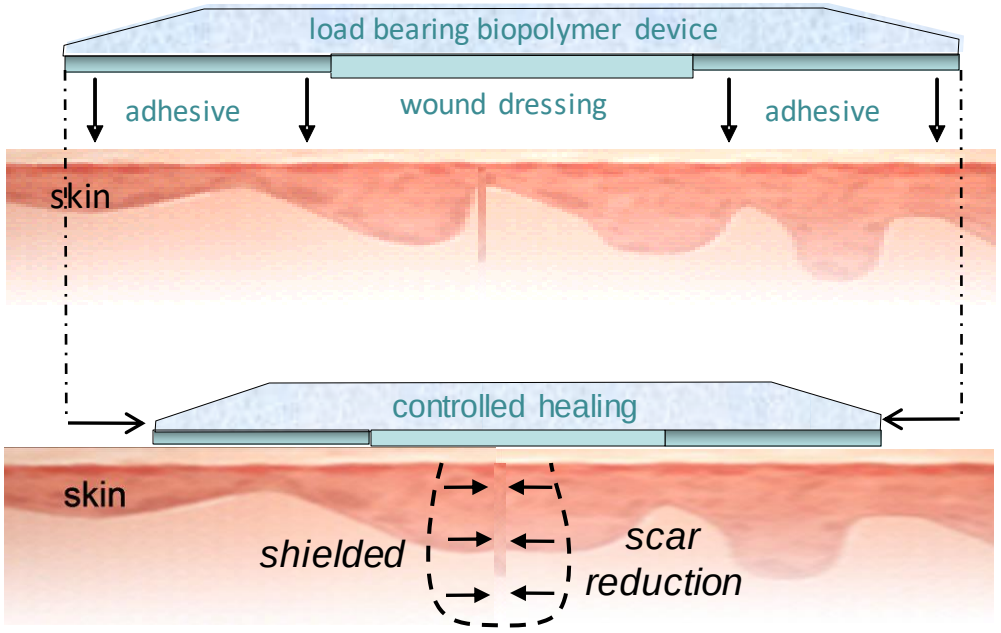
Untreated Incision

Normal scarring resulting form untreated wound

Treated Incision

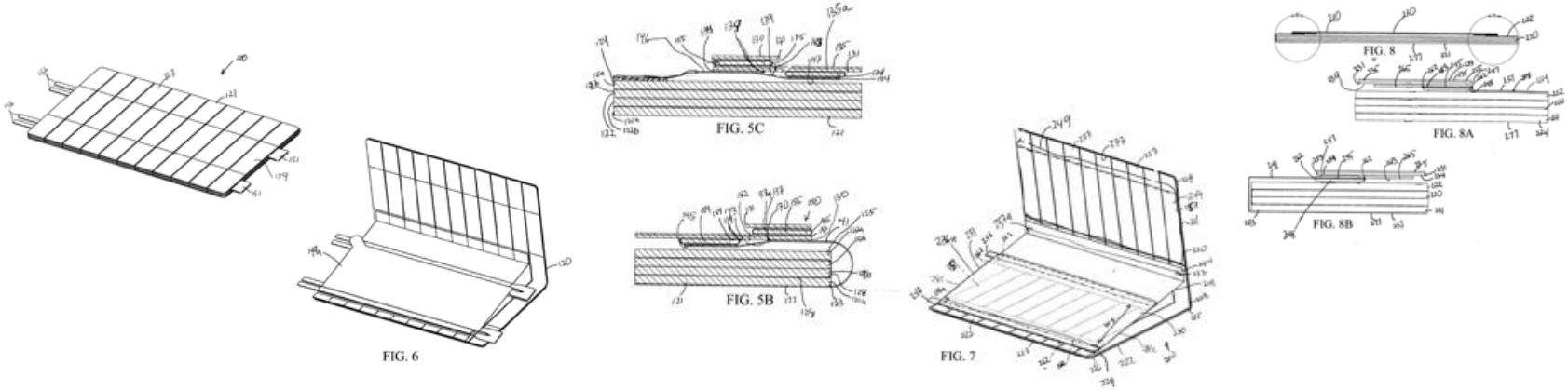
Stretch device and adhere across wound with pressure sensitive adhesive (PSA)

Release and allow device to relieve stresses across wound.

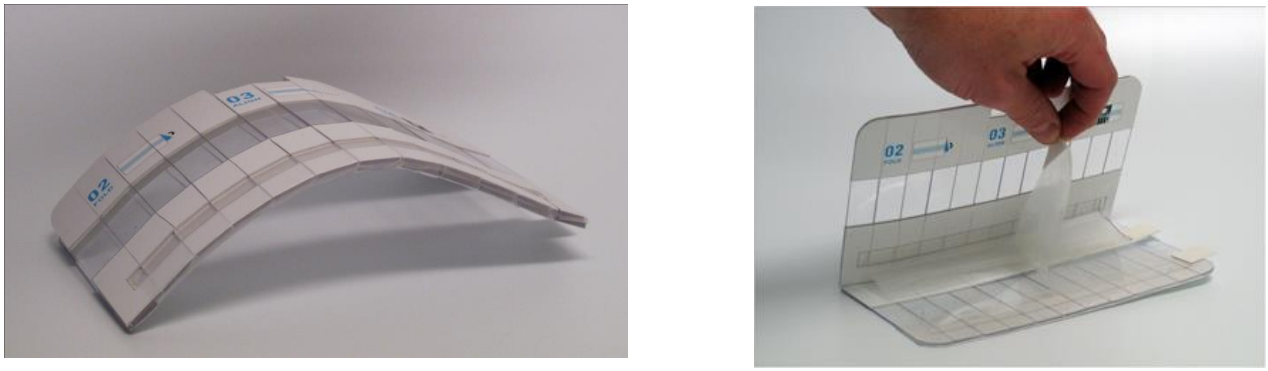


Relieves stress across wounds during healing

Dynamic Stress Shielding Dressing



Schematics of third generation device designed to precisely apply dynamic stress-shielding polymer to wounds



Photographs of third generation device being prepared for commercialization. The device has proven user-friendly, disposable, and highly effective for both volunteer patients and physicians.

Abdominal Scar Treatment Study

Subject	03-05	Time since surgery	12 months

Abdominal Scar Treatment Study

Subject	03-06	Time since surgery	9 months

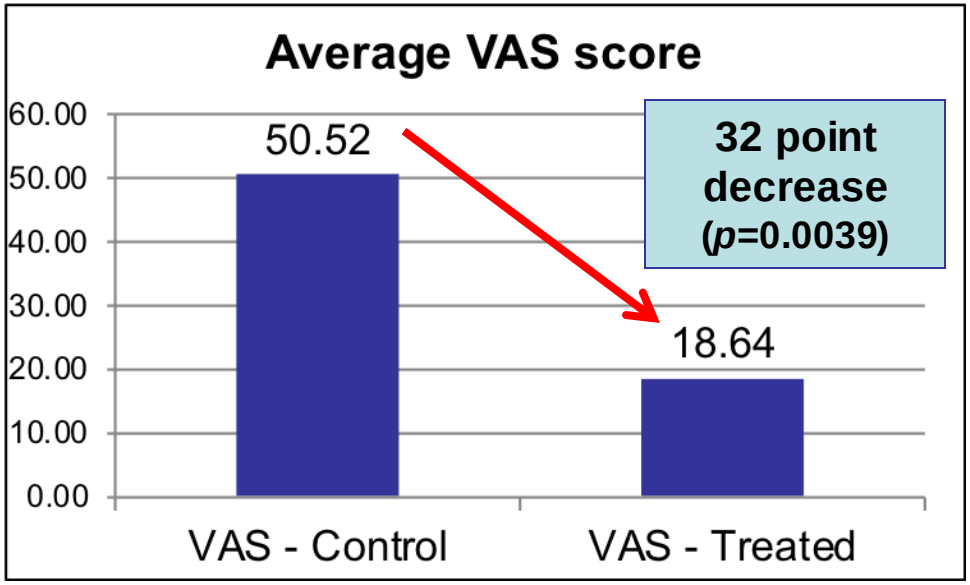
Abdominal Scar Treatment Study

Subject	03-09	Time since surgery	12 months

Independent scar photo analysis

Results

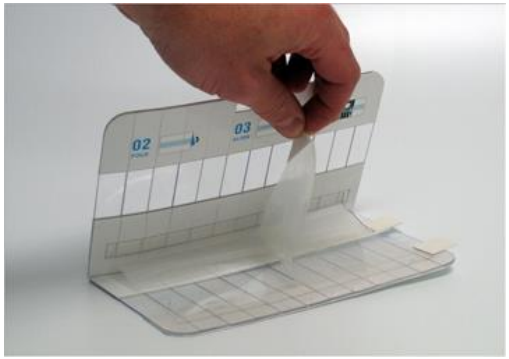
- Statistically significantly reduction in VAS scores for the treated side vs. control side of 32 points (p=0.0039, VAS Scale ranging from 0 to 100)
- For paired scar ranking, in no case was the control chosen over the treated
- Informal lay people panel also conducted with similar results (p=0.004)



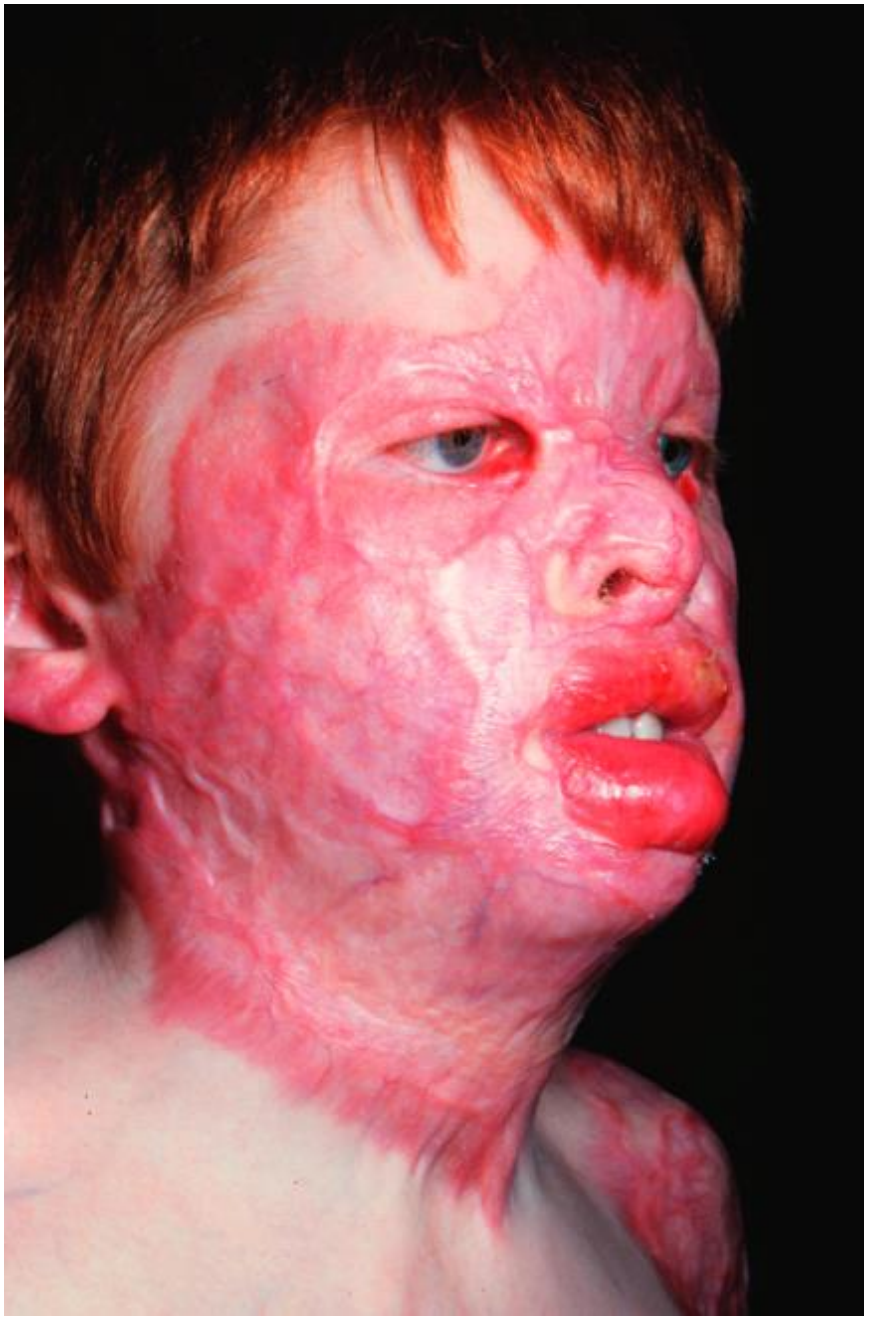
Annals of Surgery 2011

Multiple Successful Randomized Clinical Trials

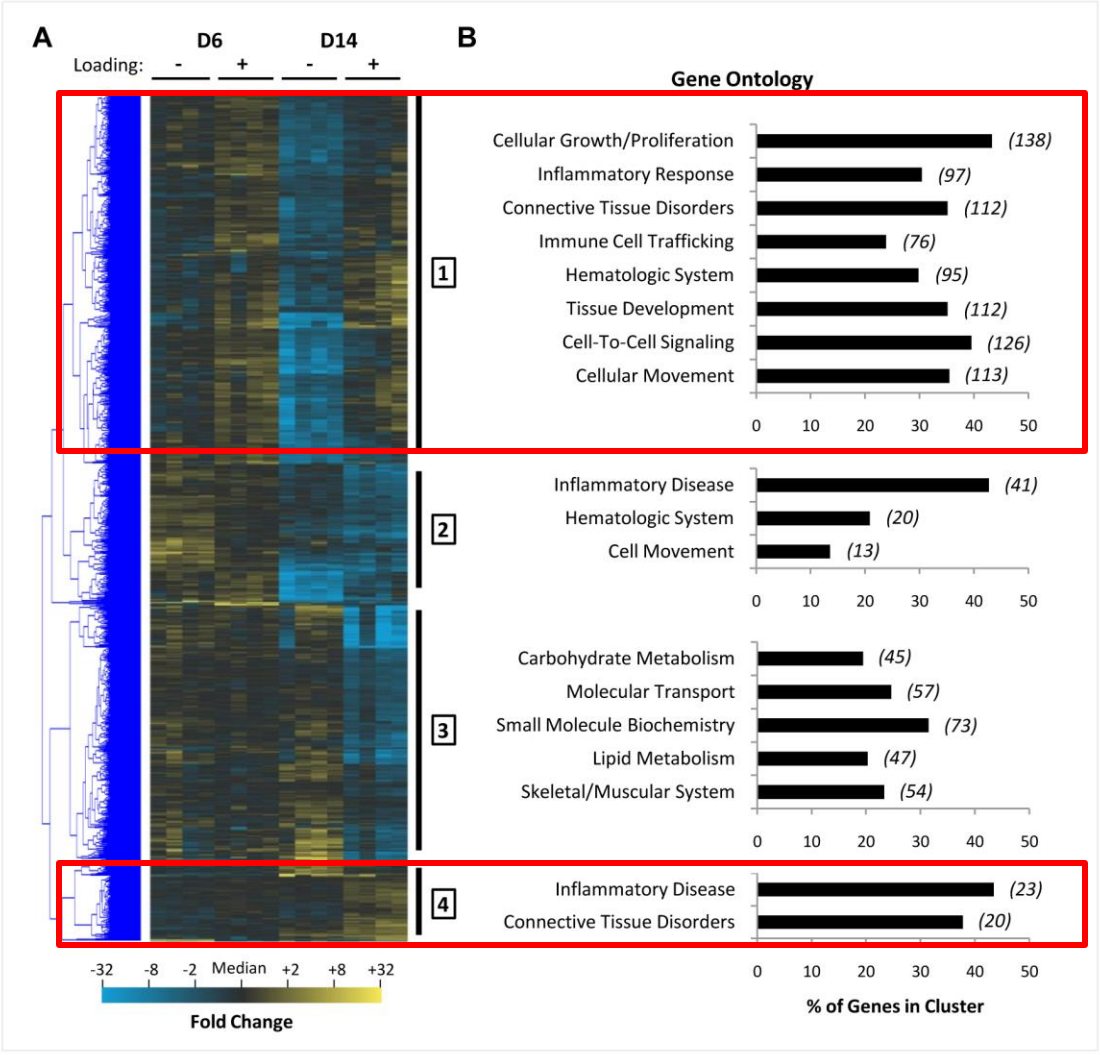
- Commercially Available for Treating Incisional Scars
- Device name: Embrace®
- 250,000 patients treated
- 93% approval rating on realself.com



	Studies Performed				
Study	**Species**	**Metrics Analyzed**	**Duration**	**P value**	**Publications**
Proof-of-concept animal study	Red Duroc swine (n=6)	Excision & incisions	8 wk	n/a	Gurtner et. al. 2011, Annals of Surgery
"Mona Lisa"	Humans (n=9; 1 center)	Abdominoplasty, w/in patient controls.	8 wk; 6-12 mo. follow-up	0.0039	Gurtner et. al. 2011, Annals of Surgery
"Louvre"	Humans (n=56; 8 centers	Abdominoplasty, revision and breast, w/in patient controls	8-12 wk; 6, 12 mo. follow-up	0.01	n/a
"REFINE"	Humans (n=67; 12 centers)	Abdominoplasty, w/in patient controls	12 wk; 6, 12 mo. follow-up	<0.007	Longaker et. al. 2014, PRS
"IMPROVE"	Humans (n=10, 1 center)	Scar revisions w/in patient controls.	10-12 wk; 6, 12 mo. follow-up	0.002	Lim et. al. 2014, PRS



Microarray Analysis of Hypertrophic Scars



Affymetrix gene chip

~1000 genes regulated by wound tension

Chemokine pathways activated

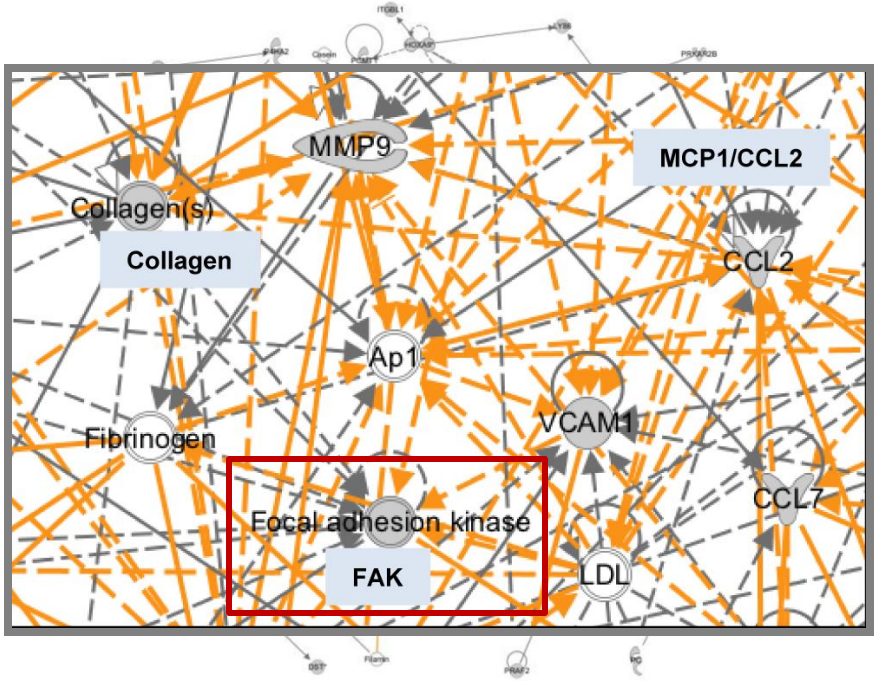
Upregulation of fibrotic pathways

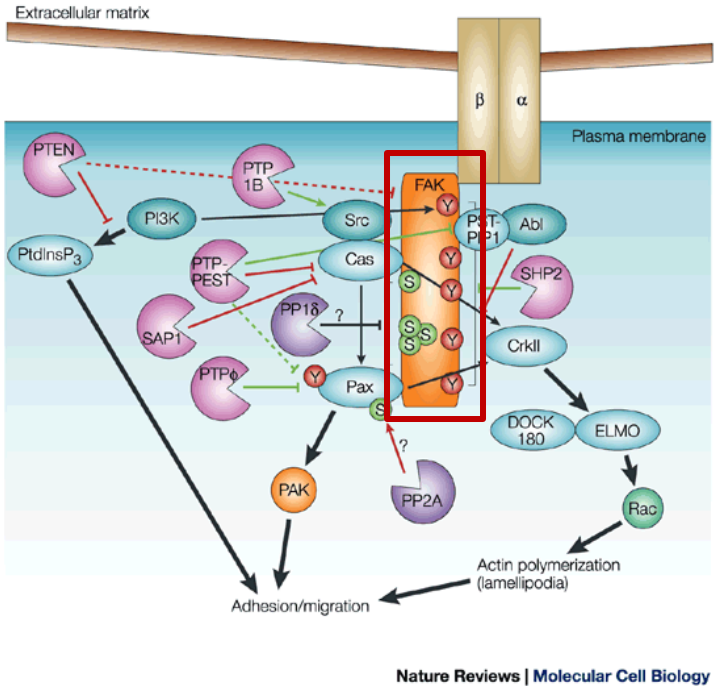
Consistent with *in vivo* phenotype

Wong VW et al. 2011 Nat Med 18(1)

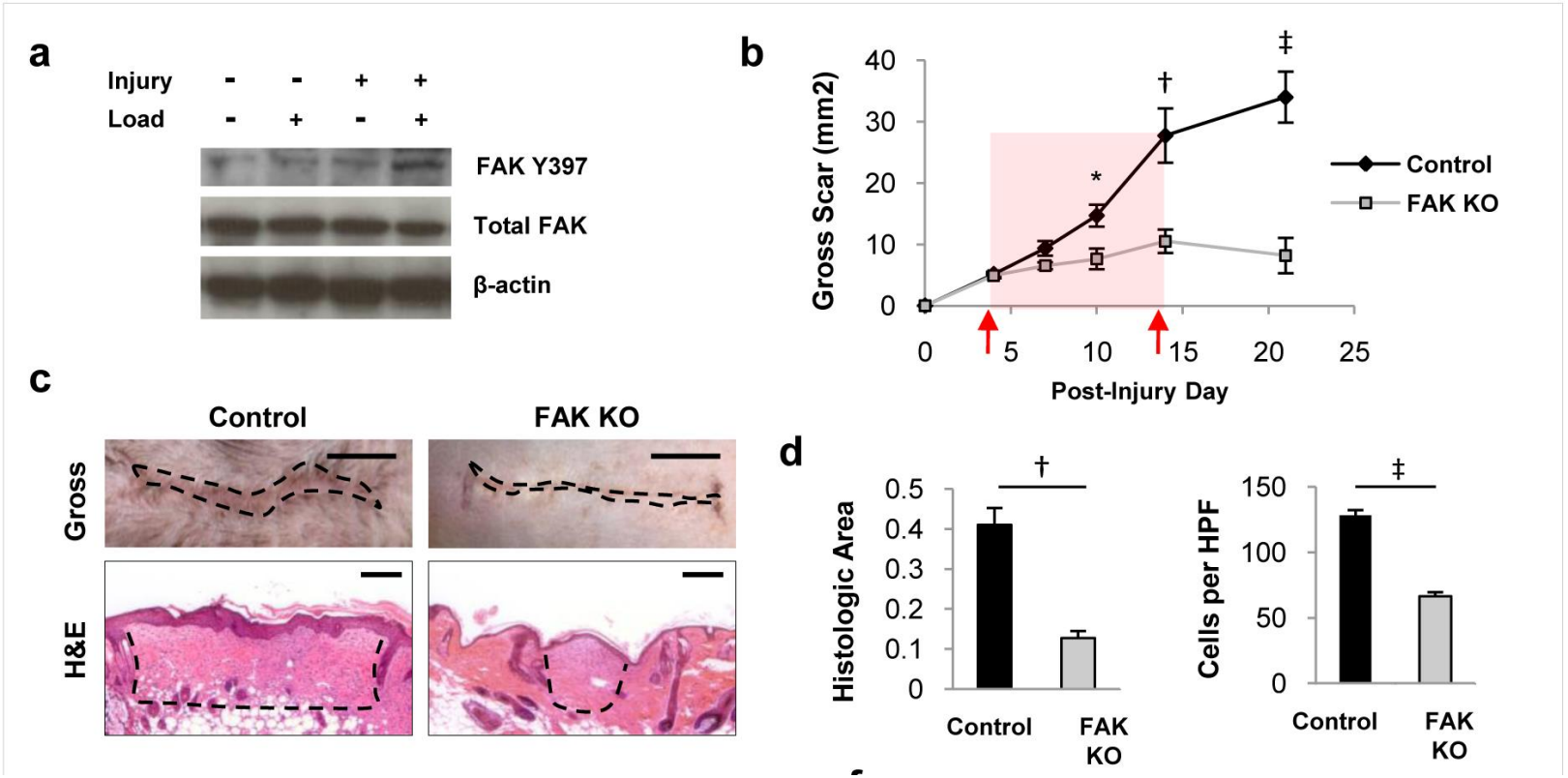
Focal Adhesion Kinase (FAK)

- Ingenuity Pathways Analysis (IPA): transcriptome map
- FAK → important mechanosensor links cells and ECM
- Fibroblasts are both mechanoresponsive and end effectors of fibrosis
- **HYPOTHESIS: Fibroblast-specific FAK is critical in scar formation**





Mice lacking FAK do not form hypertrophic scars



Wong *et al.*, *Nature Medicine* 2011

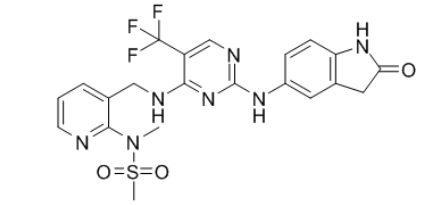
Blocking Mechanotransduction Using Small Molecules

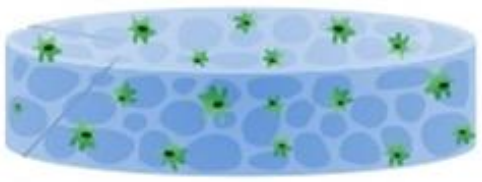
Verastem
novel drugs targeting cancer stem cells

VOLUME 30 · NUMBER 13 · MAY 1 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Safety, Pharmacokinetic, and Pharmacodynamic Phase I Dose-Escalation Trial of PF-00562271, an Inhibitor of Focal Adhesion Kinase, in Advanced Solid Tumors

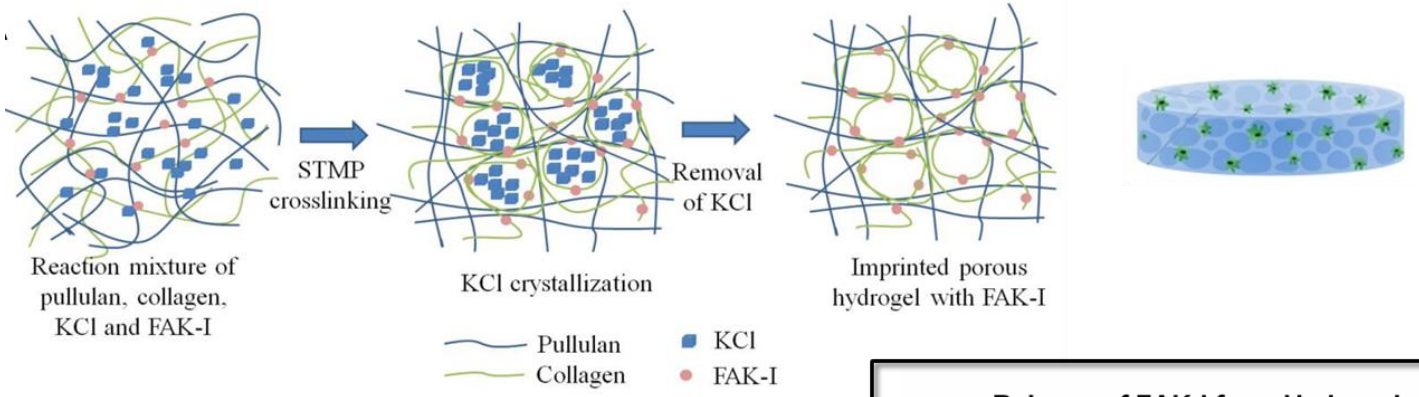
Jeffrey R. Infante, D. Ross Camidge, Linda R. Mileshkin, Eric X. Chen, Rodney J. Hicks, Danny Rischin, Howard Fingert, Kristen J. Pierce, Huiping Xu, W. Gregory Roberts, S. Martin Shreeve, Howard A. Burris, and Lillian L. Siu



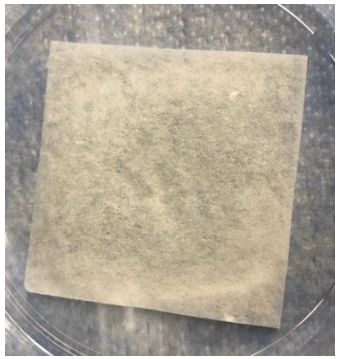


- Small molecule blockade of FAK
- VS-6062, (Verastem, Needham, MA) for cancer therapy
- FDA-IND and Phase I clinical studies completed
- Licensed from Verastem
- Two US patents to protect it:
  - US patent 9,655,967 : Inhibition of FAK for control of scar formation
  - US patent 9,636,362: Pullulan-collagen hydrogel regenerative matrix

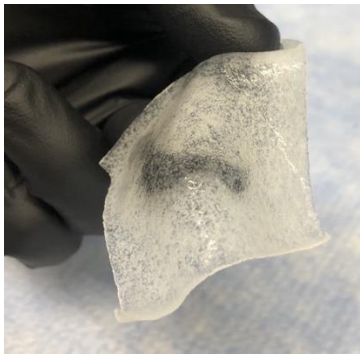
Formulated in Hydrogel for Sustained Release of Drug

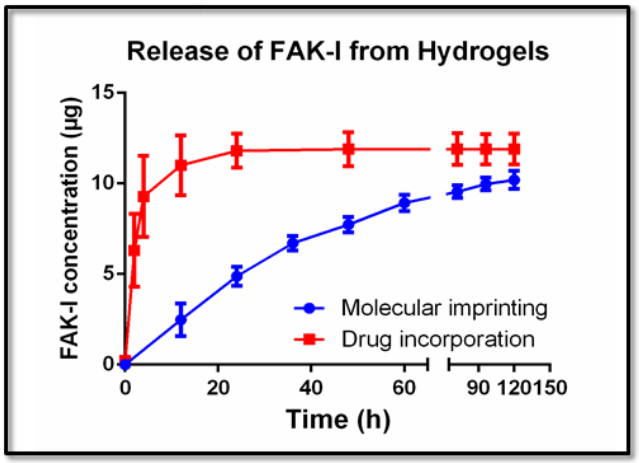


Dry hydrogel



Wet hydrogel

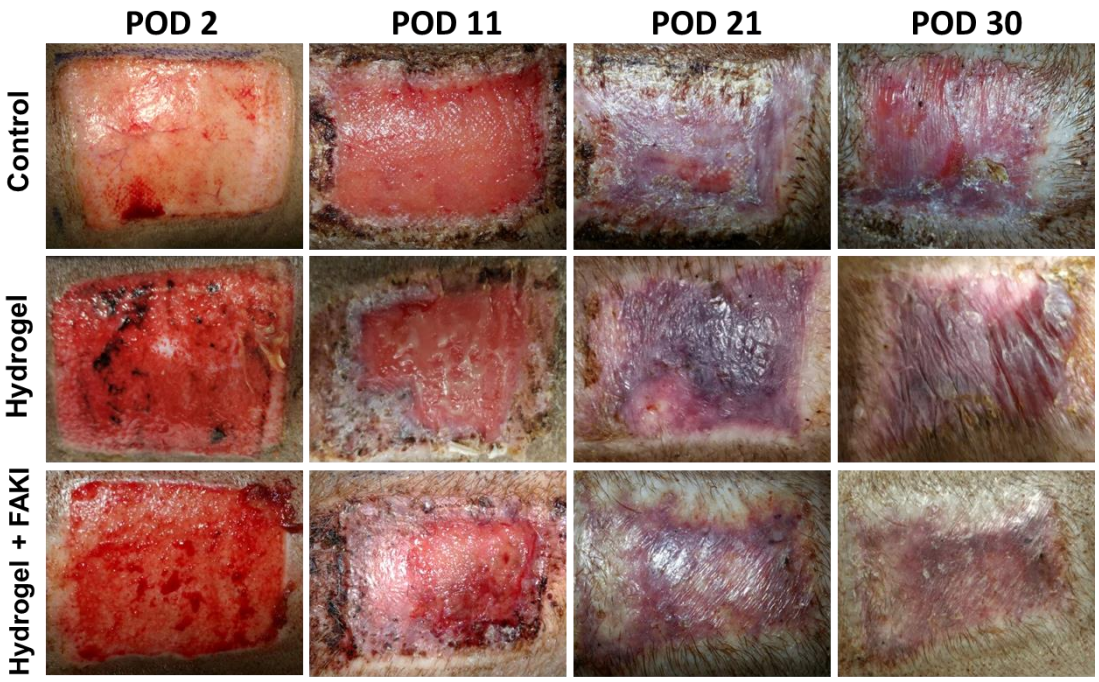




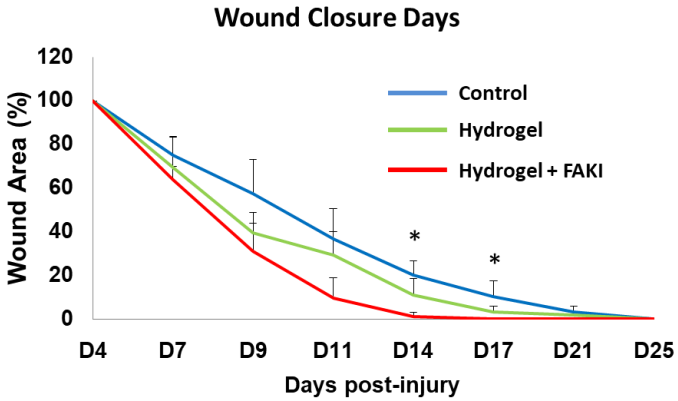
- Biodegradable porous dermal hydrogel matrix
- FAK-I was physically encapsulated via molecular imprinting
- Hydrogels are loaded with 100 microG/sq.cm of FAK-I and releases FAK-I for over 72 hours in in vitro studies.

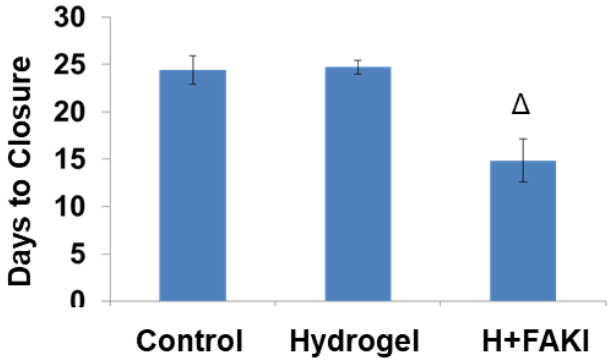
Ma et al. 2018 J Invest Dermatol

Accelerated Healing at Early Time Points



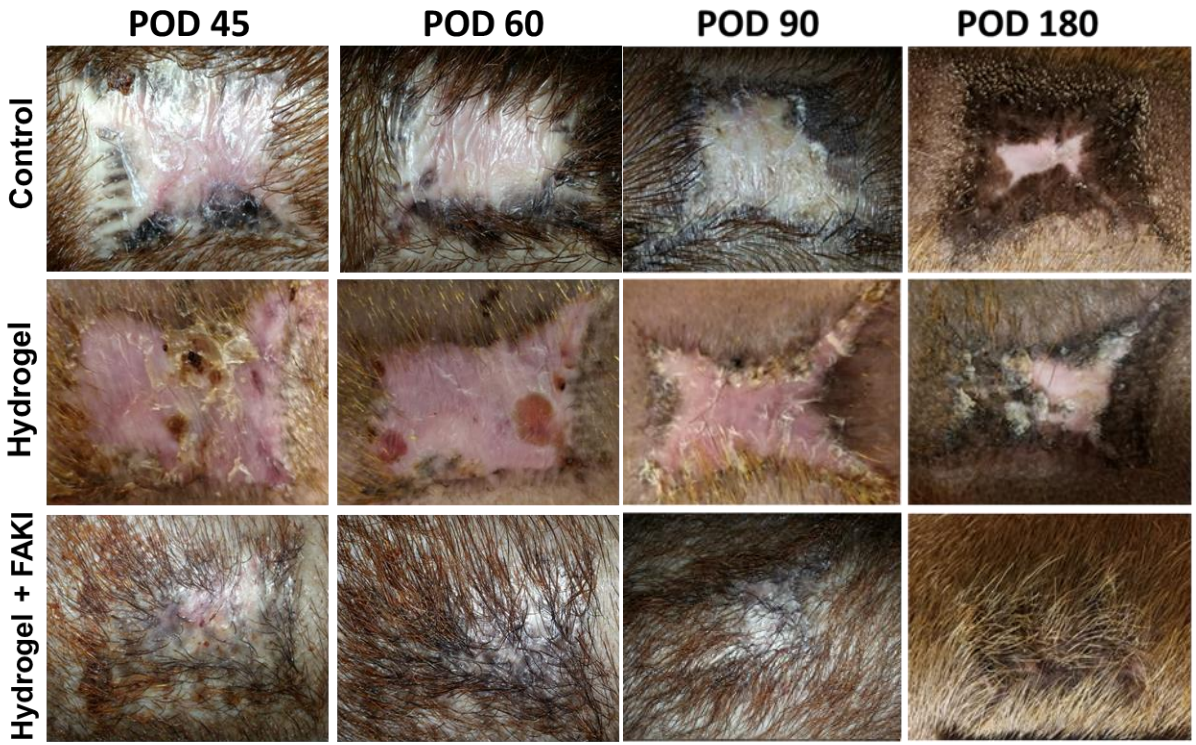
N=8 wounds for each condition. Initial wound size = 25cm^2.

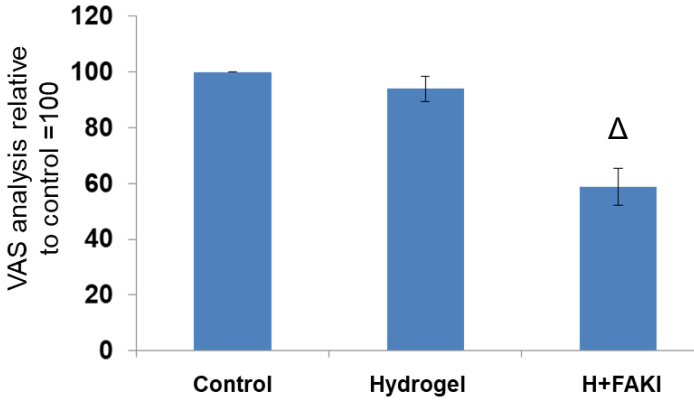




Kwon et al. Nat Comm 2021

Skin Regeneration without Scar at Late Timepoints

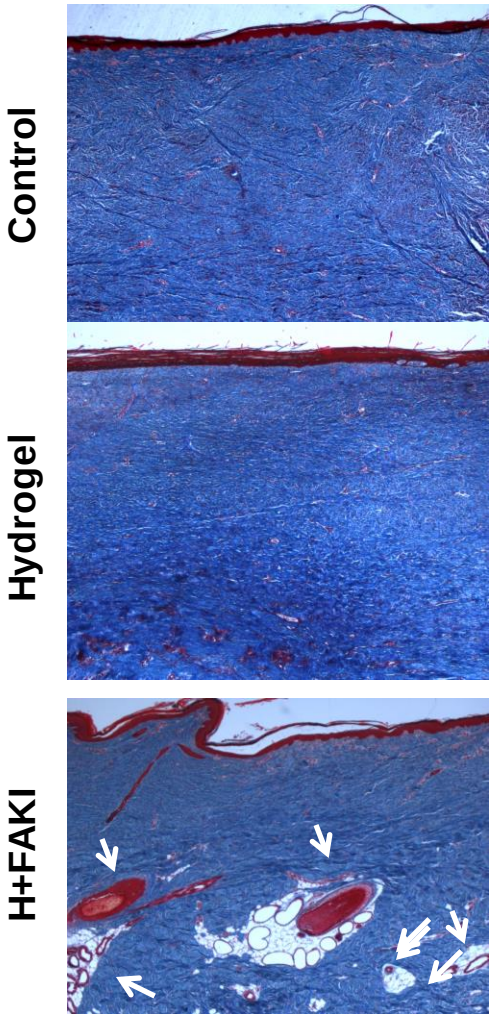


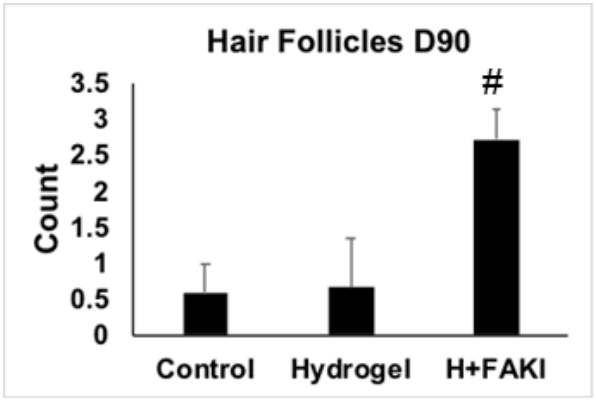


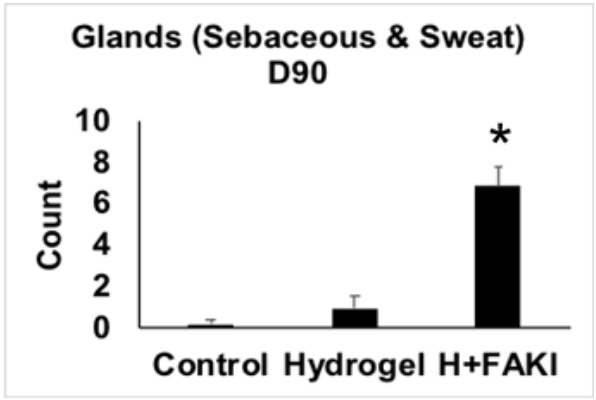
- **Visual Analog Scale (VAS) scores were assessed by <u>four blinded</u> scar experts**
- ($^{\Delta}P < 0.0001$ Control vs. H+FAKI).

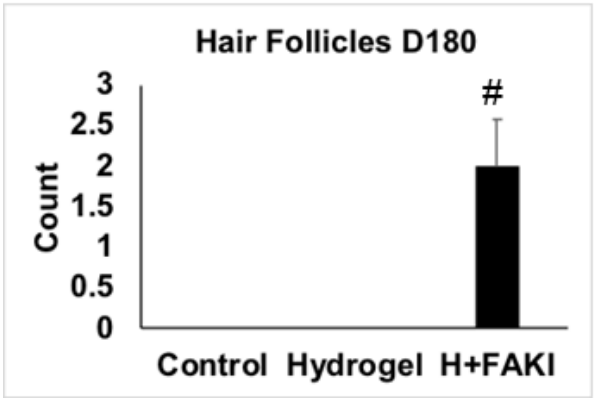
Kwon et al. Nat Comm, 2021

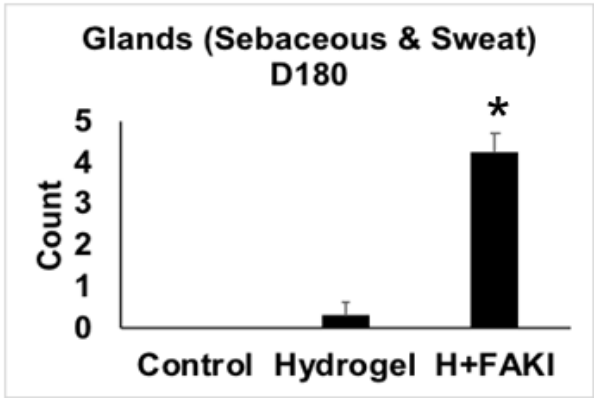
Normal hair follicles and skin appendages







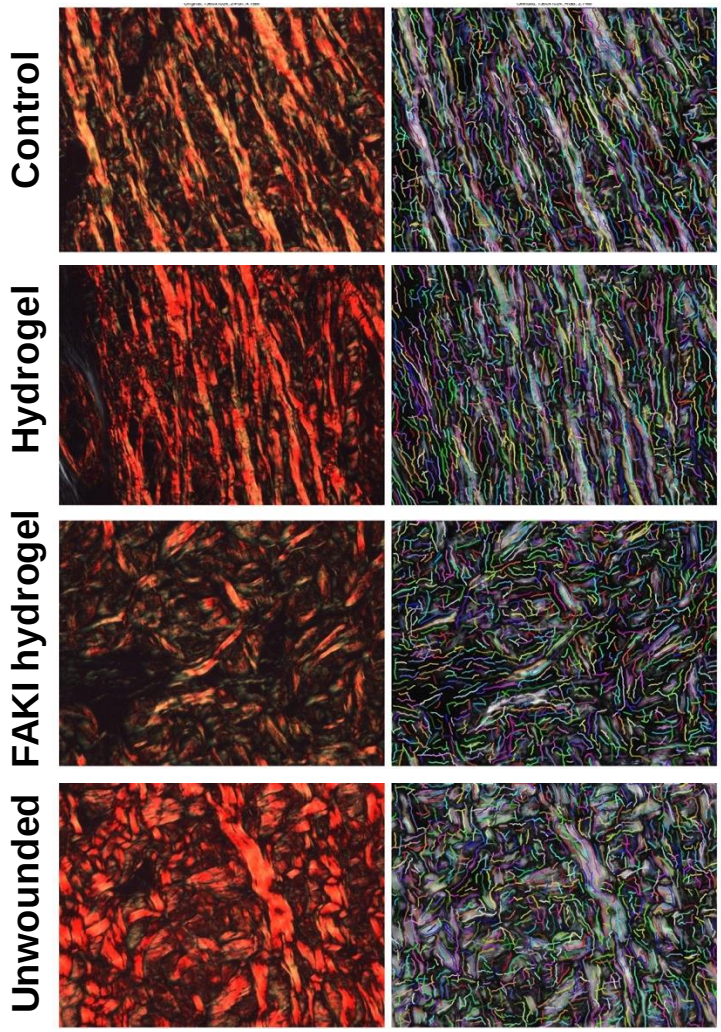


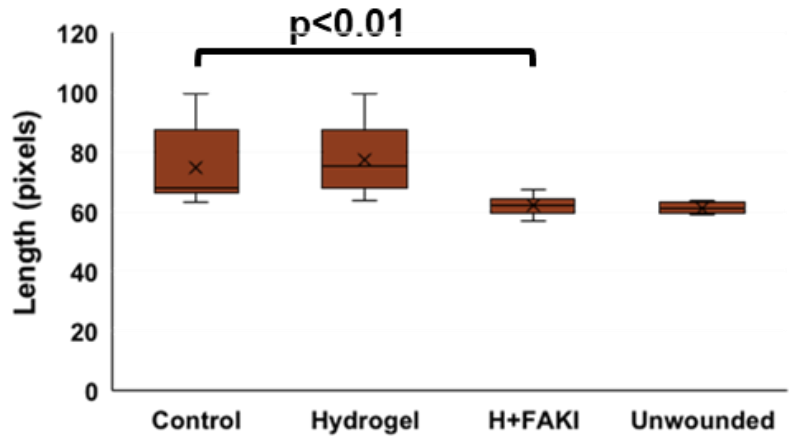


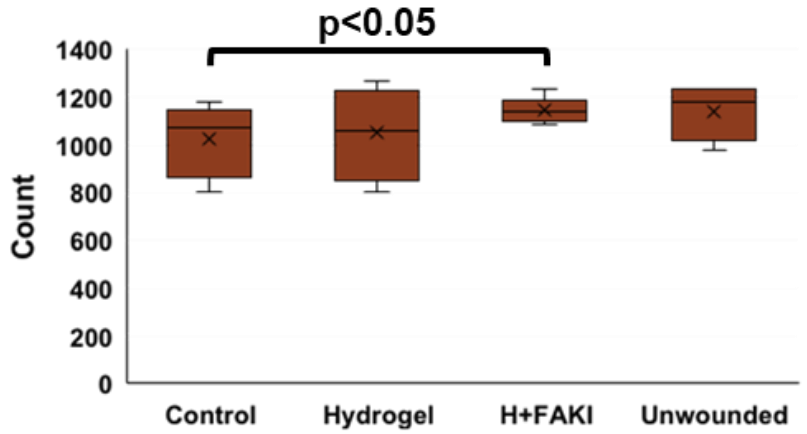
Images show Trichrome staining at POD90.
$^{\#}P < 0.01$ Control vs. H+FAKI $^{*}P < 0.001$ Control vs. H+FAKI $^{\Delta}P < 0.0001$ Control vs. H+FAKI

Kwon et al. unpublished data

Dermal Collagen Structure Nearly Identical to Unwounded Skin



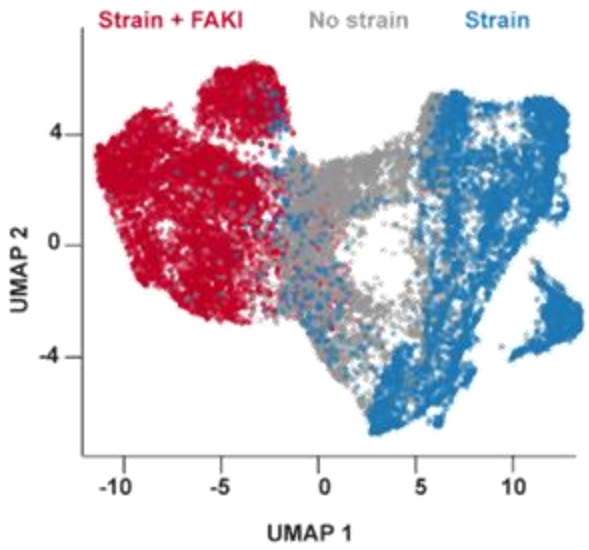


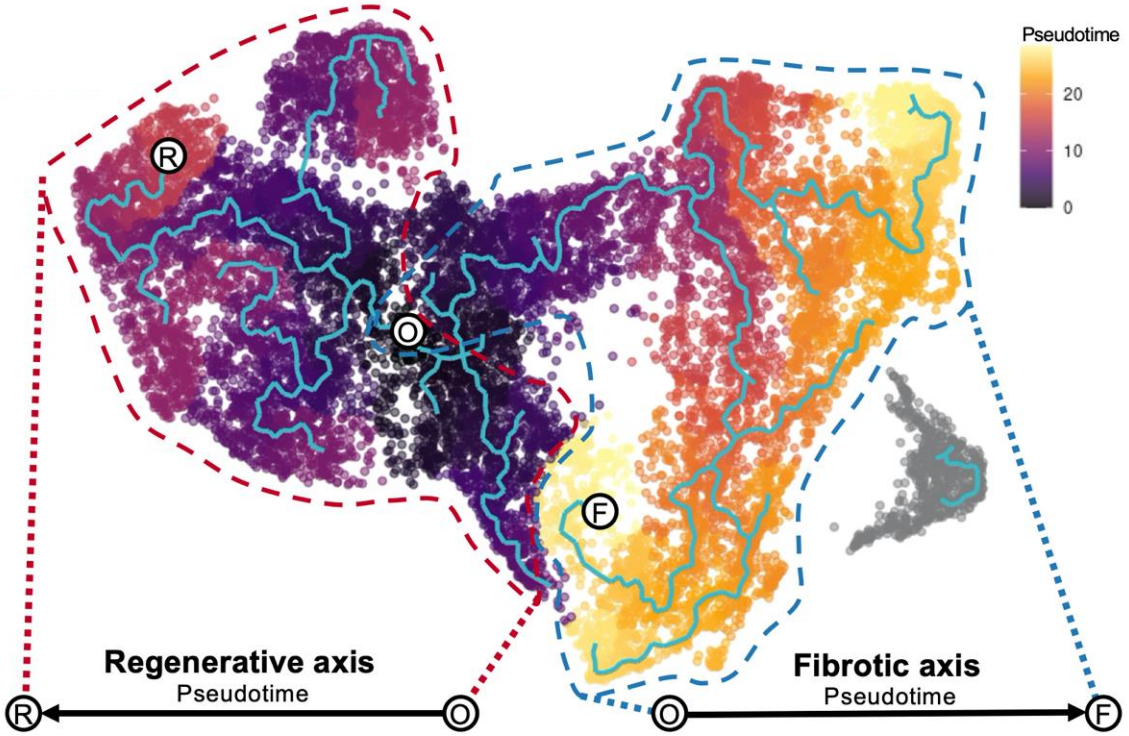


N = 9 images for control, hydrogel & H+FAKI. N=4 images for unwounded. Statistical differences are as indicated Control vs. H+FAKI

Kwon et al. Nat Comm 2021

Pseudotime analysis reveals potential fibroblast regenerative and fibrotic axes





Kwon, Nat Comm, 2021

The New York Times | https://www.nytimes.com/2021/04/22/health/surgery-scar.html

Imagine, Surgery Without a Scar

A new study shows that a 20-year-old drug prevents scarring in mice. If it works on humans, it could change the lives of those with disfiguring wounds.

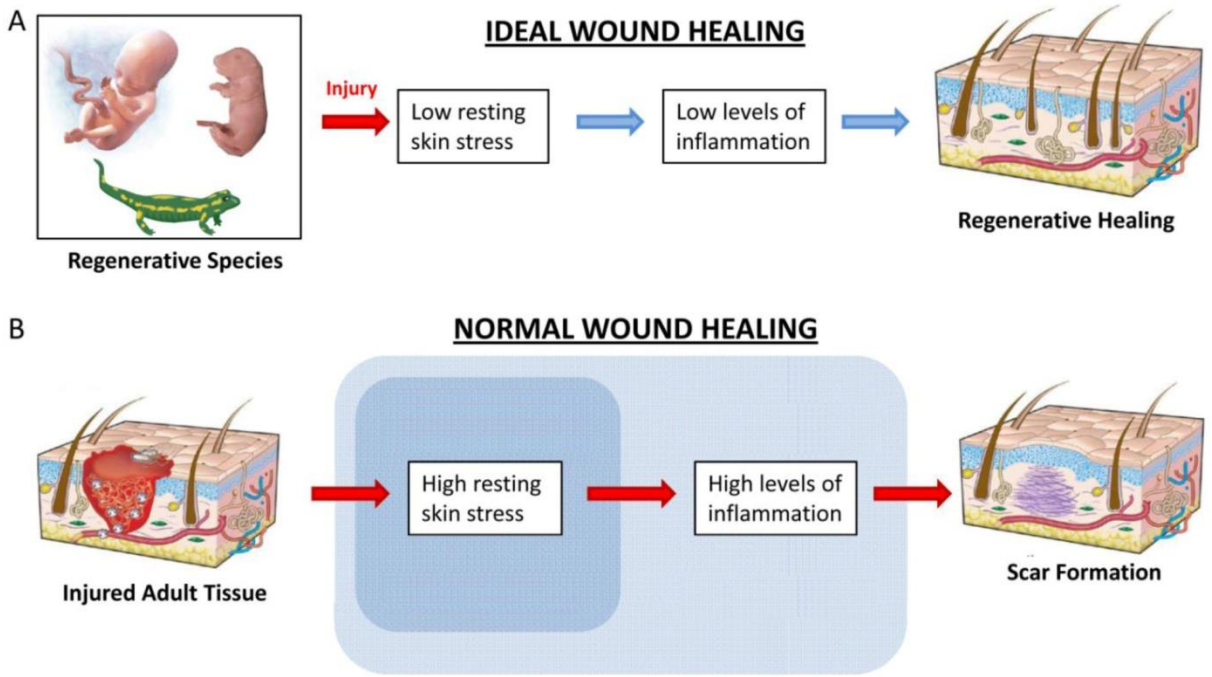
By Gina Kolata

April 22, 2021

Cleft palates that close without scars. Burn wounds that recover without a trace of injury. Years-old disfiguring scars that disappear, leaving skin smooth and flawless.

It sounds like science fiction, but healing without scarring may become a tantalizing possibility. In a study published Thursday in Science, two researchers at Stanford University report that they have figured out the molecular signals that make scars form and found a simple way to block them — at least in mice.

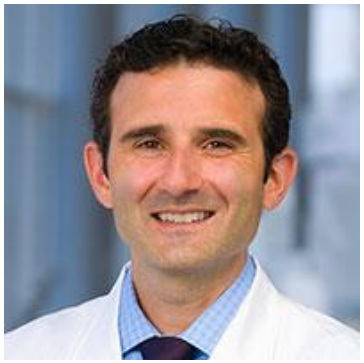
Removing the stimulus for fibrosis (mechanical signaling) allows skin regeneration to occur

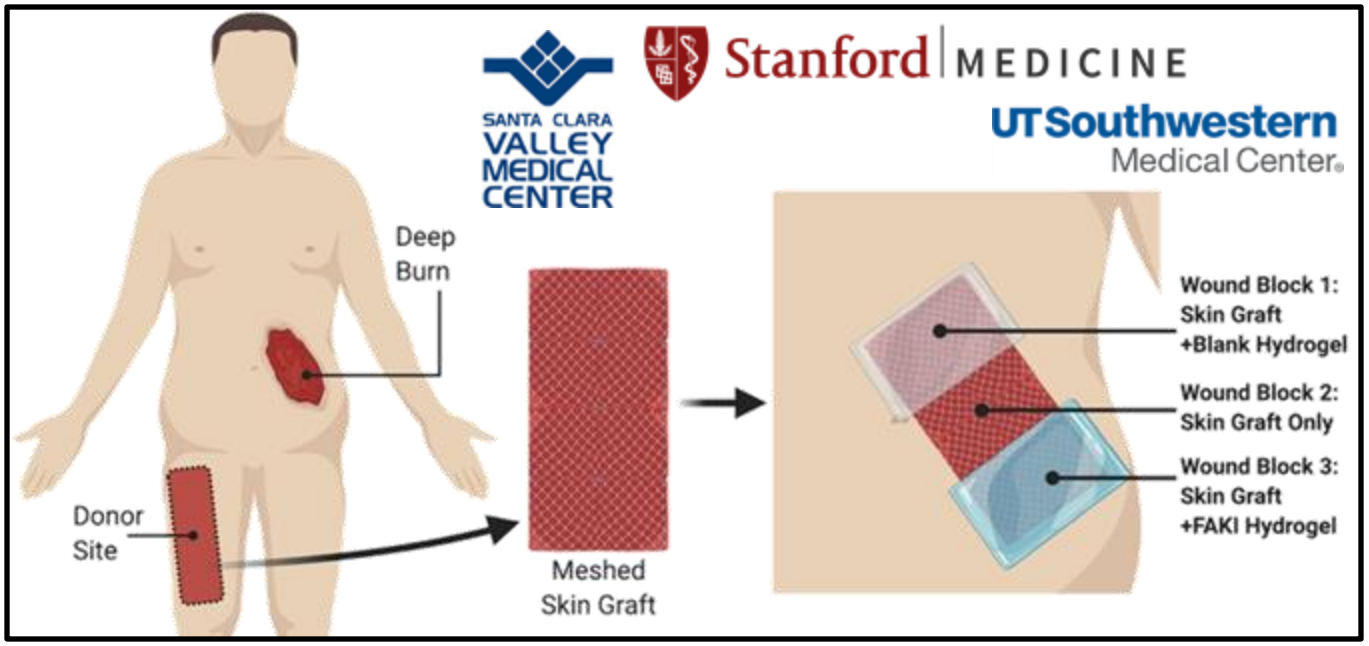


VS-6062
Verteporfin

Clinical Trials Underway

- Favorable PIND meeting May 2021
- No healthy human study required
- Orphan Application submission 7/21
- IND filing Q4 2021
- PI Ben Levi, UTSW

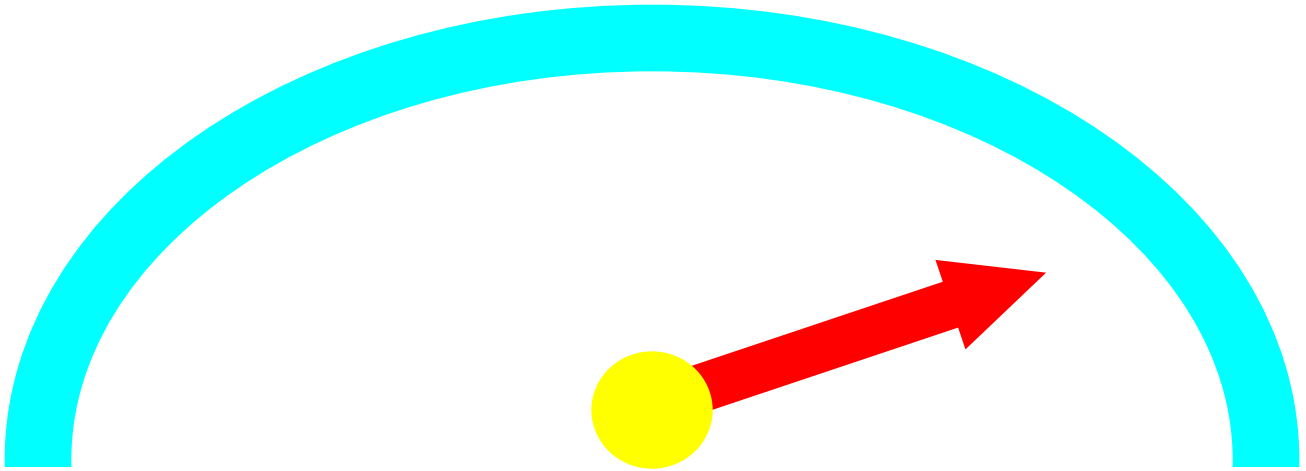




Cutometer

Developing Drugs for Burns and Skin Injuries

Normal Adult Wound Healing

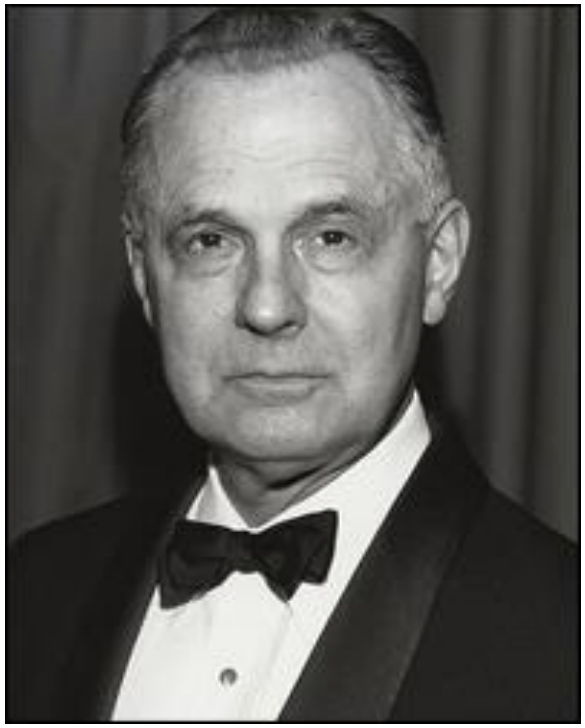


Hypertrophic Scar
Keloids

Chronic Wounds

Frank Cole Spencer (1925-2018)

”A patient with diabetes heals about as well as a hole in your pants”

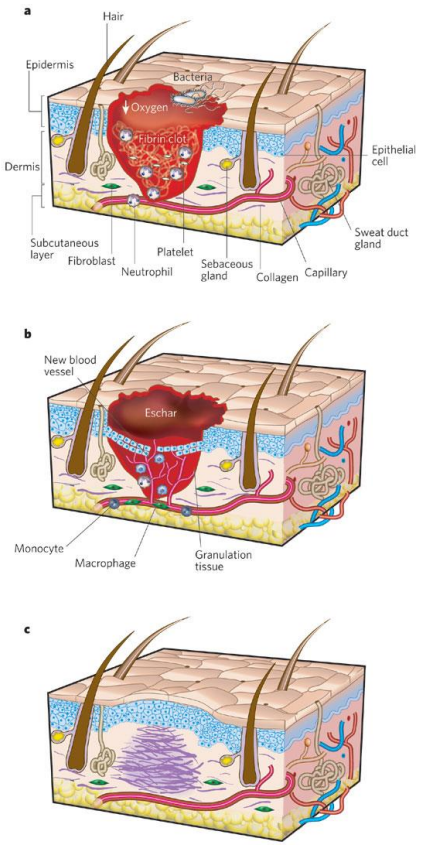


Chair of Surgery, NYU

Diabetic Wound Healing

- 20% of diabetics will develop non-healing wounds
- Medicare spends $30,000 per uncomplicated wound and over $130,000 per complicated wound
- Multi-billion dollar problem
- No effective therapeutics

Understanding Normal and Abnormal Wound Healing



Gurtner, Nature, 2008

<u>Inflammatory phase</u>

- *0-3 days*
- *Neutrophils, Platelets*

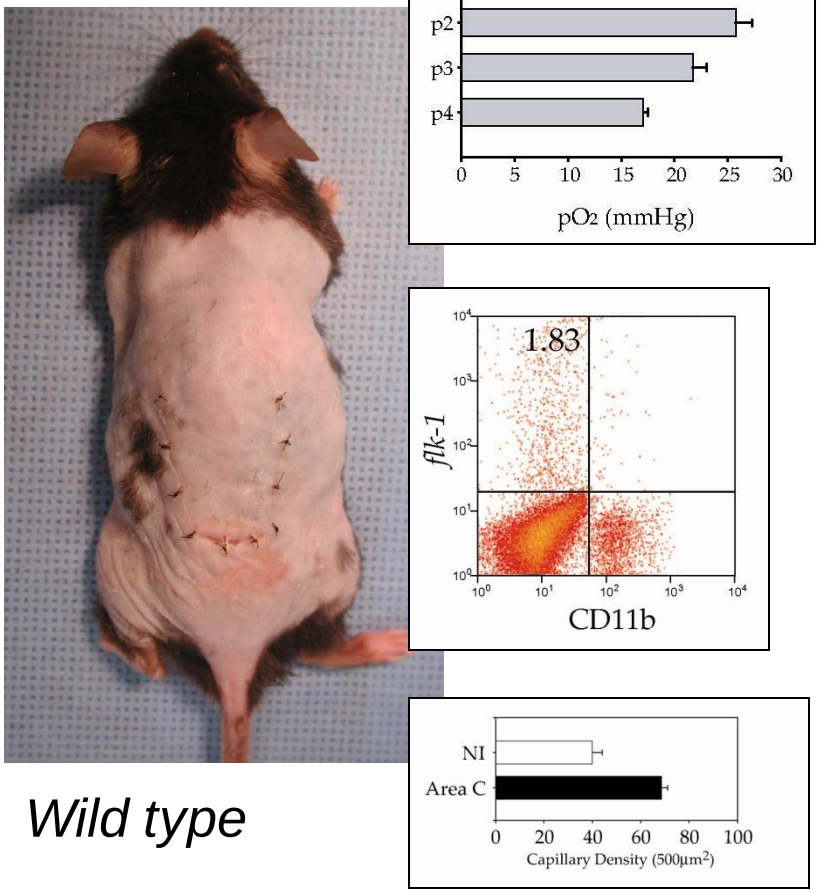
<u>Proliferative phase</u>

- *5-21 day*
- *Macrophages, Endothelial Cells*
- *Fibroblasts*

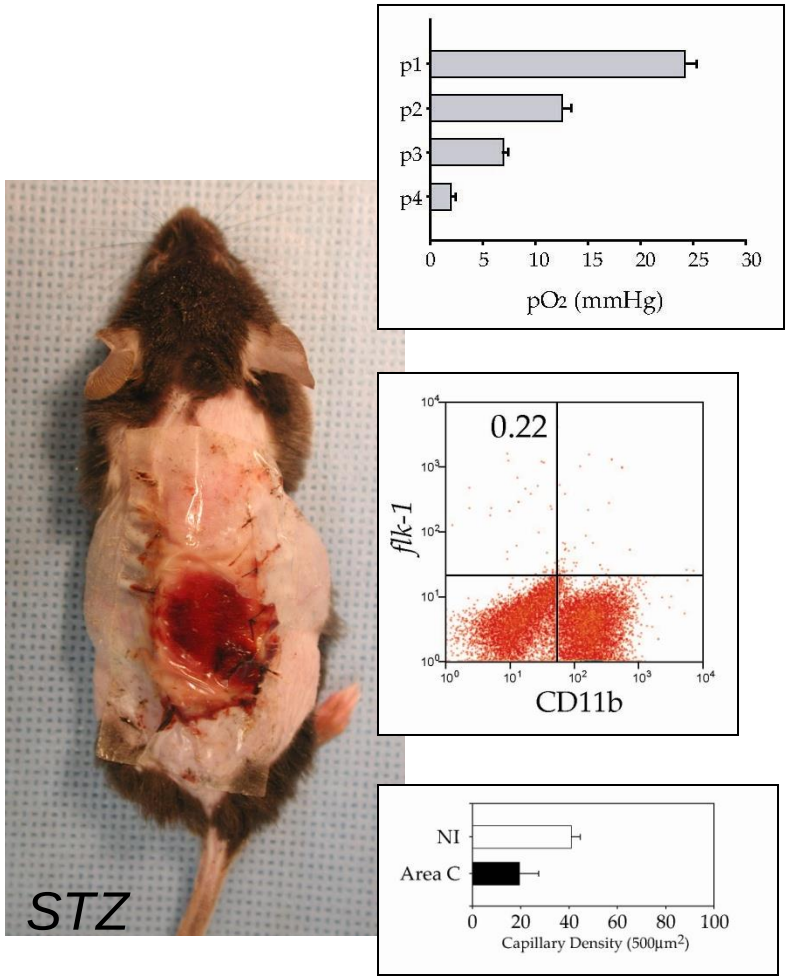
<u>Remodeling phase</u>

- *21 days –One year*
- *Fibroblasts*
- *?Lymphocytes*
- *?Mast Cells*

Diabetes Decreases Tissue Survival Following Ischemia



Wild type



STZ

Ceradini and Gurtner, JBC 2008

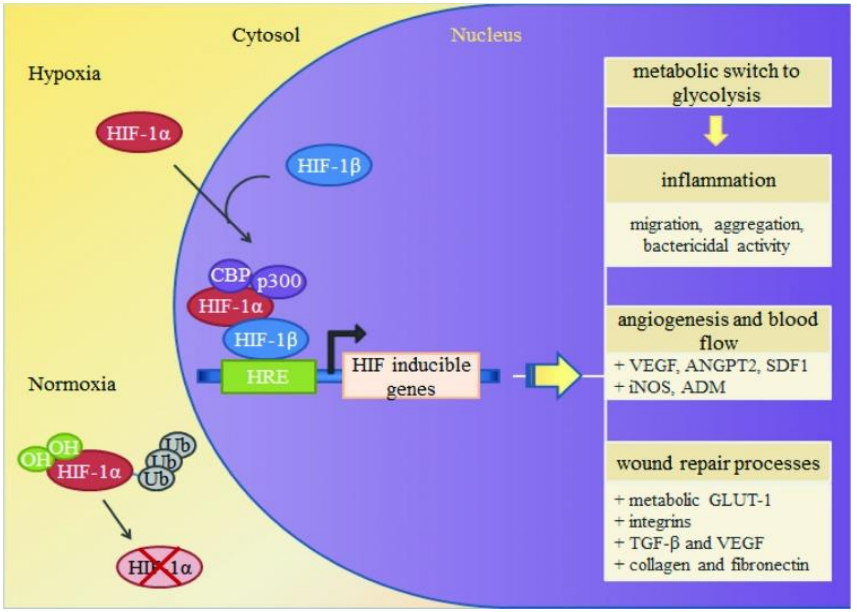
HIF-1α is important for neovascularization and normal wound repair

LETTERS

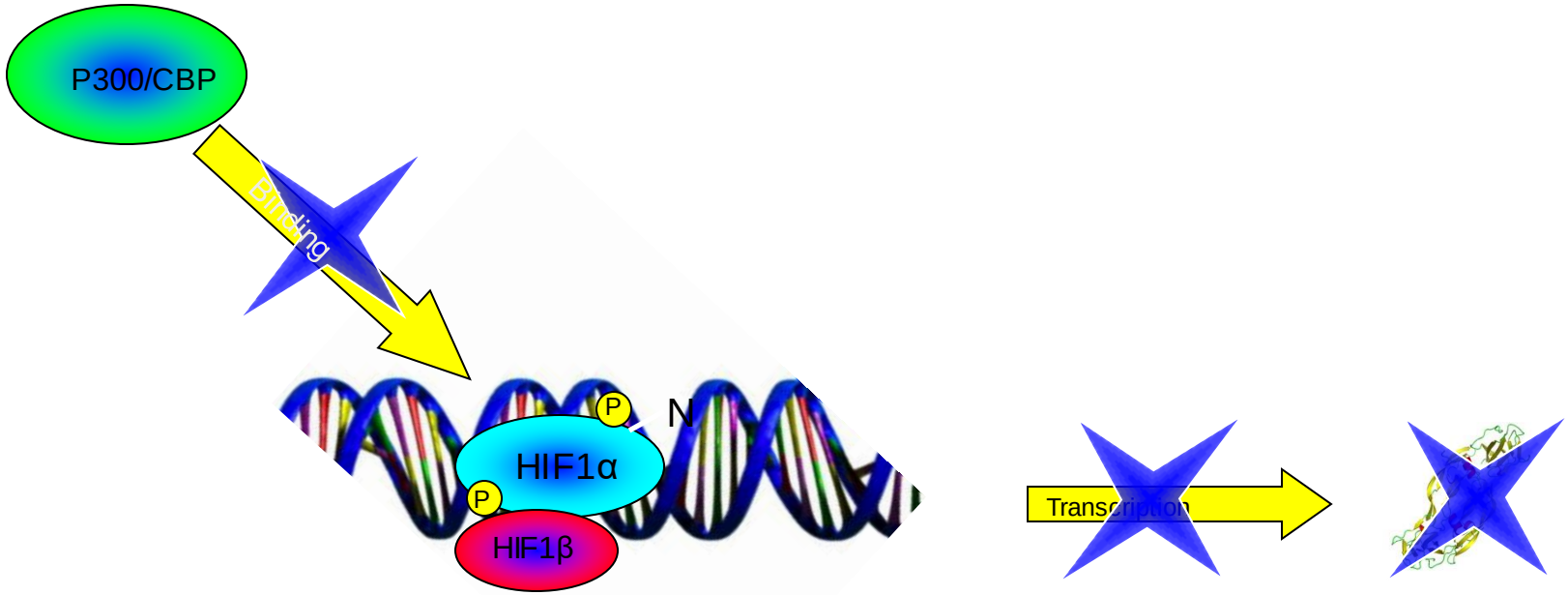
nature medicine

Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1

Daniel J Ceradini, Anita R Kulkarni, Matthew J Callaghan, Oren M Tepper, Nicholas Bastidas, Mark E Kleinman, Jennifer M Capla, Robert D Galiano, Jamie P Levine & Geoffrey C Gurtner



Diabetes and Hyperglycemia Blocks the HIF -1α Mediated Hypoxia Response



This occurs because of methylglyoxal (MG) modification of arginine 354 in p300

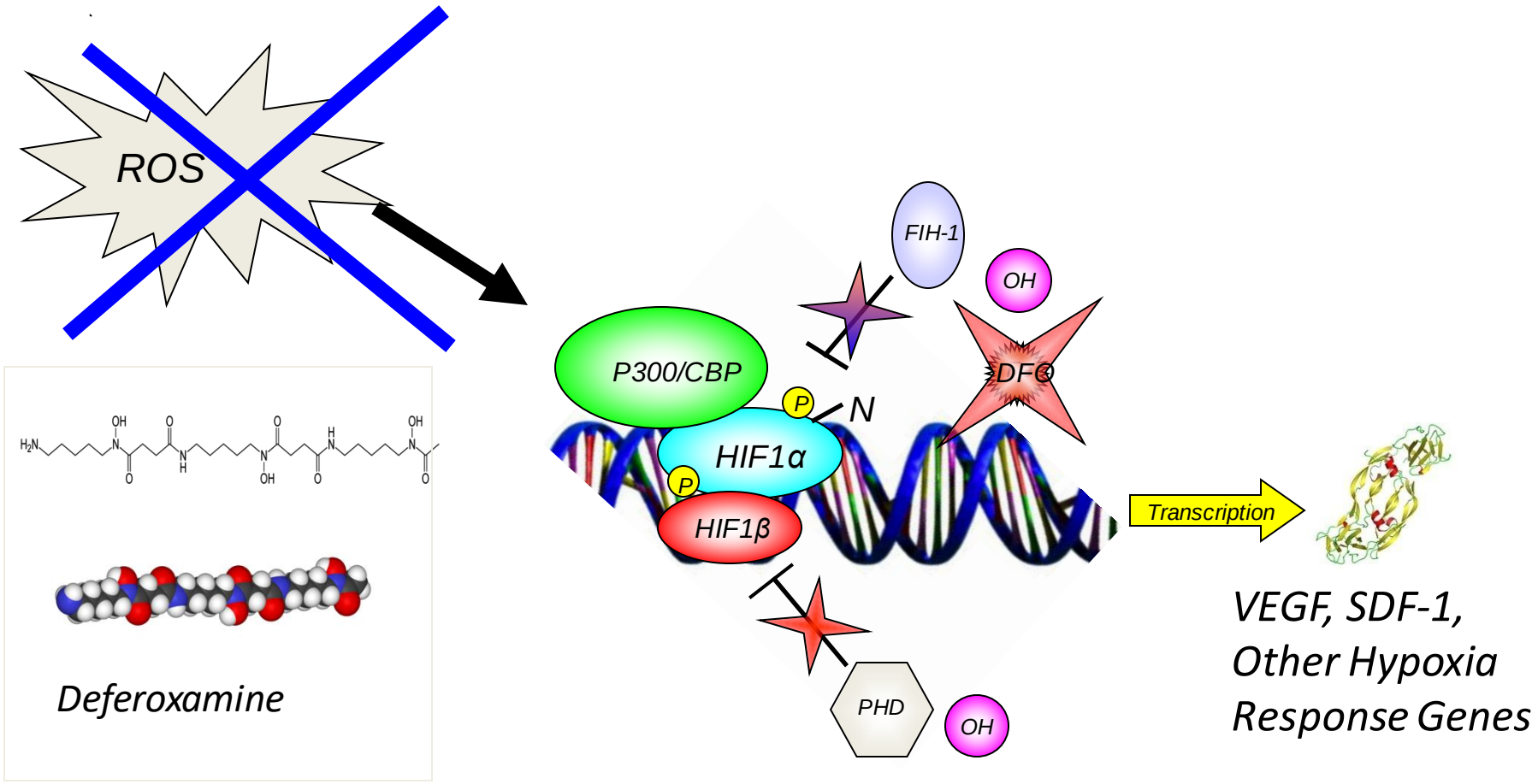
Thangarajah, PNAS, 2010

Searching for the Right Molecule: An Eight-Year Journey

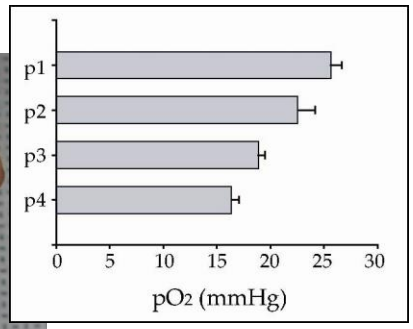
- <u>The key requirements for our drug search were:</u>
  1. Stabilizes (up-regulates) HIF-1a
  2. Reduce oxidative stress
  3. Able to be delivered transdermally through intact skin (using passive/inexpensive technology)
  4. FDA approved (repurposed) or readily approvable
  5. Off-patent, or patentable (novel)

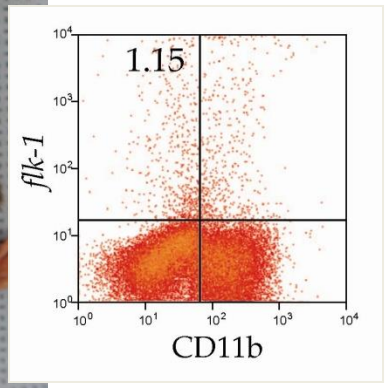
- <u>Some of the compounds considered were:</u>
  - MnTBAP, DMOG, Cobalt Chloride, VEGF/ANG1/ANG2, super oxide dimutase, PHD2 regulators
  - Iron chelators such as DFO (deferoxamine mesylate), deferasirox, and deferiprone

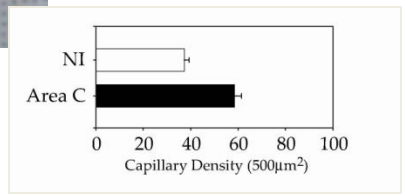
Deferoxamine Prevents Reactive Oxygen Generation and Stabilizes HIF-1a



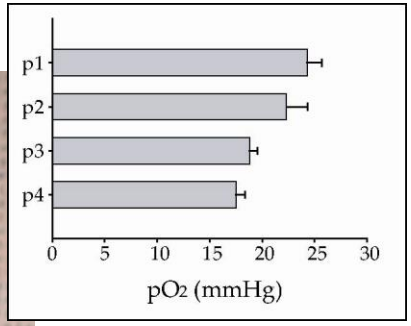
DFO Prevents Diabetic Ischemic Vascular Complications

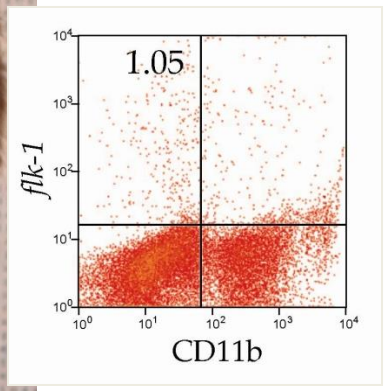


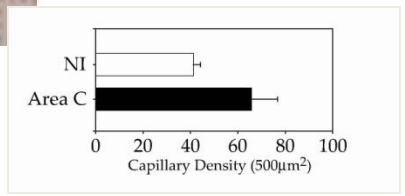




Wild Type



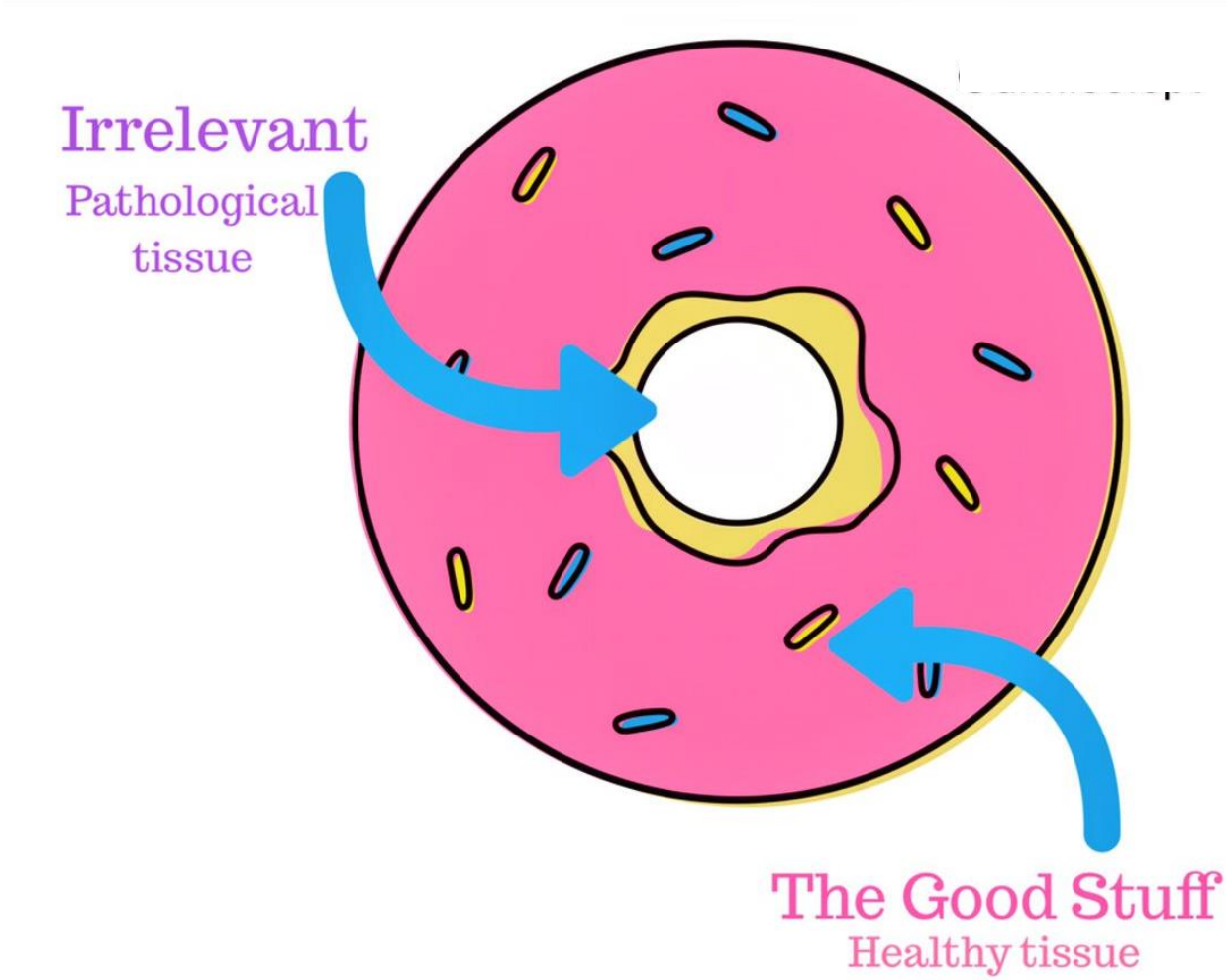




STZ.DFO

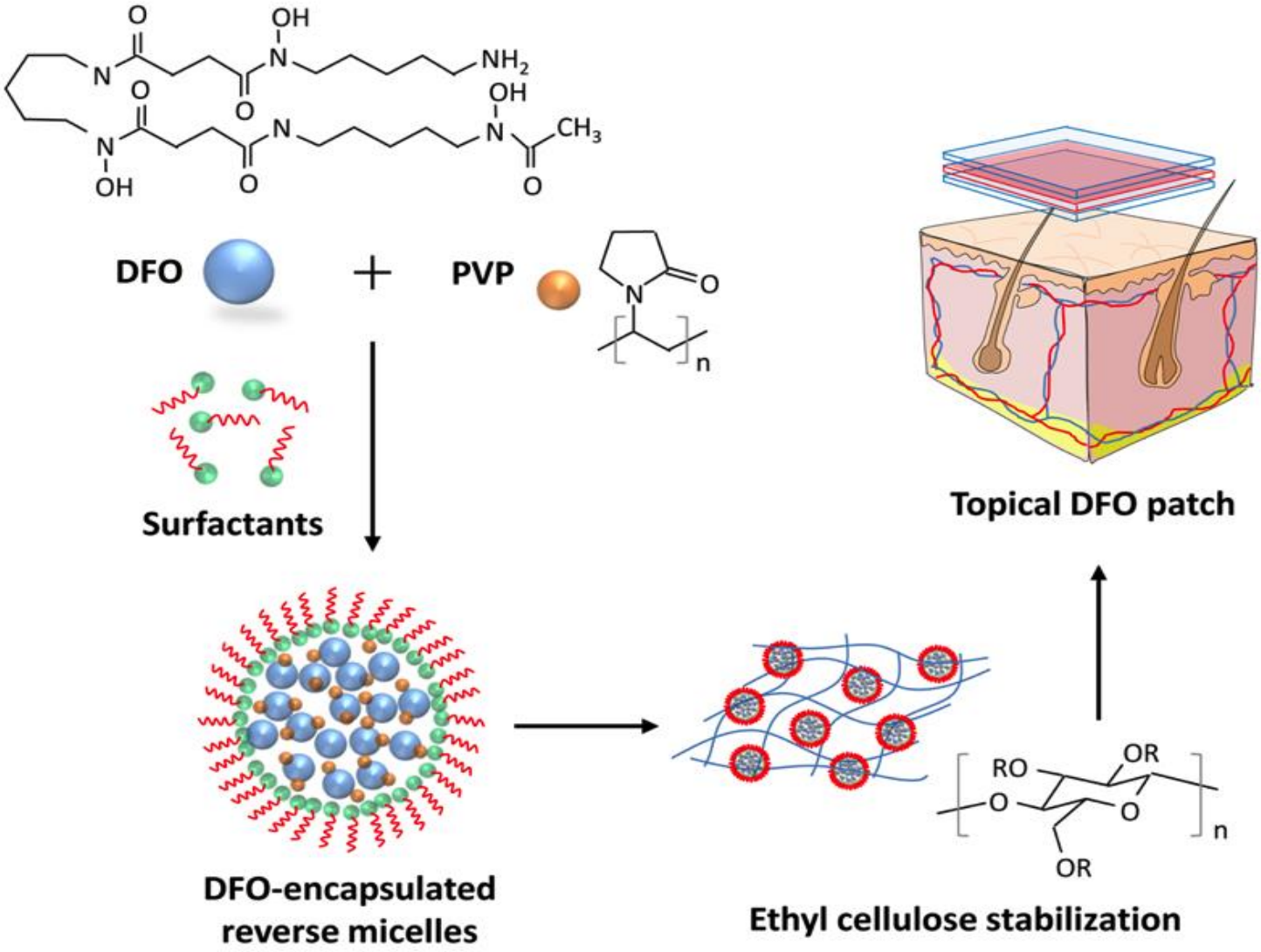
Ceradini, JBC 2008

“Treat the donut, not the hole”

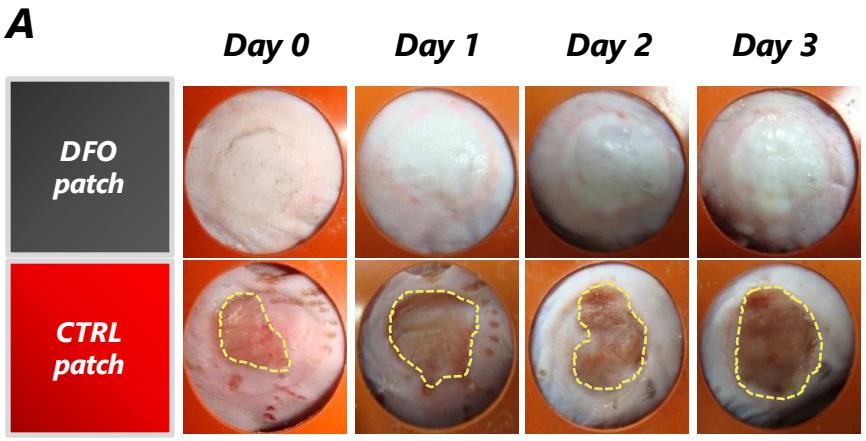


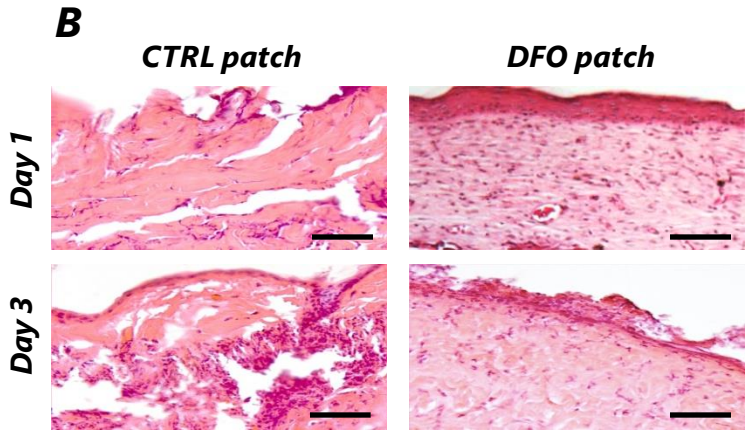
Well established concept in cardiovascular disease, orthopedics, etc

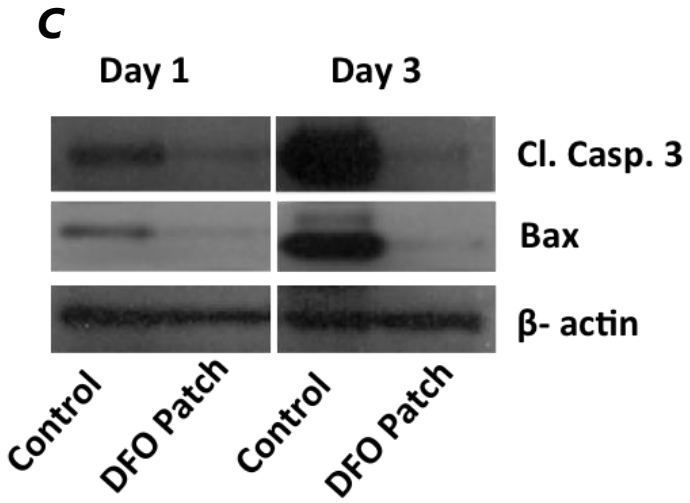
DFO Delivery System

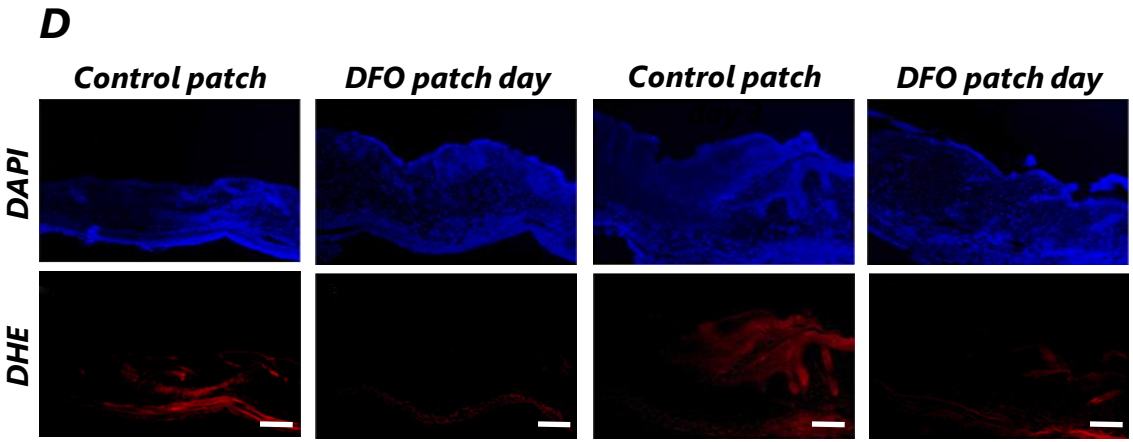


Transdermal DFO Treatment Prevents Diabetic Ulcer Formation (Primary Prevention)



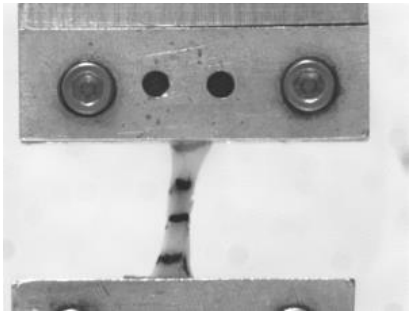


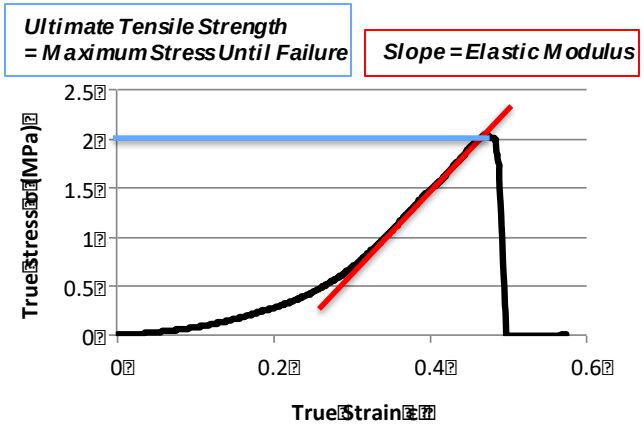


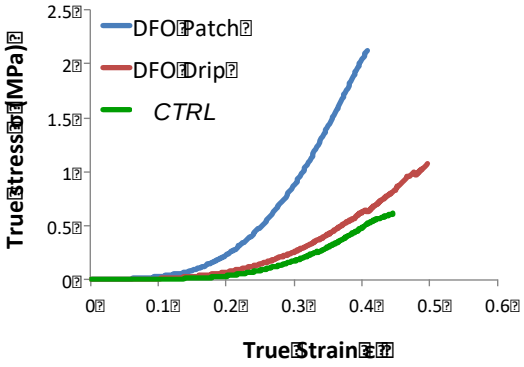


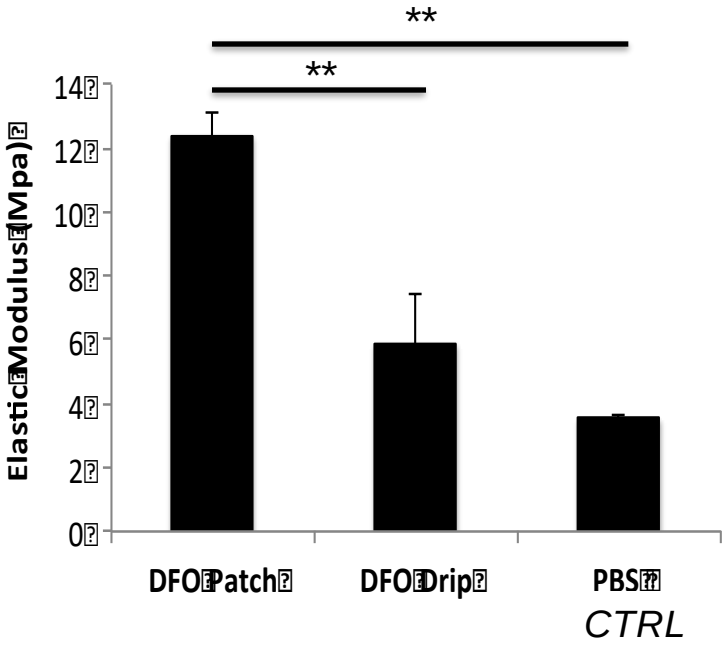
Duscher,PNAS,2015

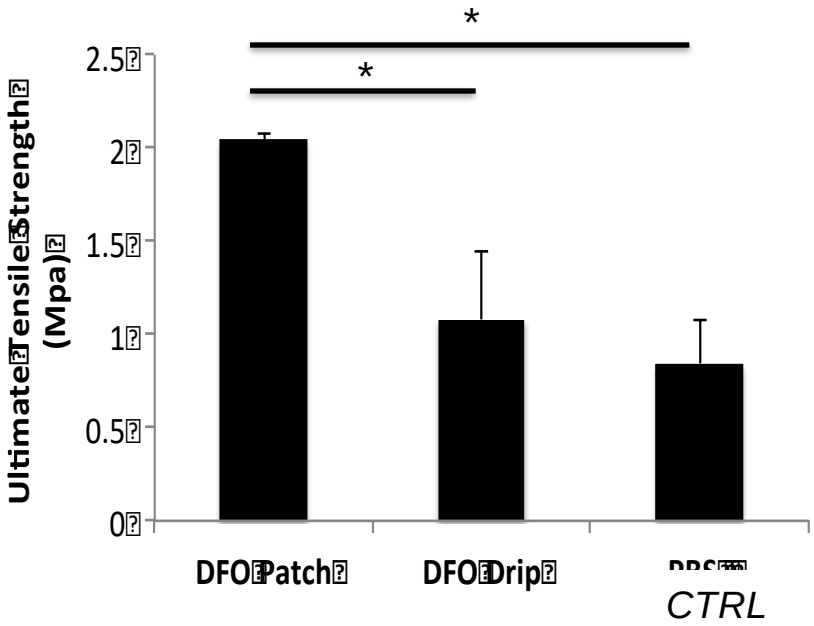
Transdermal DFO Increases Wound Strength (Secondary Prevention)









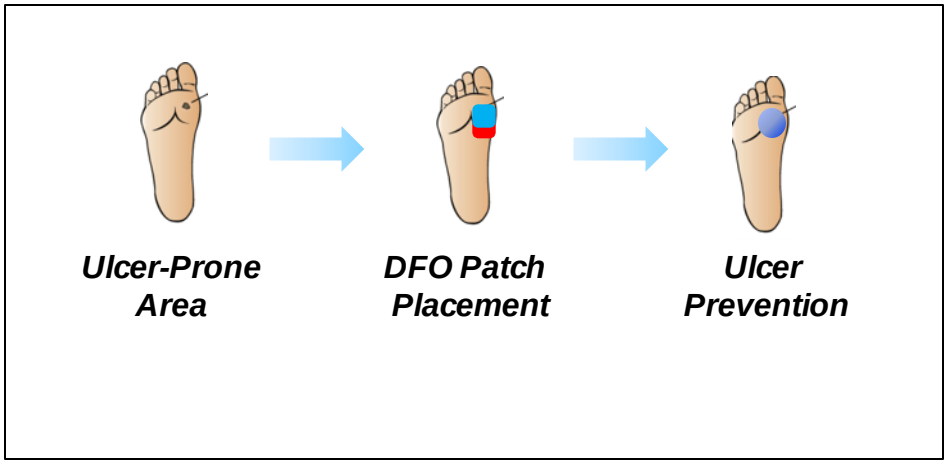


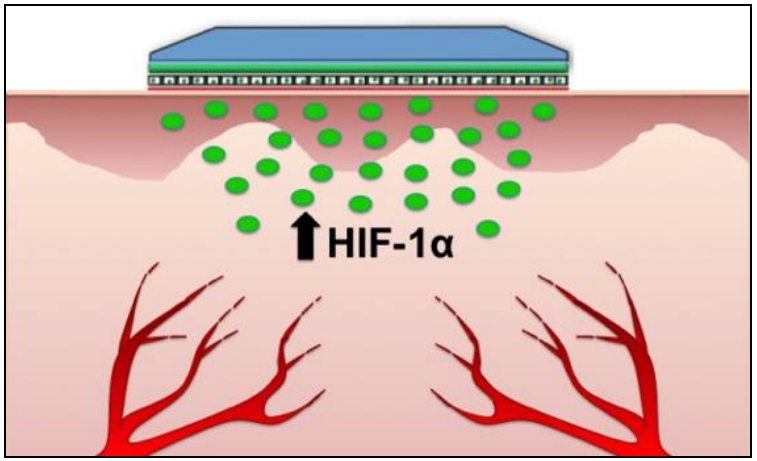
Duscher, PNAS, 2015

Target Product Profile:

1. DFO delivered as a transdermal to stabilize HIF-1$^{\alpha}$ locally in at risk areas to both prevent and treat chronic wounds
2. Multiple issued patents on both use (US Patent 9,737,511) and delivery system (US Patent 10,098,857)
3. First clinical indication?

(Actual Product)





However, there are significant challenges in conducting a diabetic wound trial

- Inherent “procedural” component, such as debridement
- Importance of “off loading” which is difficult to control
- Heterogenous co-morbidities
- FDA recognizes “complete wound closure” as the only primary healing outcome

innocoll

ADOCIA

DIPEXIUM Pharmaceuticals, Inc.

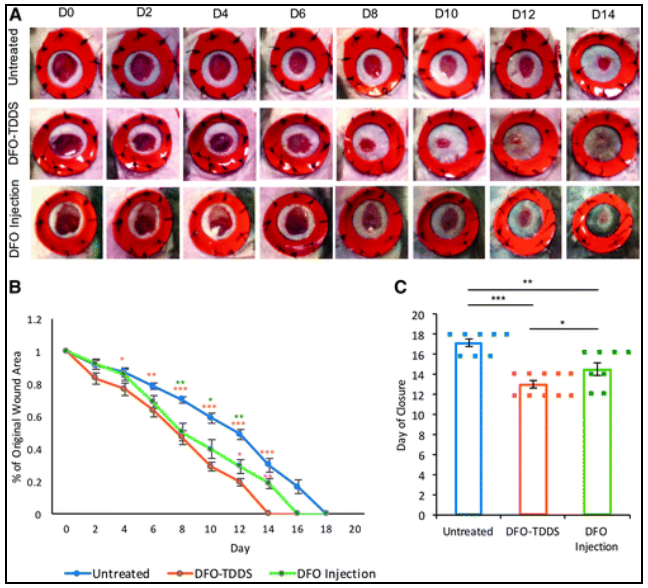
DERMASCIENCES
A TISSUE REGENERATION COMPANY

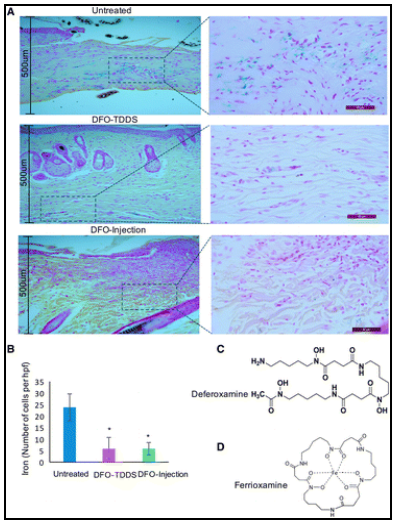
MACROCURE

Would it work in another, simpler indication?

- **Orphan Drug Designation:** FDA Program
  - Lowest cost, shortest time to approval
    - Smaller clinical trials, approval more safety based
  - Eligible for government grants and tax credits
  - 7 year marketing exclusivity
  - Can set higher pricing and reimbursement
- **Sickle Cell Ulcers**
  - Viewed as “incurable”
  - Est 14,000 SCUs annual incidence
  - 65% of SCUs covered by Medicaid and Medicare
  - 20% covered by private payors
  - DFO already used systemically in many patients
  - Compelling MOA in this and other blood dyscrasias

DFO Accelerates Wound Healing in Sickle Cell Ulcers



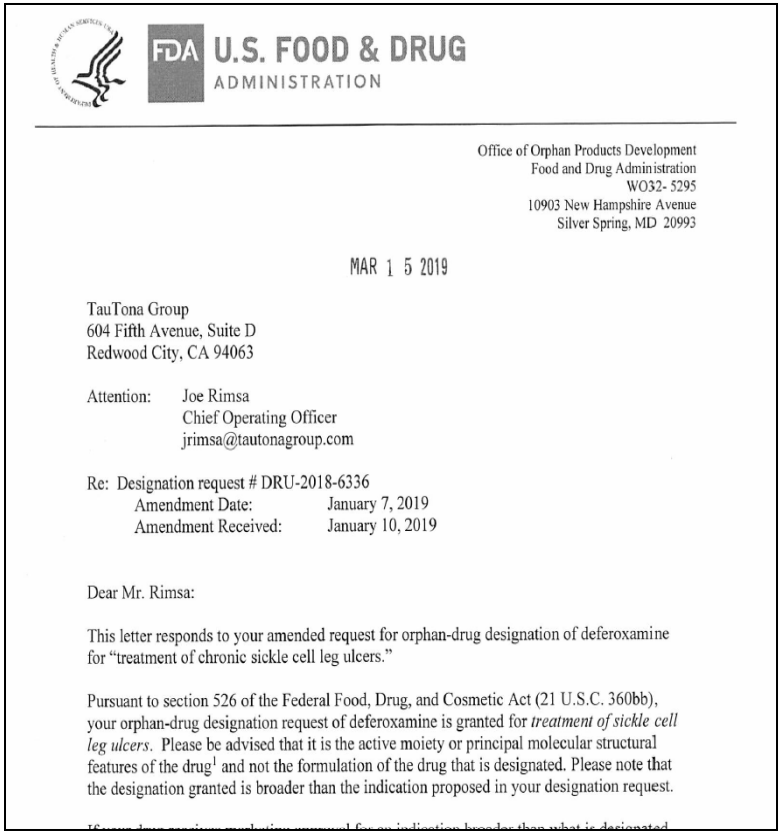


- HbSS-BERK mice carry human sickle cell transgenes and experience delayed wound healing
- DFO accelerates healing of sickle cell wounds
- DFO-treated wounds displayed lesser free iron in the wound bed and a thicker dermis following regeneration
- DFO-TDDS was particularly effective in comparison to subcutaneous injection

Rodrigues et al. Advances in Wound Care, 2018

Pivot Development Path to Sickle Cell Ulcers

- IND opened April 2019
  - Pre-IND meeting August 2017
  - IND enabling studies lasted 18 months
  - *"Nice to see someone working on a truly unmet need"*
- Awarded Orphan Drug Designation (March 2019)
- FDA audit of Redwood City manufacturing facility, January 2020
- Clinical trial begun summer 2020
  - 48 pts, 3 sentinel pts (2 active, one placebo)
  - Double blind, placebo control, 12 week healing endpoint
  - Multi center (4 sites)
  - Secondary endpoints: Rate of healing (to 80%), Pain/QoL



FDA U.S. FOOD & DRUG ADMINISTRATION

Office of Orphan Products Development
Food and Drug Administration
WO32- 5295
10903 New Hampshire Avenue
Silver Spring, MD 20993

MAR 1 5 2019

TauTona Group
604 Fifth Avenue, Suite D
Redwood City, CA 94063

Attention: Joe Rimsa
Chief Operating Officer
jrimsa@tautonagroup.com

Re: Designation request # DRU-2018-6336
Amendment Date: January 7, 2019
Amendment Received: January 10, 2019

Dear Mr. Rimsa:

This letter responds to your amended request for orphan-drug designation of deferoxamine for "treatment of chronic sickle cell leg ulcers."

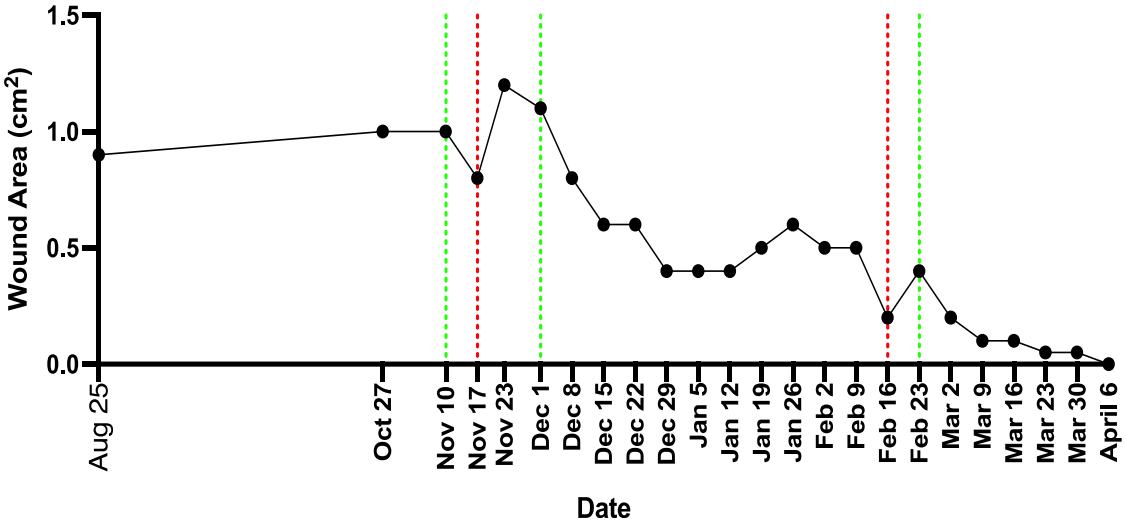
Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of deferoxamine is granted for *treatment of sickle cell leg ulcers*. Please be advised that it is the active moiety or principal molecular structural features of the drug[1] and not the formulation of the drug that is designated. Please note that the designation granted is broader than the indication proposed in your designation request.

FDA Approved Expanded Access Patient

43 year-old African American woman with B-Thalassemia and non-healing ulcer for 3 years

Received NPWT, HBO amniotic membrane, Apligraf and many other “advanced therapies”

Received Theris drug on a “compassionate use” basis



8/25/21

11/10/21 *(Treatment Start)*

11/17/21 *(Treatment Stop)*

11/23/21

12/1/21 *(Treatment Start)*

12/22/21

03/23/22

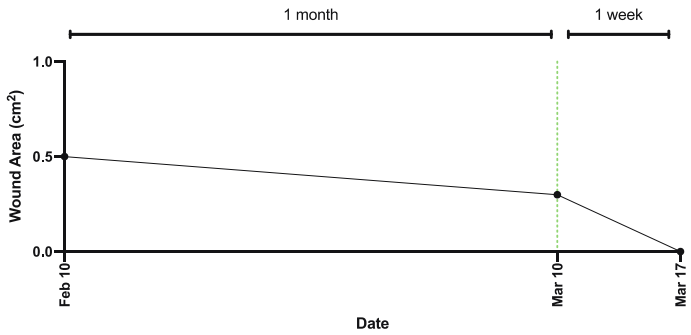
04/6/22

“I lost my hope before I started this, because nothing was helping anymore. I thought I would give this patch a try…and it worked, thankfully!”

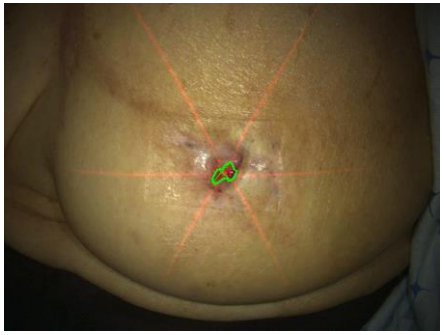
FDA Expanded Access: Chronic Radiation Wound

71-year-old female with inflammatory breast carcinoma who had a 7 month non-healing radiation wound after mastectomy, breast reconstruction, and radiation therapy (5000 cGy).

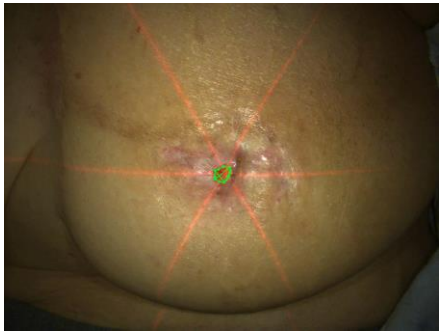
Wound healed after 3 weeks of treatment with a Deferoxamine Intradermal Delivery Patch.



1 month pre-treatment



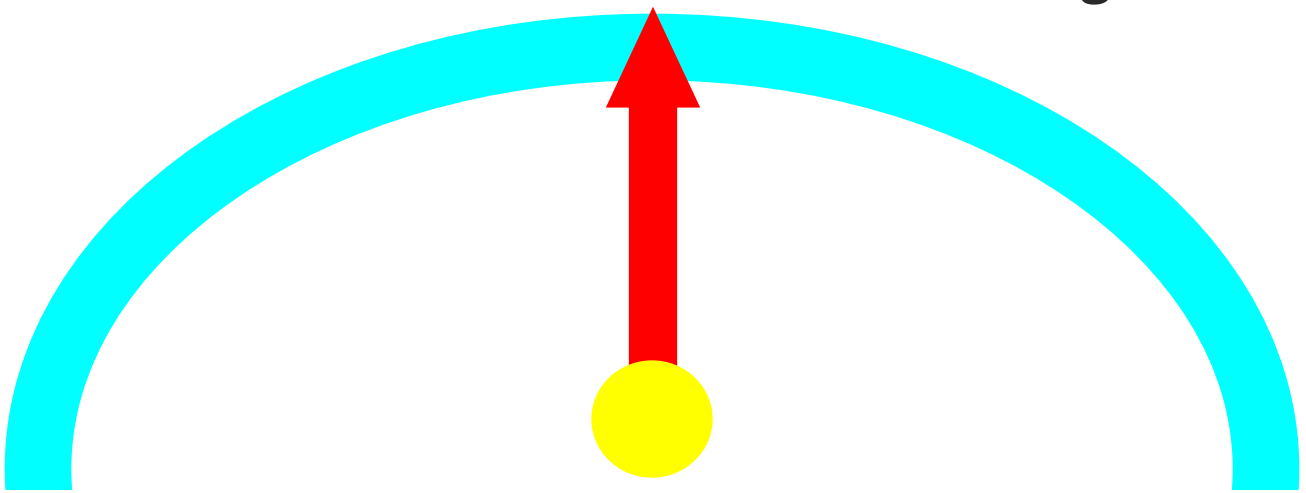
Treatment Start



1 week post-treatment

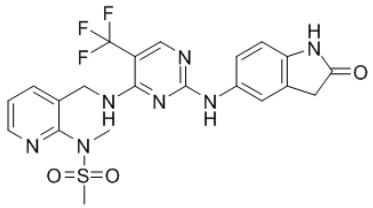
Bringing Small Molecule Therapeutics to Skin Injury

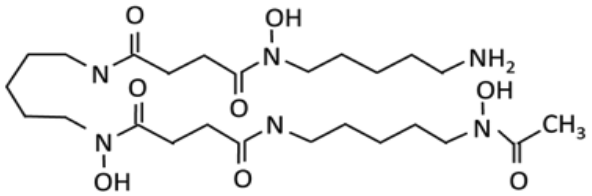
Normal Adult Wound Healing



Hypertrophic Scar
Keloids

Chronic Wounds





Questions?

gurtner@surgery.arizona.edu

Banner
University Medicine

THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE TUCSON
Surgery