



Diabetic Foot Italy  
Gruppo interassociativo AMD - SID  
podopatia diabetica



## 6° Congresso Nazionale del Gruppo di Studio della Podopatia Diabetica

La Sindrome del Piede Diabetico in Italia nel terzo millennio:  
un approccio globale, discipline diverse, professionalità integrate  
in un percorso unitario con "il paziente diabetico al centro"

Presidente del Congresso: Dr. Roberto Da Ros  
Responsabile Scientifico: Dr. Roberto Anichini



Starhotels Savoia Excelsior Palace  
Trieste, 31 gennaio / 2 febbraio 2019

**Dottor Marco Meloni**  
**MD, PhD**  
*Università di Roma*  
*Tor Vergata*

**NUOVE TECNOLOGIE**

***Sessione di Lavoro: Gestione delle lesioni e nuove tecnologie***

**Il /la dr./sa Marco Meloni dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche**

**Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).**



## Emergency in Diabetic Foot

Uccioli L\*, Meloni M, Giurato L, Ruotolo V, Izzo V, Vainieri E, Gandini R and Pampana E

Department of Internal Medicine, University of Tor Vergata, Rome, Italy

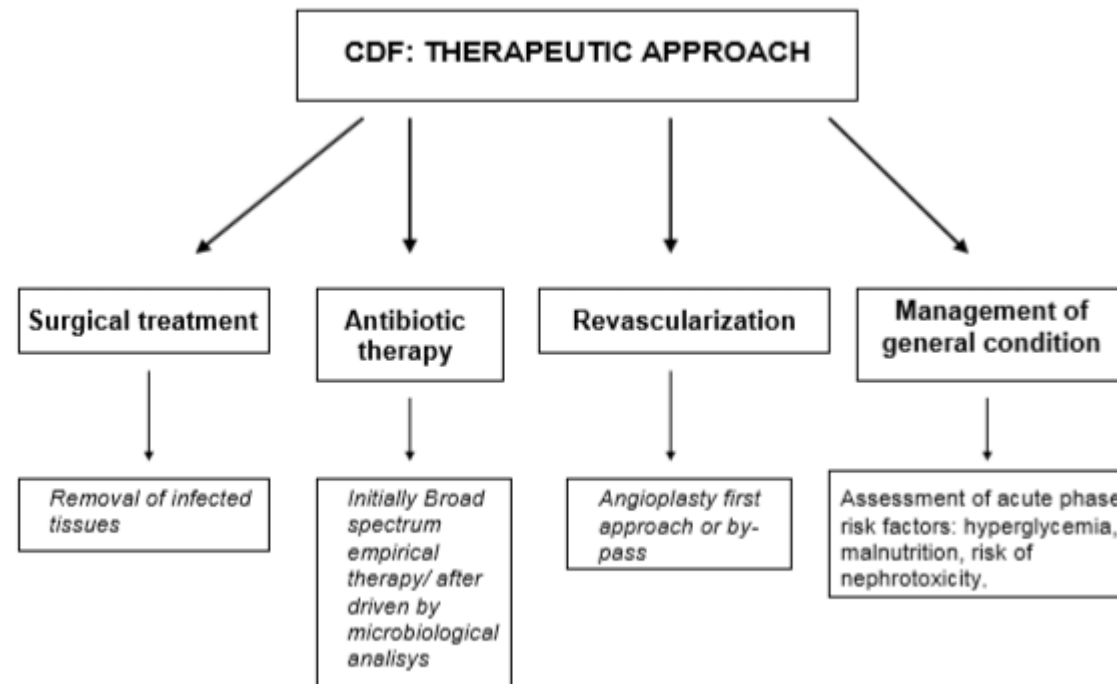


Figure 1: Therapeutic approach in critical diabetic foot.

**+ LOCAL WOUND CARE?**

Type	Actions	Indications/use	Precautions/contraindications
Alginate/CMC*	Absorb fluid Promote autolytic debridement Moisture control Conformability to wound bed	Moderate to high exuding wounds Cavity presentations in the form of rope or ribbon form Combined presentation with silver for antimicrobial activity	Do not use on dry/necrotic wounds Use with caution on friable tissue (may cause bleeding) Do not pack cavity wounds tightly
Foams	Absorb fluid Moisture control Conformability to wound bed	Moderate to high exuding wounds Special cavity presentations in the form of strips or ribbon Low adherent versions available for patients with fragile skin Combined presentation with silver or PHMB for antimicrobial activity	Do not use on dry/necrotic wounds or those with minimal exudate
Honey	Rehydrate wound bed Promote autolytic debridement Antimicrobial action	Sloughy, low to moderate exuding wounds Critically colonised wounds or clinical signs of infection	May cause 'drawing' pain (osmotic effect) Known sensitivity
Hydrocolloids	Absorb fluid Promote autolytic debridement	Clean, low to moderate exuding wounds	Do not use on dry/necrotic wounds or
Hydrogels	Rehydrate wound bed Moisture control Promote autolytic debridement Cooling	Antimicrobial activity	May cause maceration
Iodine	Antimicrobial action	Critically colonised wounds or clinical signs of infection	Do not use on dry necrotic tissue
Low-adherent wound contact layer (silicone)	Protect new tissue growth Atraumatic to periwound skin Conformable to body contours	wounds	
PHMB	Antimicrobial action	Low to high exuding wounds Critically colonised wounds or clinical signs of infection May require secondary dressing	Do not use on dry/necrotic wounds Patients with known sensitivity
Odour control (eg activated charcoal)	Odour absorption	Malodorous wounds (due to excess exudate) May require antimicrobial if due to increased bioburden	Do not use on dry wounds
Protease modulating	Active or passive control of wound protease levels	Clean wounds that are not progressing despite correction of underlying causes, exclusion of infection and optimal wound care	Do not use on dry wounds or those with leathery eschar
Silver	Antimicrobial action	Critically colonised wounds or clinical signs of infection Low to high exuding wounds Combined presentation with foam and alginates/CMC for increased absorbency. Also in paste form	Some may cause discolouration Known sensitivity Discontinue after 2-weeks if no improvement and re-evaluate
Polyurethane film	Moisture control Breathable bacterial barrier Transparent (allow visualisation of wound)	Primary dressing over superficial low exuding wounds Secondary dressing over alginate or hydrogel for rehydration of wound bed	Do not use on patients with fragile/compromised periwound skin Do not use on moderate to high exuding wounds

Other more advanced dressings (eg collagen and bioengineered tissue products, may be considered for wounds that are hard to heal (Int Consensus, 2010).  
\*Wound dressings may contain alginates or CMC only; alginates may also be combined with CMC (Hydrofiber).

Type of tissue in the wound	Therapeutic goal	Role of dressing	Treatment options		
			Wound bed preparation	Primary dressing	Secondary dressing
Necrotic, black, dry	Remove devitalised tissue Do not attempt debridement if vascular insufficiency suspected Keep dry and refer for vascular assessment	Hydration of wound bed Promote autolytic debridement	Surgical or mechanical debridement	Hydrogel Honey	Polyurethane film dressing
Sloughy, yellow, brown, black or grey Dry to low exudate	Remove slough Provide clean wound bed for granulation tissue	Rehydrate wound bed Control moisture balance Promote autolytic debridement	Surgical or mechanical debridement if appropriate Wound cleansing (consider antiseptic wound cleansing solution)	Hydrogel Honey	Polyurethane film dressing Low adherent (silicone) dressing
Therapeutic				Absorbent dressing (alginate/CMC/foam) For deep wounds, use cavity strips, rope or ribbon versions	Retention bandage or polyurethane film dressing
		ment	wound cleansing solution) Consider barrier products		
a clinical				Hydrogel Low adherent (silicone) dressing For deep wounds use cavity strips, rope or ribbon versions	Pad and/or retention bandage. Avoid bandages that may cause occlusion and maceration. Tapes should be used with caution due to allergy potential and secondary complications
Granulating, clean, red Moderate to high exudate	Exudate management Provide healthy wound bed for epithelialisation	Maintain moisture balance Protect new tissue growth	Wound cleansing Consider barrier products	Absorbent dressing (alginate/CMC/foam) Low adherent (silicone) dressing For deep wounds, use cavity strips, rope or ribbon versions	
Epithelialising, red, pink No to low exudate	Promote epithelialisation and wound maturation (contraction)	Protect new tissue growth		Hydrocolloid (thin) Polyurethane film dressing Low adherent (silicone) dressing	
Infected Low to high exudate	Reduce bacterial load Exudate management Odour control	Antimicrobial action Moist wound healing Odour absorption	Wound cleansing (consider antiseptic wound cleansing solution) Consider barrier products	Antimicrobial dressing (see Table 5 for combined presentations)	





## Recommendations

1. Clean ulcers regularly with clean water or saline, debride them when possible in order to remove debris from the wound surface and dress them with a sterile, inert dressing in order to control excessive exudate and maintain a warm, moist environment in order to promote healing. (GRADE strength of recommendation: Strong; Quality of Evidence: Low)
2. In general remove slough, necrotic tissue and surrounding callus with sharp debridement in preference to other methods, taking relative contra-indications such as severe ischemia into account. (Strong; Low)
3. Select dressings principally on the basis of exudate control, comfort and cost. (Strong; Low)
4. Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection. (Strong; Moderate)
5. Consider the use of systemic hyperbaric oxygen therapy, even though further blinded and randomised trials are required to confirm its cost-effectiveness, as well as to identify the population most likely to benefit from its use. (Weak; Moderate)
6. Topical negative pressure wound therapy may be considered in post-operative wounds even though the effectiveness and cost-effectiveness of the approach remains to be established. (Weak; Moderate)
7. Do not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care. (Strong; Low)
8. Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care. (Strong; Low)
9. Do not select systemic treatments reported to improve wound healing, including drugs and herbal therapies, in preference to accepted standards of good quality care. (Strong; Low)

# Recommendations & Rationale

## What is the best dressing to use?

- **Recommendation 3:** Select dressings principally on the basis of exudate control, comfort and cost. (Strong; Low)
- **Recommendation 4:** Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection. (Strong; Moderate)

In general, the evidence to support the adoption of any particular intervention is poor, because the available studies are small and at high risk of bias...There

The conclusion for the whole group of topical interventions is that there was either insufficient or no evidence to justify the use of any of the preparations considered in preference to any other. In the absence of any specific indication, practitioners should use the dressing/application with the lowest acquisition cost, but which supports moist wound healing whilst controlling any exudate.

# Recommendations & Rationale

Is there a place for the use of other topically applied treatments?

- **Recommendation 7:** Do not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care. (Strong; Low)
- **Recommendation 8:** Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care. (Strong; Low)
- **Recommendation 9:** Do not select systemic treatments reported to improve wound healing, including drugs and herbal therapies, in preference to accepted standards of good quality care. (Strong; Low)

**Criticità: criteri utilizzati per la farmacologia e specifiche discutibili**

# Nuove tecnologie

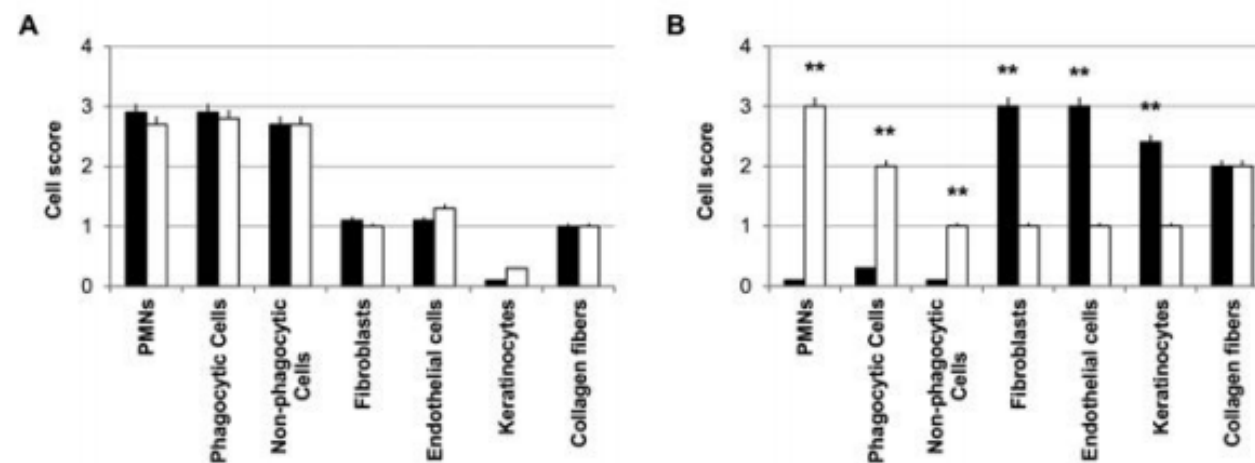
- Campi elettromagnetici
- Fotobiomodulazione
- Medicazioni topiche
- Modulatori di metalloproteasi
- Terapia rigenerativa

## Treatment of diabetic foot ulcers with Therapeutic Magnetic Resonance (TMR®) improves the quality of granulation tissue

Letizia Ferroni,<sup>1</sup> Chiara Gardin,<sup>1</sup>  
Andrea De Pieri,<sup>1</sup> Maria Sambataro,<sup>2</sup>  
Elena Seganfredo,<sup>2</sup> Elisabetta Iacopi,<sup>3</sup>  
Chiara Goretti,<sup>3</sup> Barbara Zavan,<sup>1</sup>  
Alberto Piaggese<sup>3</sup>

Table 1. Clinical characteristics of the patients participating in the study.

	Group A	Group B
Number of patients	20	20
Age (yrs)	64.7±18.4	65.2±16.7
Duration of diabetes (yrs)	18.5±6.3	17.9±7.1
Glycated haemoglobin (%)	7.9±1.1	8.3±1.8
Insulin/oral hypoglycemic drugs	14/6	15/5
Statins (Y/N)	16/4	18/2
Acetilsalicylic acid (Y/N)	18/2	19/1
Retinopathy (background/proliferative)	17/3	19/1
Albuminuria (micro/macro)	18/2	18/2
Hypertension (Y/N)	16/4	17/3



**Figure 4.** Histomorphometric analysis of biopsies from Sham Group (white bars) and Active Group (black bars): A) at baseline; B) after two week of TMR® treatment. PMNs are polymorphic nuclear cells, *i.e.* granulocytes; phagocytic cells include macrophages and monocyte-derived giant cells; non-phagocytic cells include lymphocytes, plasma cells and mast cells. Cells were scored as absent (score 0), scarcely present (score 1), present (score 2), and abundantly present (score 3). A *t*-test was used to determine significant differences ( $P < 0.05$ ): \* $P < 0.05$  and \*\* $P < 0.01$ .



**Treatment of diabetic foot  
ulcers with Therapeutic  
Magnetic Resonance (TMR®)  
improves the quality  
of granulation tissue**

Letizia Ferroni,<sup>1</sup> Chiara Gardin,<sup>1</sup>  
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Chiara Goretti,<sup>3</sup> Barbara Zavan,<sup>1</sup>  
Alberto Piaggese<sup>3</sup>

- ✓ During the follow-up, significantly **more lesions healed in the Active Group** (14/20 in Group B vs 4/20 in Group A,  $P < 0.05$ ). Moreover, the healing time was faster in Active Group than in Sham group ( $44.8 \pm 12.1$  vs  $96.7 \pm 23.5$  days, respectively,  $P < 0.05$ ).
- ✓ In conclusion, our data suggest that **TMR® magnetic fields may act reducing the inflammatory state**, triggering a chain of events that promotes the shifting of the lesion towards the proliferative phase. The clinical correlates of the activity of TMR® demonstrated a more frequent and faster healing of DFUs; while the absence of side effects confirms the very positive safety profile of this approach to wound healing.

**LIMITATIONS:** cost-effectiveness, duration of ulcers, size, localization

# Evaluation of fluorescence biomodulation in the real-life management of chronic wounds: the EUREKA trial

Marco Romanelli,<sup>1</sup> MD, PhD; Alberto Piaggese,<sup>2</sup> MD; Giovanni Scapagnini,<sup>3</sup> MD, PhD; Valentina Dini,<sup>1</sup> MD, PhD; Agata Janowska,<sup>1</sup> MD; Elisabetta Iacopi,<sup>2</sup> MD; Carlotta Scarpa,<sup>4</sup> MD; Stéphane Fauverghe,<sup>5</sup> MD; Franco Bassetto,<sup>4</sup> MD; EUREKA Study Group

## Aim:

The primary aim of the EUREKA study was to confirm the efficacy and safety of a system based on FB, known as LumiHeal (KLOX Technologies Inc., Canada). Secondary aims were to examine quality of life (QoL) in subjects who received the treatment and collect feedback from health professionals on the usability of the FB System in the management of chronic wounds

## Multicentre, prospective, observational, uncontrolled trial

Table 2. Wounds characteristics at study entry, all wounds (n=99)

	VLU	DFU	PU	All wounds
Gender F:M %	44.2 : 55.8	21.9 : 78.1	13.3 : 86.7	32.3 : 67.7
Age, mean±SD years	70.80±11.03	69.27±11.58	60.18±14.56	68.70±12.23
Size at entry, mean±SD cm <sup>2</sup>	10.96±11.39	3.03±3.40	4.29±5.36	7.39±9.47
Median duration at entry, months	9.30	3.90	12.50	8.90
Source: ORS-K1002-P001 database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer; F—female; M—male; SD—standard deviation				

Table 3. Prognostic factors of poor healing at study entry, all wounds (n=99)

	VLU	DFU	PU	All wounds
None	19.2%	43.8%	33.3%	29.3%
*One	51.9%	46.9%	60.0%	51.5%
*Two (both factors present)	28.8%	9.4%	6.7%	19.2%
Total	100.0%	100.0%	100.0%	100.0%
*Area>10cm <sup>2</sup> (or 5cm <sup>2</sup> for DFU), or duration >6 months Source: ORS-K1002-P001 database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer				

# Evaluation of fluorescence biomodulation in the real-life management of chronic wounds: the EUREKA trial

Marco Romanelli,<sup>1</sup> MD, PhD; Alberto Piaggese,<sup>2</sup> MD; Giovanni Scapagnini,<sup>3</sup> MD, PhD; Valentina Dini,<sup>1</sup> MD, PhD; Agata Janowska,<sup>1</sup> MD; Elisabetta Iacopi,<sup>2</sup> MD; Carlotta Scarpa,<sup>4</sup> MD; Stéphane Fauverghe,<sup>5</sup> MD; Franco Bassetto,<sup>4</sup> MD; EUREKA Study Group

Table 4. Comparison of wound closure rate between interim and final analysis

	Interim results on 33 patients		Final results on 99 patients	
	n	Mean (%)	n	Mean (%)
VLU	7	53.8%	26	50.0%
DFU	9	52.9%	16	50.0%
PU	1	33.3%	5	33.3%
Total	17	51.5%	47	47.5%

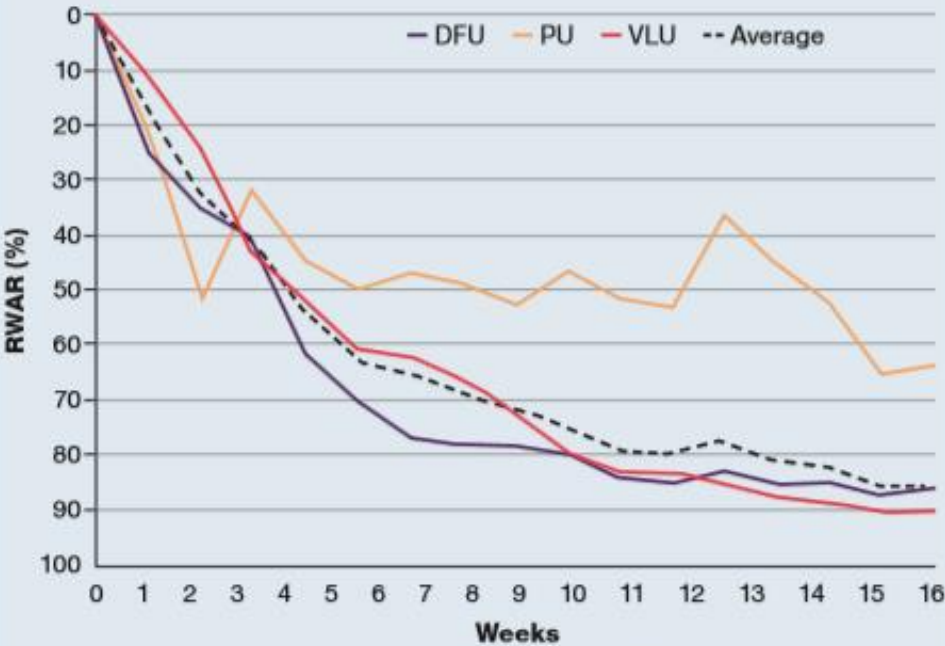
VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer

Table 5. Median wound area regression versus baseline (n=99)

Wound type	Median wound area regression at last visit	p-value
VLU	94.2%	<0.001
DFU	78.1%	0.001
PU	36.8%	0.268

Source: ORS-K1002-P001 database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer

Fig 1. Mean relative wound area reduction within the ‘responders’ group, all wounds (n=81)



Source—EUREKA study database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer; RWAR—relative wound area reduction; Mean RWAR at week 4: 54.4%; Mean RWAR at week 10: 79.2%

# Evaluation of fluorescence biomodulation in the real-life management of chronic wounds: the EUREKA trial

JOURNAL OF WOUND CARE VOL 27, NO 11, NOVEMBER 2018

Marco Romanelli,<sup>1</sup> MD, PhD; Alberto Piaggese,<sup>2</sup> MD; Giovanni Scapagnini,<sup>3</sup> MD, PhD; Valentina Dini,<sup>1</sup> MD, PhD; Agata Janowska,<sup>1</sup> MD; Elisabetta Iacopi,<sup>2</sup> MD; Carlotta Scarpa,<sup>4</sup> MD; Stéphane Fauvergne,<sup>5</sup> MD; Franco Bassetto,<sup>4</sup> MD; EUREKA Study Group


Overall, the system was considered as [very easy to use](#), and [92.4% of the questionnaires reported that investigators would recommend the system to their colleagues](#). Mean reasons given to investigators to explain this high level of satisfaction were [the ease of use and the efficacy](#) of the treatment.

Despite the chronicity and heterogeneity of the different wounds treated in this study, [the overall clinical profile is considered promising](#). The study results revealed the interesting clinical potential of the system [in terms of rate of wound closure, mean time to reach wound closure, extremely low rate of wound breakdown and mean RWAR](#)

**LIMITATIONS:** there was [no formal sample size calculation for each group, no randomisation and no control group](#). There was also [a limited number of inclusion and exclusion criteria...different grade of DFUs](#)

**CONCLUSIONS:** These results confirm that the studied system based on FB offers an [important and innovative approach](#) in the management of chronic hard-to-heal wounds

# The Use of a Novel Super-Oxidized Solution on Top of Standard Treatment in the Home Care Management of Postsurgical Lesions of the Diabetic Foot Reduces Reinfections and Shortens Healing Time

Elisabetta Iacopi, MD<sup>1</sup> , Lorenza Abbruzzese, DPM<sup>1</sup>, Chiara Goretti, MD<sup>1</sup>, Nicola Riitano, DPM<sup>1</sup>, and Alberto Piaggese, MD<sup>1</sup>

The International Journal of Lower  
Extremity Wounds  
1–7

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Nexodyn is a sprayable acid-oxidizing solution developed for the topical management of acute and chronic wounds able to create a local microenvironment that reduces microbial growth and supports physiological wound healing. The main product features are the presence of stabilized hypochlorous acid (HClO), representing more than 95% of the free chlorine species contained in the solution, acidic pH (below 3), and a high oxidation reduction potential. HClO is a broad-spectrum, fast-acting antimicrobial agent naturally produced by neutrophils able to easily penetrate the bacterial wall to exert its biocidal activity, which is about 80 times stronger than the negatively charged hypochlorite ion

## AIM:

To evaluate the safety of such a composed super-oxidized solution when applied on top of standard treatment in a home care setting. Furthermore, we aimed to evaluate its effectiveness in improving outcomes of postsurgical diabetic foot lesions.



# The Use of a Novel Super-Oxidized Solution on Top of Standard Treatment in the Home Care Management of Postsurgical Lesions of the Diabetic Foot Reduces Reinfections and Shortens Healing Time

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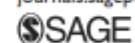
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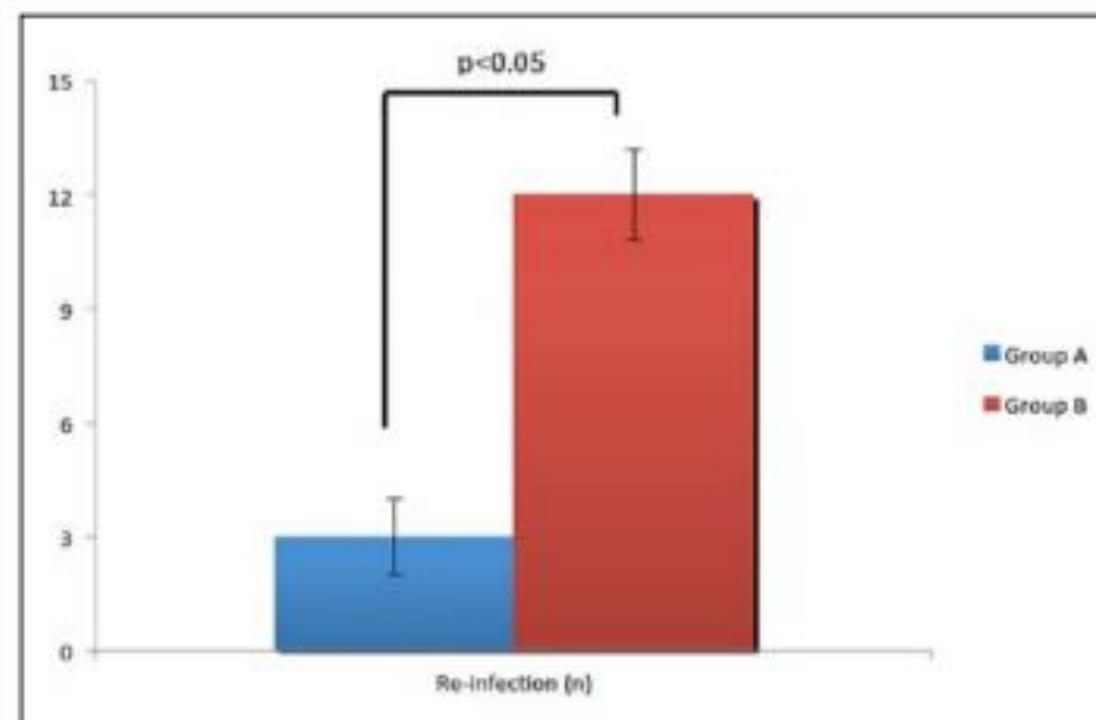
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**Table 1.** Demographic and Clinical Characteristics.

Characteristics	Group A	Group B	P
Patients (n)	25	25	—
Male/female (n/n)	17/8	16/9	ns
Age (years)	67.3 ± 12.1	68.1 ± 11.9	ns
Diabetes (type 1/2) (%)	22/3	21/4	ns
Diabetes duration (years)	14.7 ± 9.9	14.4 ± 9.4	ns
BMI (kg/m <sup>2</sup> )	25.5 ± 5.2	26.1 ± 5.0	ns
HbA1C (%)	7.9 ± 1.1	7.6 ± 1.6	ns
Total cholesterol (mg/dL)	156 ± 40	163 ± 36	ns
Creatininemia (mg/dL)	1.1 ± 0.9	1.0 ± 0.8	ns
eGFR (mL/min)	46.7 ± 23.4	47.2 ± 21.1	ns
Cardiovascular disease (%)	22.1	20.9	ns
Hypertension (%)	34.5	37.2	ns
Cerebrovascular disease (%)	12.1	13.4	ns
Renal failure (%)	16.5	17.1	ns
Diabetic retinopathy (%)	23.9	21.8	ns
Diabetic neuropathy (%)	66.7	64.2	ns

Abbreviation: BMI, body mass index; HbA1C, hemoglobin A1C; eGFR, estimated glomerular filtration rate test; ns, nonsignificant.



**Figure 2.** Number of patients who experienced a reinfection during the study period.

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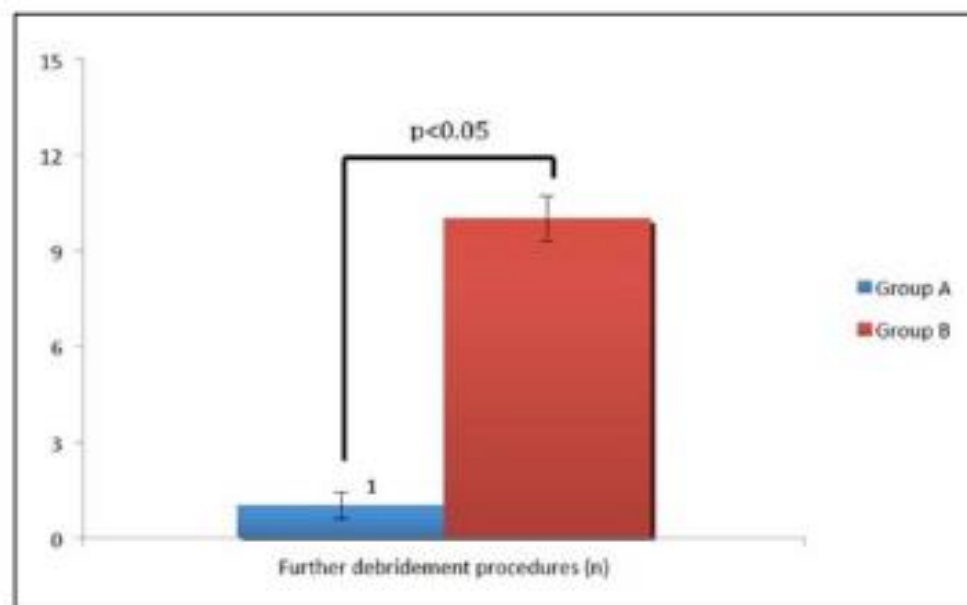
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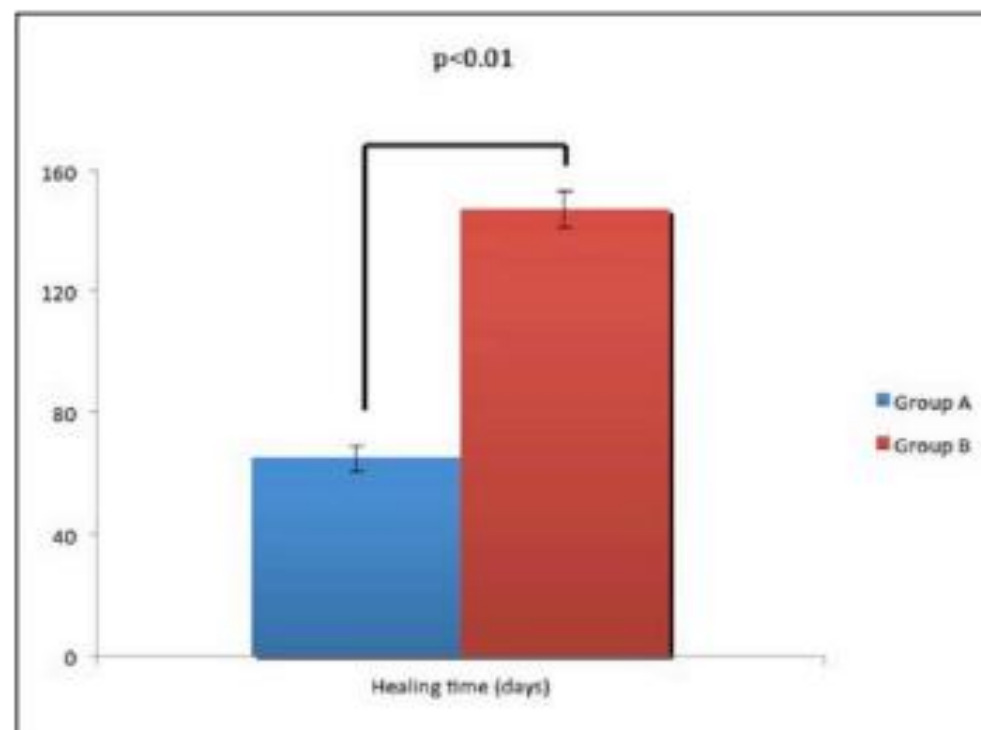
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**Figure 3.** Further debridement procedures needed in both the groups.



**Figure 5.** Healing time in both the groups.

# The Use of a Novel Super-Oxidized Solution on Top of Standard Treatment in the Home Care Management of Postsurgical Lesions of the Diabetic Foot Reduces Reinfections and Shortens Healing Time

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The [chemical reasons...](#): the creation of a [microenvironment unfavorable to bacterial proliferation](#) with consequent reduction of inflammatory pattern and the creation of an [ideal pabulum for](#) the development of the [healing process](#).

Despite our study not taking into account the role of systemic antibiotic therapy, [we expect](#) that the adoption of super-oxidized solution will associate with [a reduction of antibiotic use and a positive effect on antibiotic resistance](#).

Despite our study representing a [single-center pilot experience](#), the data derived allows to consider [this novel solution as an effective part of the integrated therapeutic approach](#) in all diabetic foot cases, alongside surgery, systemic antibiotics treatment, and revascularization if necessary

**LIMITATIONS:** wound location, depth, absence of comparison with other anti-septic agent, ability to walk

# Multicenter, randomized controlled, observer-blinded study of a nitric oxide generating treatment in foot ulcers of patients with diabetes—ProNOx1 study

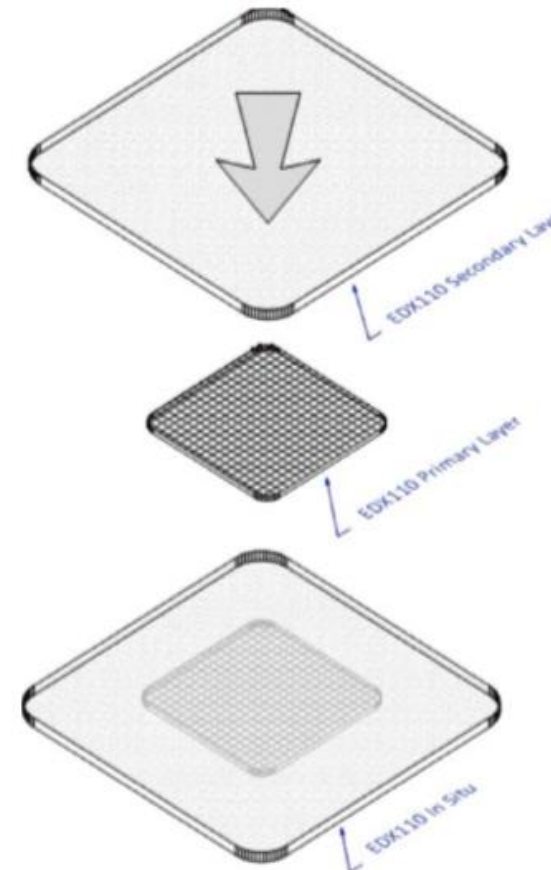
Michael E. Edmonds, FRCP <sup>1</sup>; Harvey J. Bodansky, FRCP<sup>2</sup>; Andrew J.M. Boulton, FRCP<sup>3</sup>; Paul J. Chadwick, PhD<sup>4</sup>; Cuong N. Dang, FRCP<sup>5</sup>; Ryan D'Costa, FRCP<sup>6</sup>; Atholl Johnston, FRCP<sup>7</sup>; Brian Kennon, FRCP<sup>8</sup>; Graham Leese, FRCPEd<sup>9</sup>; Satyan M. Rajbhandari, FRCP<sup>10</sup>; Thomas E. Serena, MAPWCA<sup>11</sup>; Matthew J. Young, FRCP<sup>12</sup>; Joanne E. Stewart, PhD<sup>7</sup>; Arthur T. Tucker, PhD<sup>7</sup>; Marissa J. Carter, PhD<sup>13</sup>

## AIM

..was to assess the [safety and efficacy of EDX110](#), a Class III medical device, compared to standard of care (SOC) dressings—the control group—in the treatment of diabetic foot ulcers

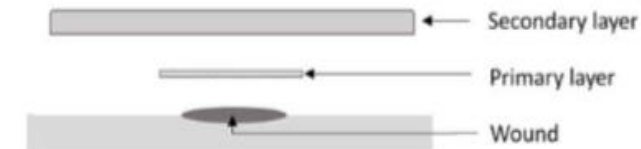
EDX110 (Edixomed, London, UK) is a [two-layer system designed to generate NO in situ](#). EDX110 provides a moist wound environment, absorbs exudate, triggers autolytic debridement and, when the two layers are placed in contact and applied to the wound, nitric oxide (NO) is generated as an ancillary function

Wound Repair and Regeneration



A sterile wound treatment as two components:

1. A primary nonadherent mesh
2. A protective layer which generates nitric oxide when placed on the primary layer



# Multicenter, randomized controlled, observer-blinded study of a nitric oxide generating treatment in foot ulcers of patients with diabetes—ProNOx1 study

**Table 1.** Baseline demographics of the intention-to-treat population

Parameter	EDX110	Control
Age (years)*	59.3 (SD 12.41)	59.0 (SD 11.85)
Male*	63 (87%)	59 (82%)
Female*	9 (13%)	13 (18%)
Palpable foot pulse*		
Yes	68 (94%)	62 (87%)
No	4 (6%)	9 (13%)
Blood pressure (mmHg)*		
Systolic	143.9 (21.11)	143.3 (21.89)
Diastolic	81.9 (13.13)	81.2 (15.45)
Blood glucose (mmol/L)*	9.9 (5.68)	10.2 (4.11)
ABPI*	1.26 (0.55)	1.24 (0.28)
Bypass graft	3 (4)	7 (10)
DFU age (weeks) <sup>⊥</sup>		
Mean	28.9 (35.1)	41.1 (54.7)
Median	13.0 (33.1)	19.6 (44.1)
DFU age (weeks) <sup>⊥</sup>		
>26	24 (32%)	28 (39%)
≤26	51 (68%)	44 (61%)
Initial area (cm <sup>2</sup> ) <sup>†</sup>		
Mean	2.10 (3.33)	1.58 (2.22)
Median	0.86 (1.89)	0.7 (1.26)

**Table 2.** Percentage ulcer area reductions in specific ulcer populations

	Mean (SD)		Median (IQR)		p
	EDX110	Control	EDX110	Control	
PAR at 12 weeks					
ITT	n = 75 58.7 (59.20)	n = 73 37.0 (80.58)	n = 75 88.6 (73.7)	n = 73 46.9 (100)	0.016*
PP	n = 61 71.0 (50.39)	n = 63 38.6 (85.66)	n = 61 98.5 (36.9)	n = 63 52.1 (98.5)	0.012*
PAR at 4 weeks					
ITT	n = 75 45.4 (45.96)	n = 73 31.7 (47.73)	n = 75 53.7 (60.5)	n = 73 34.4 (61.1)	0.097*
PP	n = 61 55.4 (37.89)	n = 63 32.9 (49.82)	n = 61 55.9 (53.7)	n = 63 36.3 (58.7)	0.036*
PAR related to ulcer					
duration at baseline (ITT ulcer population) <sup>†</sup>					
≤ 6 months	n = 51 67.1 (56.8) <sup>⊥</sup>	n = 44 37.8 (93.0) <sup>‡</sup>	n = 51 97.0 (37.4)	n = 44 55 (88.7)	0.04
> 6 months	n = 24 40.8 (61.4) <sup>⊥</sup>	n = 28 42.8 (45.0) <sup>‡</sup>	n = 24 47 (87)	n = 28 46 (84)	0.80
PAR related to ulcer					
area at baseline (ITT ulcer population)					
≥ 1 cm <sup>2</sup>	n = 32 59.4 (45.5)	n = 32 29.3 (42.2)	n = 32 82.0 (77.6)	n = 32 29.2 (55.4)	0.007
< 1 cm <sup>2</sup>	n = 43 58.2 (68.1)	n = 41 43.0 (101.1)	n = 43 100 (70.4)	n = 41 92.1 (87.7)	0.52



## **Multicenter, randomized controlled, observer-blinded study of a nitric oxide generating treatment in foot ulcers of patients with diabetes—ProNOx1 study**



The ulcers treated with EDX110 were associated with a [significantly smaller number of SAEs](#) which were related or possibly related to the study ulcer compared to those treated with SOC dressings. Thus, there may be [a significant clinical benefit gained using EDX110](#) in a therapy area where recent overviews concluded that currently there is no robust evidence that any advanced dressing type is more effective than basic wound contact dressings

This prolonged action of NO may [be a major factor in the improved healing rate](#) and makes EDX110 [applicable to any chronic ulcer situation](#) where ischemia and infection are factors in delayed healing. In the infected ulcers treated with EDX110, there was a doubling of complete healing compared to those treated with standard of care dressings

### **LIMITATIONS:**

[Reduction in ulcer size was used as the primary outcome](#) as opposed to the commonly utilized outcome of complete healing..

..the choice of a [non standardized dressing protocol in the control group](#) with inevitable lack of blinding.

# **Others new dressings/devices**

**Topical haemoglobin spray for diabetic foot ulceration**

*Bateman SD, Br J Nurse, 2015*

**Effect of low-level light therapy on diabetic foot ulcers: a near-infrared spectroscopy study**

*Salvi M et al, J. Biomed Opt, 2017*

**Honey dressing on a leg ulcer with tendon exposure in a patient with type 2 diabetes**

*Teobaldi I et al, Endocrinol Metabolism Diab Case Rep, 2018*

**Potential cost-effectiveness of using a collagen-containing dressing in managing diabetic footulcers in the UK**

*Guest JF et al, J Wound Care, 2018*

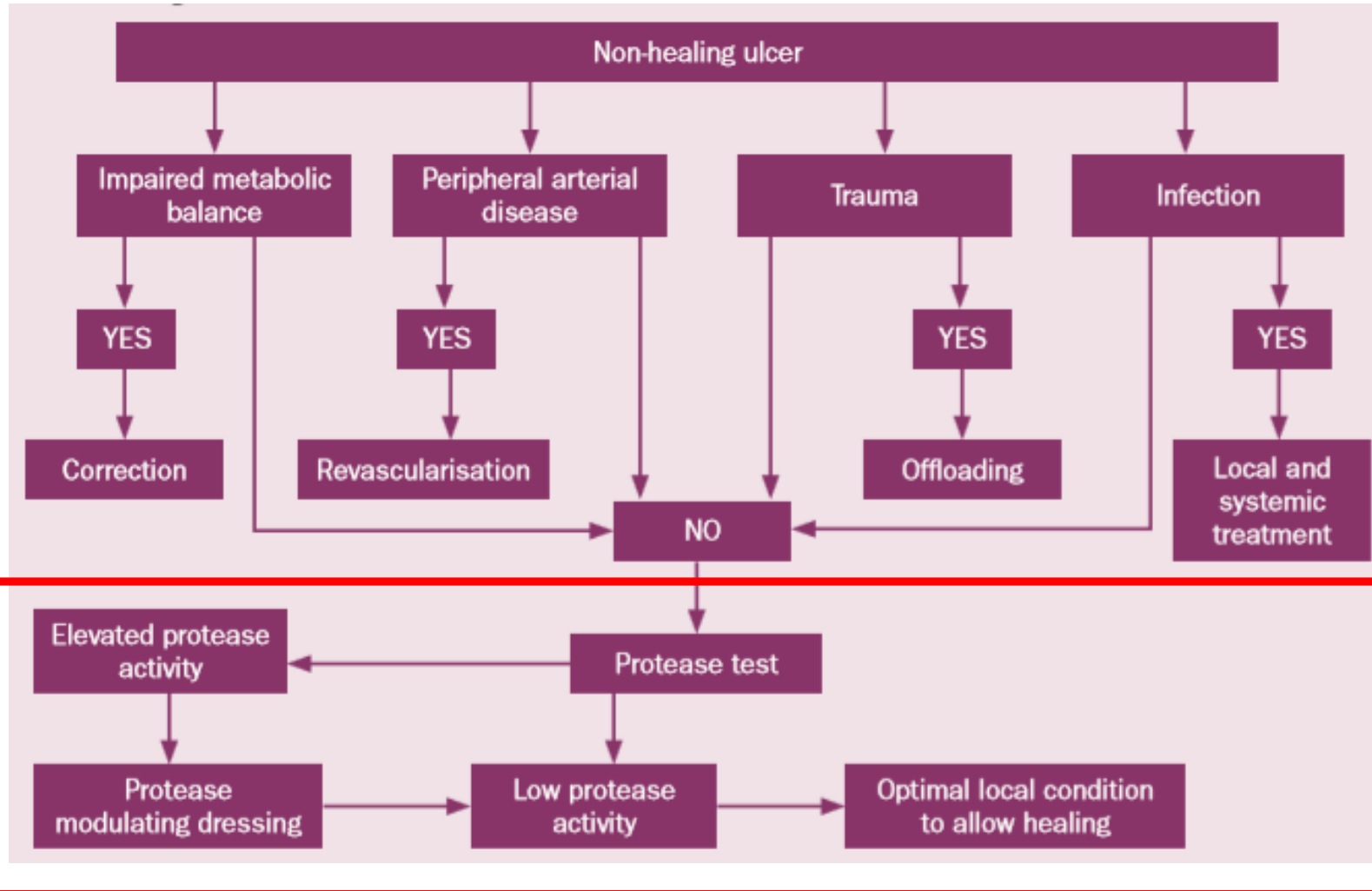
**The LeucoPatch® system in the management of hard-to-heal diabetic foot ulcers: study protocol for a randomised controlled trial**

*Game F, Trials., 2017*

**The role of chloramines in treatment of diabetic foot ulcers: an exploratory multicentre randomised controlled trial**

*Berggvist K et al, Clin Diabetes Endocrinol, 2016*

# NON-HEALING FOOT ULCERS IN DIABETIC PATIENTS: GENERAL AND LOCAL INTERFERING CONDITIONS AND MANAGEMENT OPTIONS WITH ADVANCED WOUND DRESSINGS



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# Elevated levels of matrix metalloproteinases and chronic wound healing: an updated review of clinical evidence

**Table 1. The main MMPs involved into the wound healing process**

Type of MMPs	Sub group of MMPs	Denominations
Soluble gelatinases	Gelatinases	MMP-2: Gelatinase-A MMP-9: Gelatinase-B
Archetypal MMPs	Collagenases	MMP-1: Collagenase-1, Interstitial collagenase MMP-8, Collagenase-2, Neutrophil collagenase MMP-13: Collagenase-3
	Metalloelastase	MMP-12
	Stromelysins	MMP-3: Stromelysin-1 MMP-10: Stromelysin-2 MMP-11: Stromelysin-3
	Matrilysins	MMP-7: Matrilysin MMP-26: Matrilysin-2

MMP–Matrix metalloproteinase

**Table 5. High MMP related outcomes prevalence according to published trials**

Outcomes related to an initial higher level of MMP indicators	Prevalence of the wounds with the high MMP related outcomes	Ref.
Unhealed DFUs at 12 weeks	63% (n=39/62)	46
Unhealed DFUs at 12 weeks	47% (n=14/30)	48
Poor healers (DFU) with a RWAR <82% at 4 weeks	54% (n=50/93)	49
Total (Poor + intermediate PU healers)	79% (n=44/56)	45
Poor healers (PU) with a RWAR of less than 45% over 35 days	14% (n=8/56)	
Intermediate healers (PU) with a RWAR comprise between 45 and 85% over 35 days	64% (36/56)	

...initial high levels of MMPs have been correlated to significant delayed wound healing in chronic wounds of various aetiologies (DFUs, VLU, PUs and dehiscent surgical wounds) or even in acute wounds that have become chronic. These elevated levels tend to decrease while the wounds are put back on their right healing trajectory and wound healing occurs. Therefore, it would be of interest that more research further assesses the efficacy of anti-protease treatment in these wounds.

# Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial

Michael Edmonds, José Luis Lázaro-Martínez, Jesus Manuel Alfayate-García, Jacques Martini, Jean-Michel Petit, Gerry Rayman, Ralf Lobmann, Luigi Uccioli, Anne Sauvadet, Serge Bohbot, Jean-Charles Kerihuel, Alberto Piaggese

## Summary

**Background** Diabetic foot ulcers are serious and challenging wounds associated with high risk of infection and lower-limb amputation. Ulcers are deemed neuroischaemic if peripheral neuropathy and peripheral artery disease are both present. No satisfactory treatment for neuroischaemic ulcers currently exists, and no evidence supports one particular dressing. We aimed to assess the effect of a sucrose octasulfate dressing versus a control dressing on wound closure in patients with neuroischaemic diabetic foot ulcers.

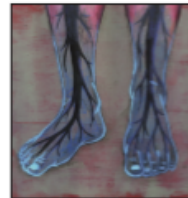
## Treatment strategies for neuroischaemic diabetic foot ulcers

The presence of diabetes increases the risk of an amputation of a leg, foot, or toe by approximately 23 times that of a person without diabetes. Most amputations in people with diabetes are preceded by ulceration of the foot, and it is estimated that around 7000 people with diabetes are affected by ulceration of the foot at any one time in England. Caring for people with ulcers and trying to improve healing to avoid amputations is hugely expensive to the UK National Health Service, with costs estimated to be approximately £1 billion per year.<sup>1</sup> In *The Lancet Diabetes & Endocrinology*,<sup>2</sup> Michael Edmonds and colleagues report the results of a large, multicentre, double-blind, randomised, controlled trial of a sucrose octasulfate dressing versus a control dressing (without sucrose octasulfate) for treatment of neuroischaemic diabetic foot ulcers. The dressings were administered for 20 weeks, and the primary outcome was the number of patients with

a control dressing, and masking to treatment allocation for the measurements of wound size. In particular, an attempt was made to standardise offloading across several countries, and although only half the participants had devices that immobilised the ankle, there was no difference in offloading between the two treatment groups.

But, should clinicians be leaping to adopt this new therapy option, in view of the size of the effect reported? The results are certainly more encouraging than findings for most interventions that have been reported to date. Additionally, although the results of a full health economic analysis are awaited, it is evident that the sucrose octasulfate dressing is easy to apply, and therefore, apart from the dressing itself, there should be no additional costs in a treated patient's clinical pathway.

However, the generalisability of the use of this dressing remains to be confirmed. Although reportedly more than



*Lancet Diabetes Endocrinol* 2017

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December 20, 2017  
[http://dx.doi.org/10.1016/S2213-8587\(17\)30439-4](http://dx.doi.org/10.1016/S2213-8587(17)30439-4)

See Online/Articles  
[http://dx.doi.org/10.1016/S2213-8587\(17\)30438-2](http://dx.doi.org/10.1016/S2213-8587(17)30438-2)

TLC-  
NOSF

## Lipido-colloid technology

- A jellified matrix of hydrocolloid (CMC) and fatty substances



TLC-  
NOSF

## NanoOligosaccharide – Factor

- A known MMP Modulator (action on MMP2 and MMP9, notably)
- MMP2 and MMP9 are the most involved in DFU
- Interacts with growth factors and cell proliferation



# The EXPLORER RCT

Objective	To demonstrate that TLC-NOSF wound dressing is superior to the same dressing without TLC-NOSF, in the local treatment of neuro-ischemic DFU
Design	Randomised, double-blind, controlled trial in two parallel groups
Treatment arms	2 treatment arms with a total of 240 patients
Indication	Neuro-ischemic DFU
Primary endpoint	Complete wound closure* rate after 20 weeks of treatment with the studied wound dressings
Investigation center	43 centres in France, Germany, Italy, Spain and the UK
Duration	20 weeks treatment with 12 weeks follow-up
Etiological treatment	Both arms were treated with standard of care, including off-loading

*\*Complete wound closure is defined as 100% reduction in DFU surface area with full epithelialization of the target DFU, without exudates and has to be confirmed 2 weeks later (Wx+2) by the investigator*

# The EXPLORER RCT - Primary Endpoint

## Primary Endpoint

To demonstrate that TLC-NOSF wound dressing is superior to the same dressing without NOSF, in the local treatment of neuro-ischemic DFU

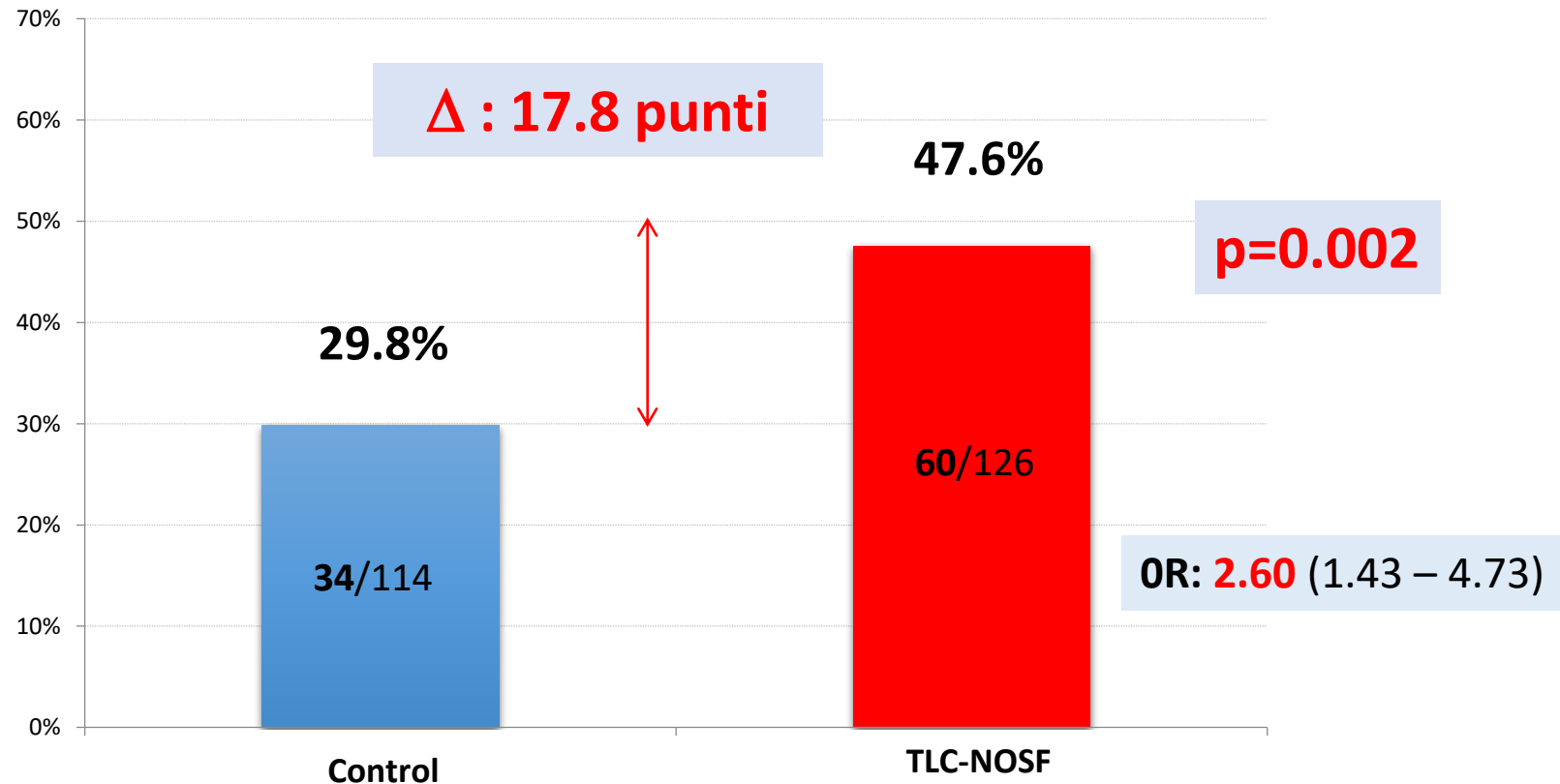
## Judgment criteria

Complete Wound Closure\* rate after 20 weeks of treatment with the tested wound dressings

\*Complete wound closure is defined as 100% reduction in DFU surface area with full epithelialization of the target DFU, without exudate and has to be confirmed 2 weeks later (Wx+2) by the investigator

# Results – FIRST ENDPOINT

## Wound closure at week 20

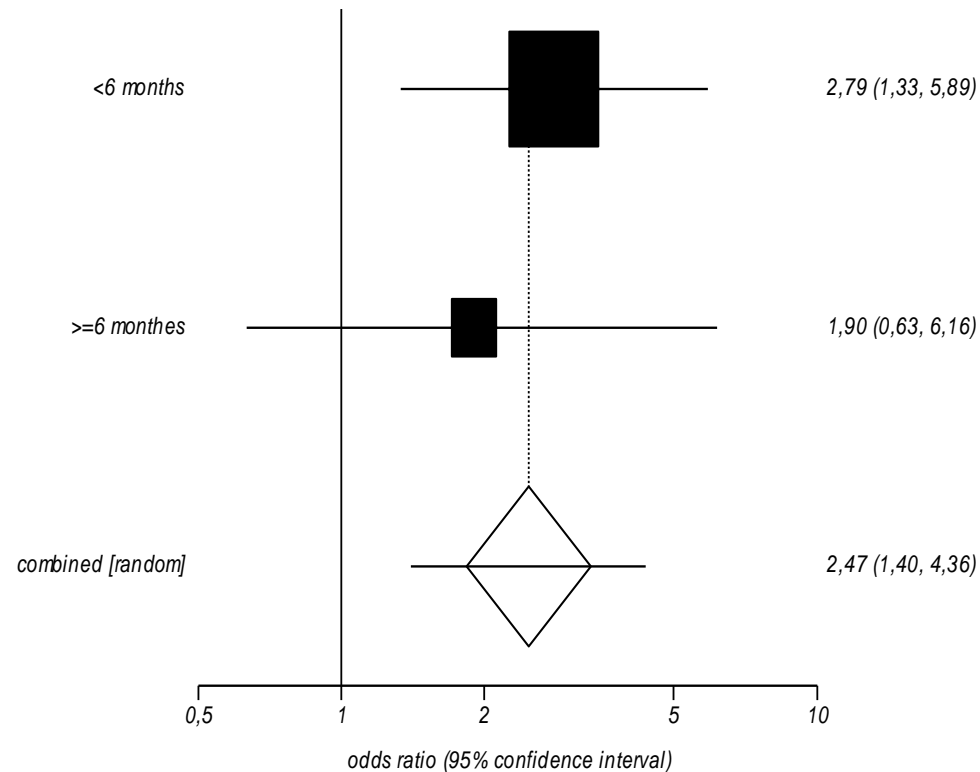


Higher rate of wound closure in the treatment-group (TLC-NOSF) with a chance of healing and wound closure > 260%

# Results – SECONDARY ENDPOINT

## Wound closure at week 20 (focus on ulcer duration)

Odds ratio meta-analysis plot [random effects]



**Δ : 25.1** (64.8% vs 39.7%)

**Δ : 10.3** (25.5% vs 15.2%)

**The chance of healing and wound closure were higher in ulcers with duration < 6 months**

# Results – SECONDARY ENDPOINT

## Wound closure at week 20 (Kaplan-Meyer analysis)

	Control group (n=114)	TLC-NOSF group (n=126)	Diffence on time of healing	Log rank (Mantel-Cox)
ITT analysis	180.5 ± 8.7 (163.4-197.7)	119.7 ± 4.7 (110.5-128.9)	<b>60.8 days</b>	<b>p=0.029</b>

*Data are given as mean ± SE (95% CI). Median value are not given as the control group did not reach 50% of wound closure. Estimation is limited to the largest survival time if it is censored. Confirmed closure population.*

**The treatment group (TLC-NOSF) shows a healing time faster than 61 days in comparison to control group**



wound closure at 20 weeks. 240 patients were randomly assigned (1:1) to either treatment group, recruited from

half of patients in Europe have neuroischaemic wounds,<sup>7</sup> the definition of this condition is not altogether clear.

TLC-NOSF sembra essere un promettente supporto nella strategia di trattamento dei pazienti diabetici con ulcera al piede non calcaneari, che non hanno mostrato una significativa riduzione dell'area dell'ulcera nonostante lo standard of care e in quelli con malattia periferica che non ha indicazione a rivascolarizzazione

125 days [IQR 56–141] for the control group and 125 days [IQR 56–141] for the sucrose octasulfate group).

To put this achievement in context, in three successive systematic reviews by the International Working Group of the Diabetic Foot (IWGDF) looking at the evidence for therapies to improve healing of diabetic foot ulcers,<sup>35</sup> the authors concluded that the quality of evidence to support the use of most therapies is poor, not least because of poor trial design and reporting. Indeed, the IWGDF, together with the European Wound Management Association, has subsequently published a guideline to support improved trial design<sup>6</sup> in an attempt to guide researchers working in this field. It is gratifying, therefore, to see a trial such as the one by Edmonds and colleagues,<sup>2</sup> which was done to a high standard, with independent randomisation,

not necessarily be suitable for all diabetic foot ulcers.

Nevertheless, this study confirms that it is possible to do high-quality studies in this field. Furthermore, sucrose octasulfate dressings seem to be a promising addition to our current treatment strategies for diabetic foot ulcers positioned away from the heel, which have not shown a significant reduction in area despite good offloading and other best practice treatments,<sup>9</sup> and where patients also have peripheral arterial disease that is not being considered for vascular intervention.

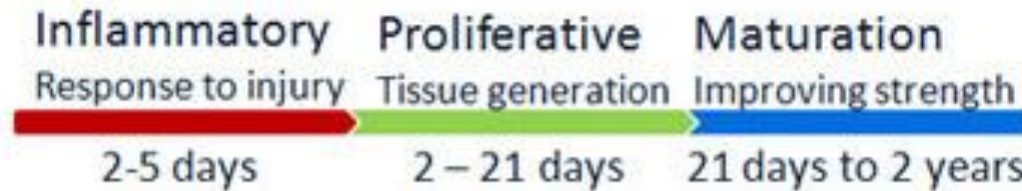
*Fran Game*

Department of Diabetes and Endocrinology, Derby Teaching Hospitals NHS Foundation Trust, Derby DE22 3NE, UK  
frances.game@nhs.net

# Diabetic foot ulcers and regenerative therapy

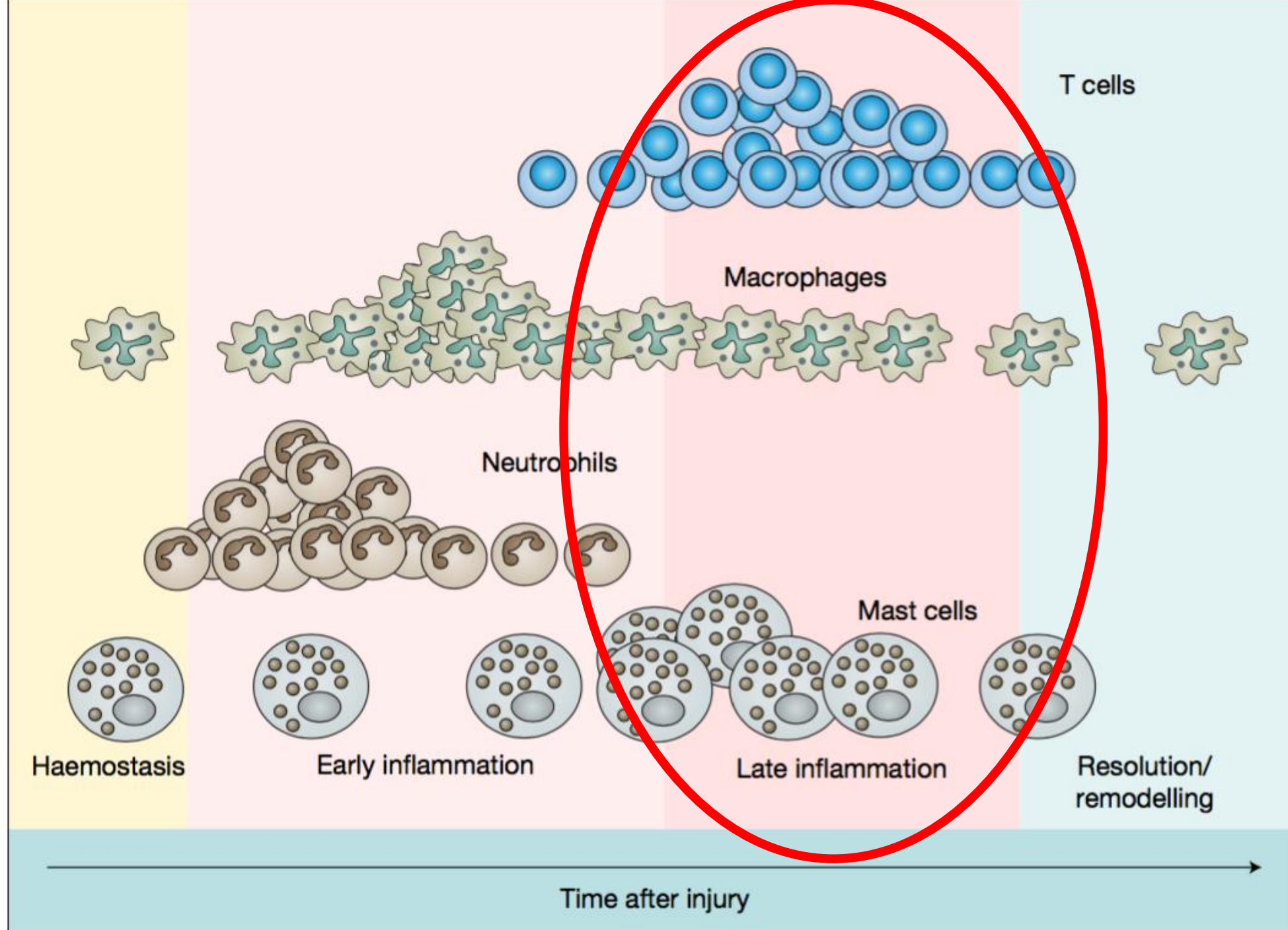
In diabetic foot ulcers often there is a persistence of inflammatory phase

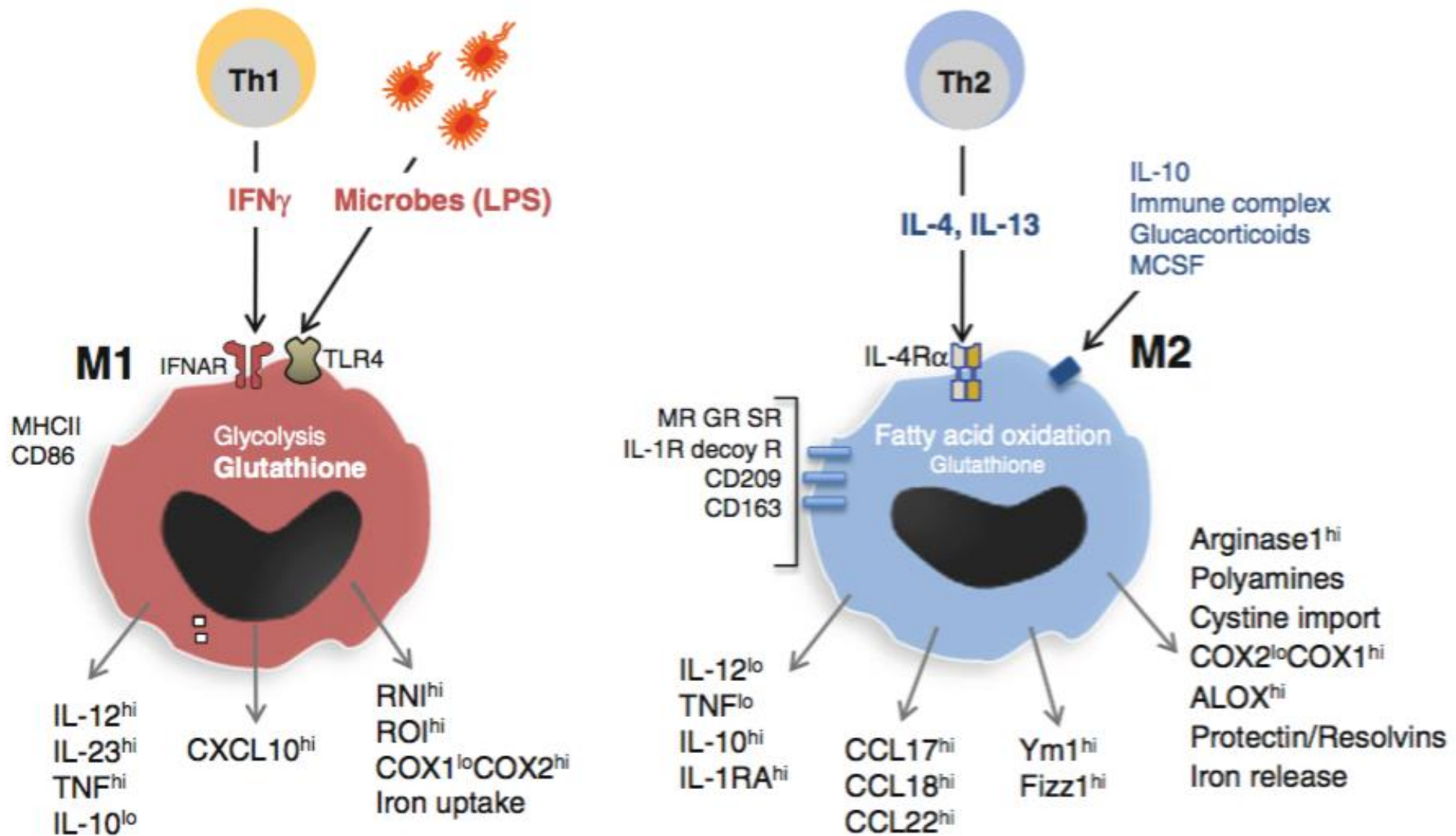
## Normal Wounds



## Infected / Necrotic Acute Wounds and Chronic Wounds







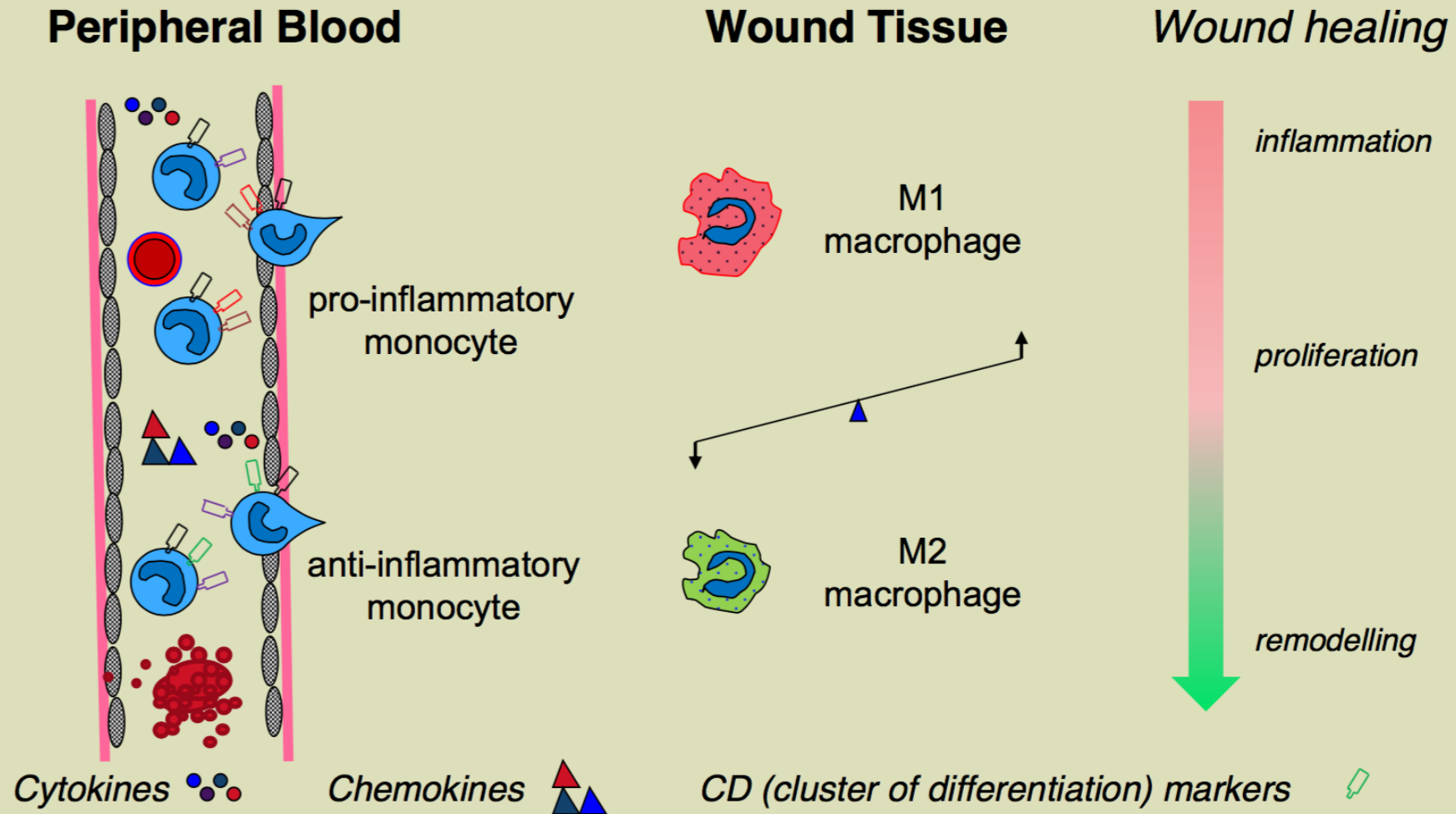
Proinflammatory

Anti-inflammatory Tissue repair Proliferative

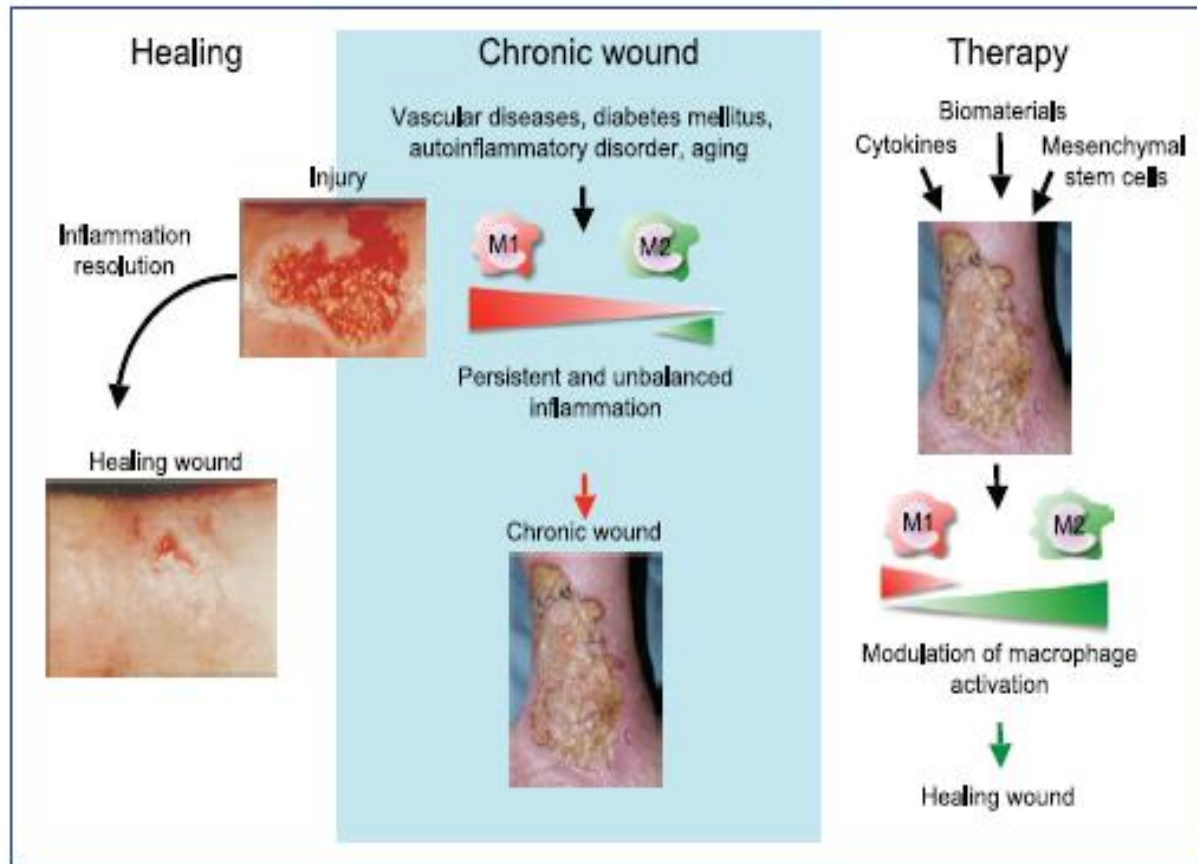
Biswas SK et al **Macrophage polarization and plasticity in health and disease.** Immunol Res 2012 Sep;53(1-3):11-24.



# Monocyte, macrophage and wound healing







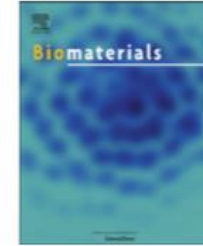
**Figure 3** Modulation of macrophage activation as therapeutic perspective for chronic wounds. Resolution of inflammation is critical for effective wound closure. Inflammatory macrophages (M1) contribute to persistent inflammation leading to tissue damage and impaired healing. Induction of immunomodulatory macrophages (M2) at the wound site may facilitate the healing response. Various molecular and cellular approaches are currently under investigation to test this hypothesis.

In patients with **Peripheral Arterial Disease, Diabetes and autoinflammatory disorders** there is a persistent and unbalanced inflammation with chronic **persistence of M1** macrophages and lack of their transformation from M1 to M2 .



Contents lists available at SciVerse ScienceDirect

Biomaterials

journal homepage: [www.elsevier.com/locate/biomaterials](http://www.elsevier.com/locate/biomaterials)

Leading opinion

## Macrophage polarization: An opportunity for improved outcomes in biomaterials and regenerative medicine<sup>☆</sup>

Bryan N. Brown<sup>a,b</sup>, Buddy D. Ratner<sup>c,d</sup>, Stuart B. Goodman<sup>e,f</sup>, Salomon Amar<sup>g</sup>, Stephen F. Badylak<sup>a,b,h,\*</sup>

..... scaffold materials composed of extracellular matrix (ECM) have been shown to promote a switch from a predominantly M1 cell population immediately following implantation to a population enriched in M2 cells by 7e14 days post implantation

# Regenerative Therapy: role of monocyte in wound healing

- To evaluate the effectiveness of a bi-layer matrix of a type I purified bovine collagen layer for promoting both dermal and epidermal regeneration.
- To evaluate if the dermal substitute promotes the polarization M1→ M2 stimulating the healing process

# Management by a pre-set limb salvage protocol

- Consecutive patients with ischemic diabetic foot ulcers (Grade II-III sec TUC).
- Revascularization (by endovascular approach)
- Surgical debridement
- Offloading
- Negative wound pressure (if required)
- Regenerative therapy---→ Bilayer matrix of type I purified collagen

**Ulcer biopsy before and after dermal substitute application**

# Characteristics of study group

- 41 patients included (ongoing)
- Man (35/41) 85.3%; Age:  $65 \pm 12$  years old
- Type 2 diabetes (95%)
- Diabetes Duration : 21 years
- HbA1c:  $64 \pm 22$  mmol/mol
- Follow-up after discharge:  $7 \pm 3$  months



# Surgical debridement

- Toe amputation: 11 cases
- Ray amputation: 14 cases
- Transmetatarsal amputation: 7 cases
- Heel gangrene: 5 cases
- Necrotizing fascitis: 4 cases

**Mean size of residual post-surgical wound:  $69.6 \pm 50 \text{ cm}^2$**

# Results after dermal substitute application

- **Healing:** 13 patients (31.7%)(size  $63.8 \pm 14 \text{ cm}^2$ )
- **>50% wound size reduction:** 18 patients (43.9%)(size  $78.8 \pm 12 \text{ cm}^2$ )
- **Recurrence of CLI:** 7 patients (17%) (size  $105 \pm 23 \text{ cm}^2$ )
- **Death:** 3 patients (7.3%) (size  $73.8 \pm 18 \text{ cm}^2$  )

**Any infection during treatment and follow-up**

















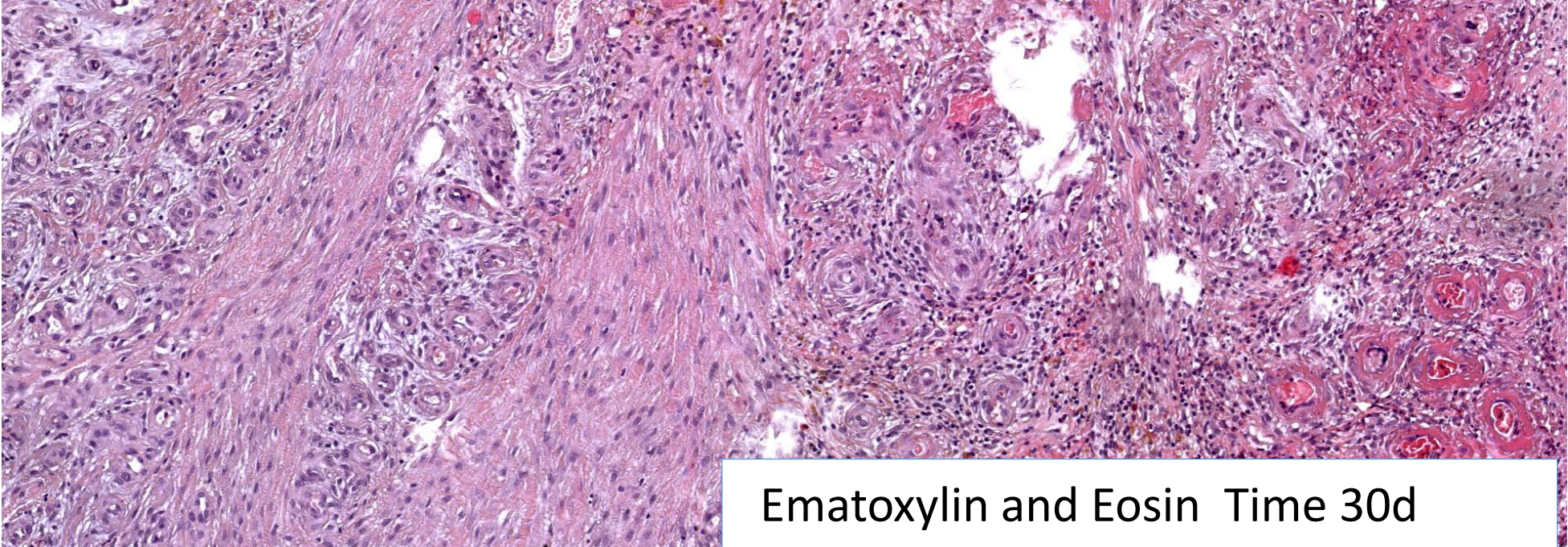
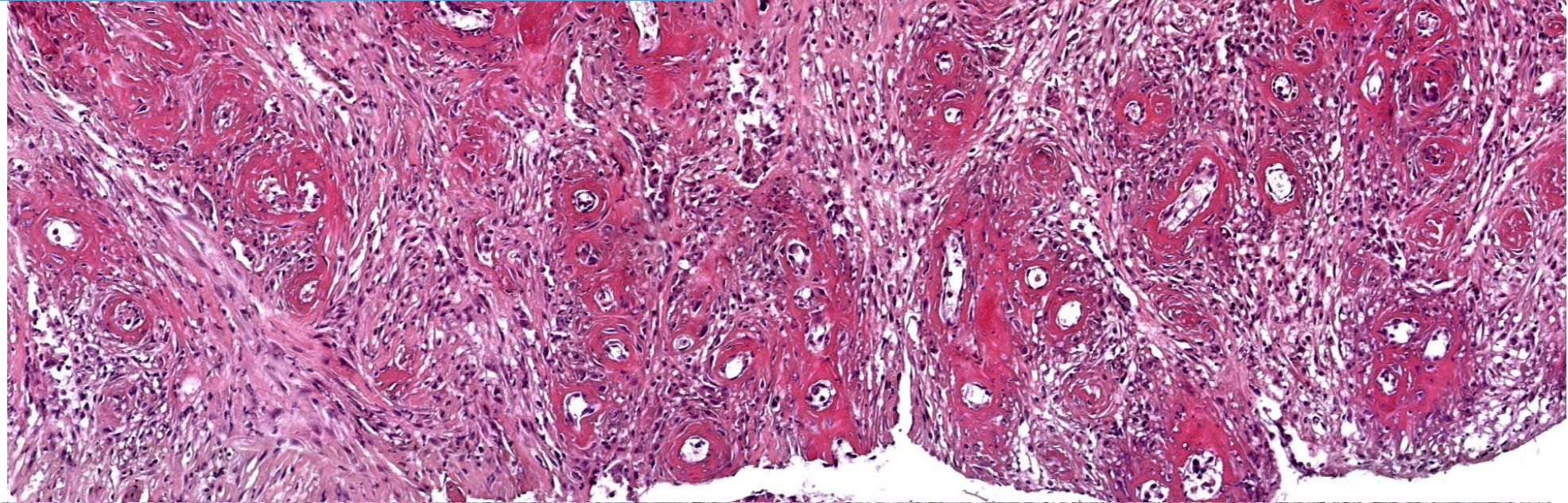








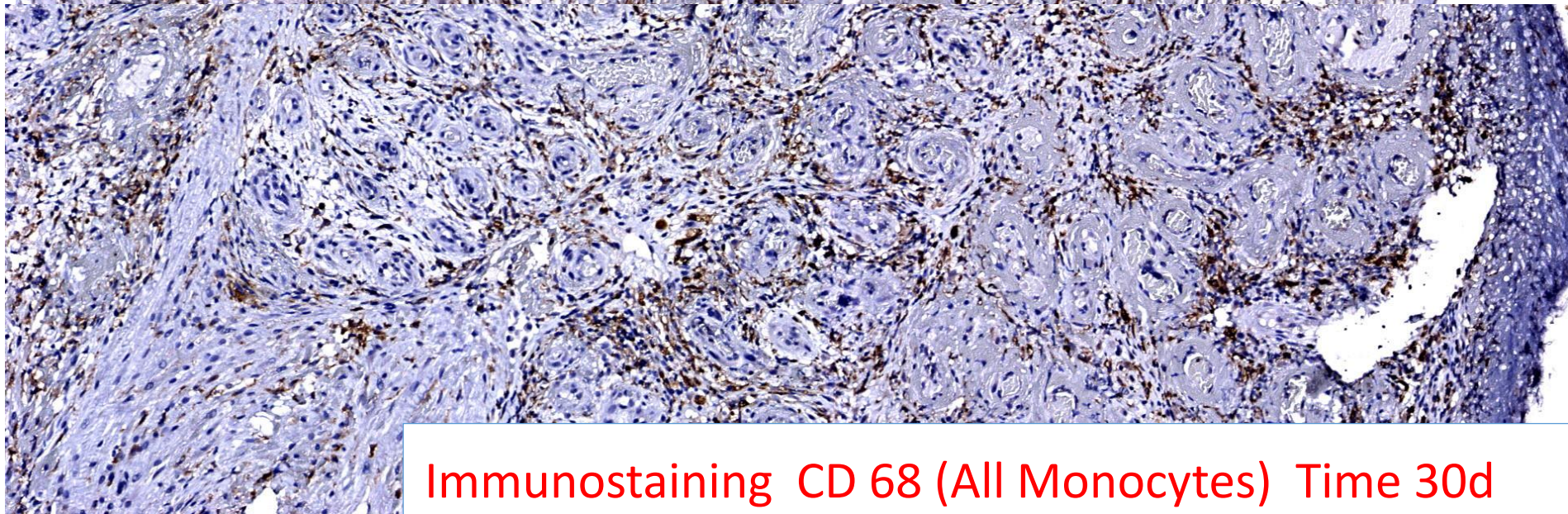
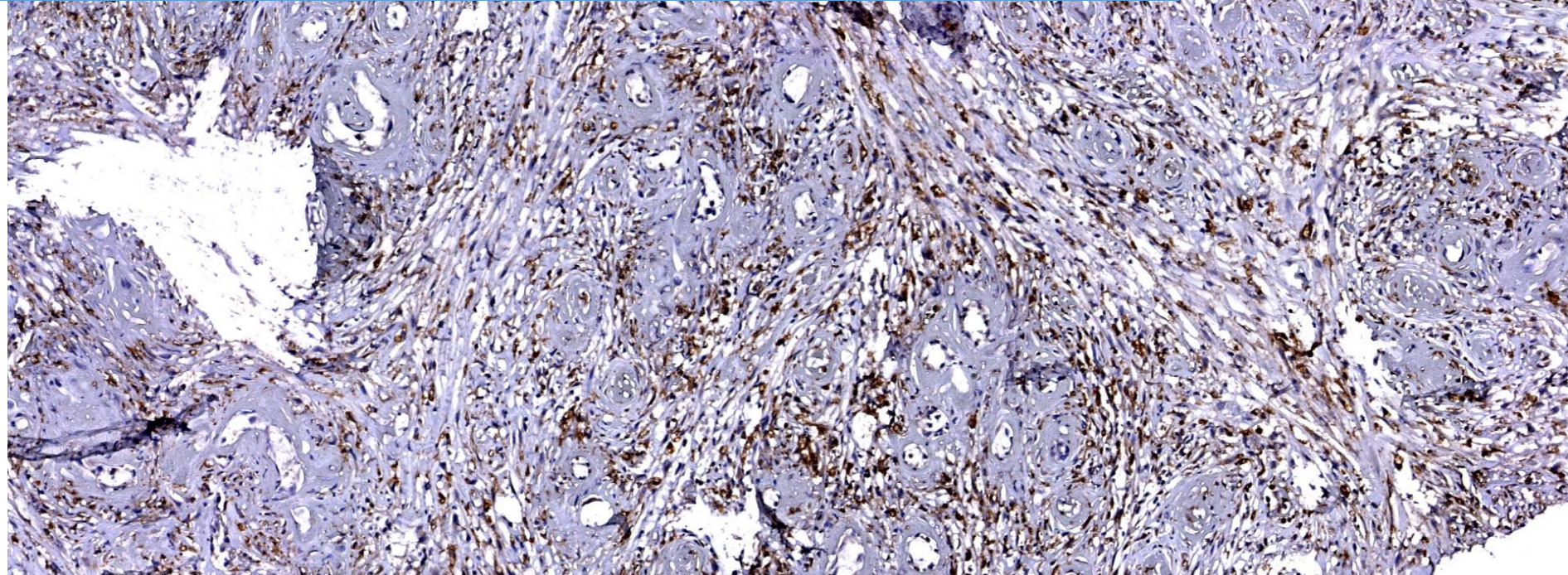
Ematoxylin and Eosin Time 0



Ematoxylin and Eosin Time 30d



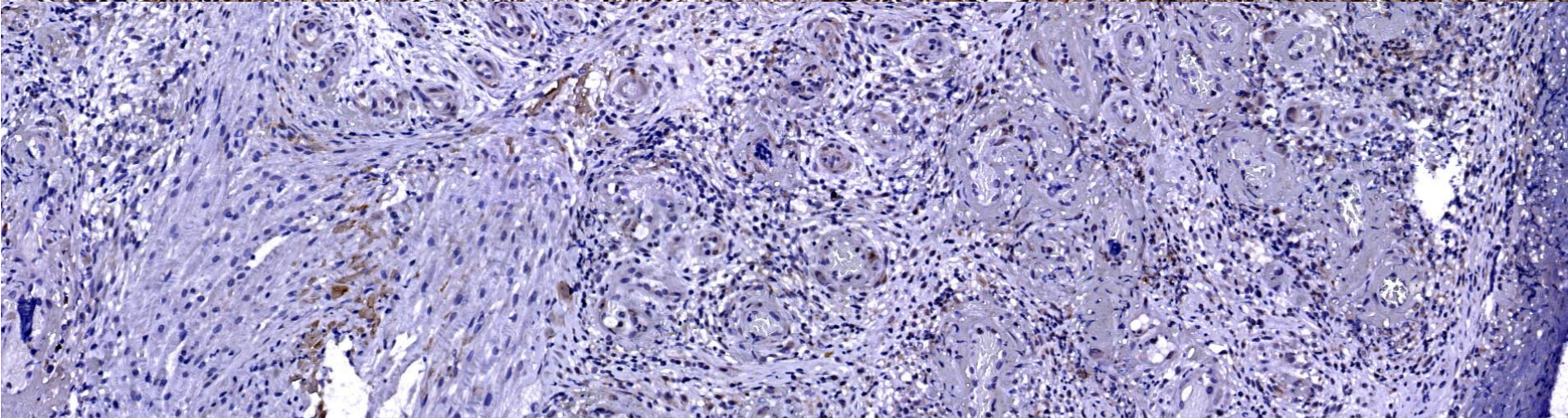
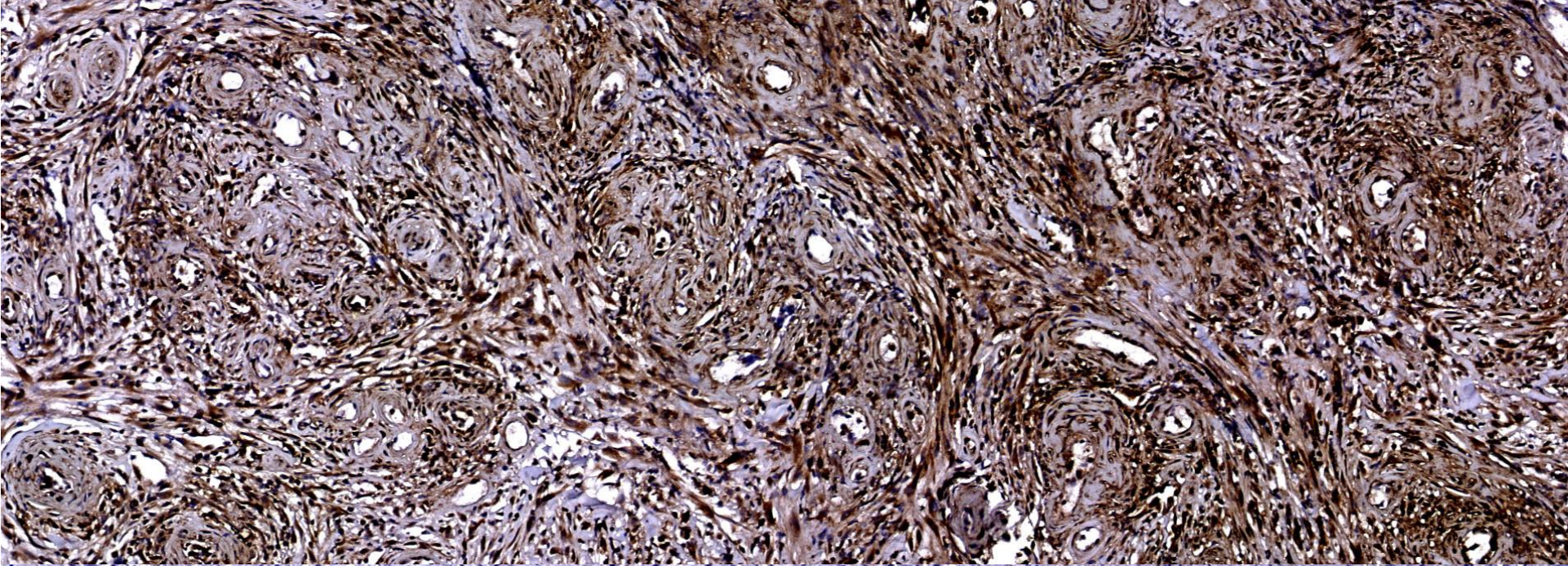
Immunostaining CD 68 (All Monocytes) Time 0



Immunostaining CD 68 (All Monocytes) Time 30d



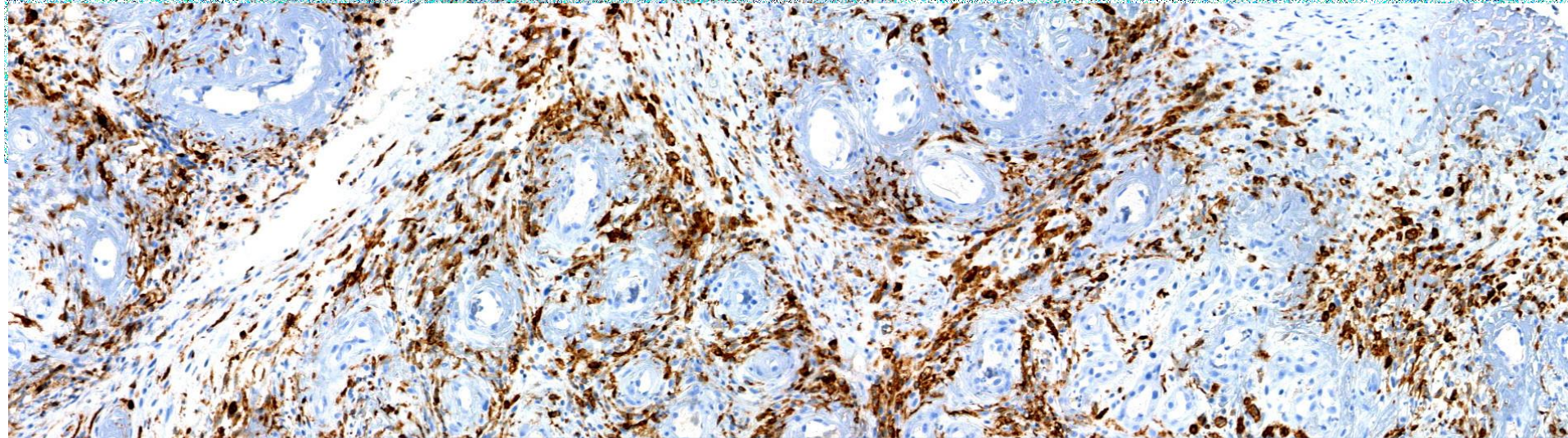
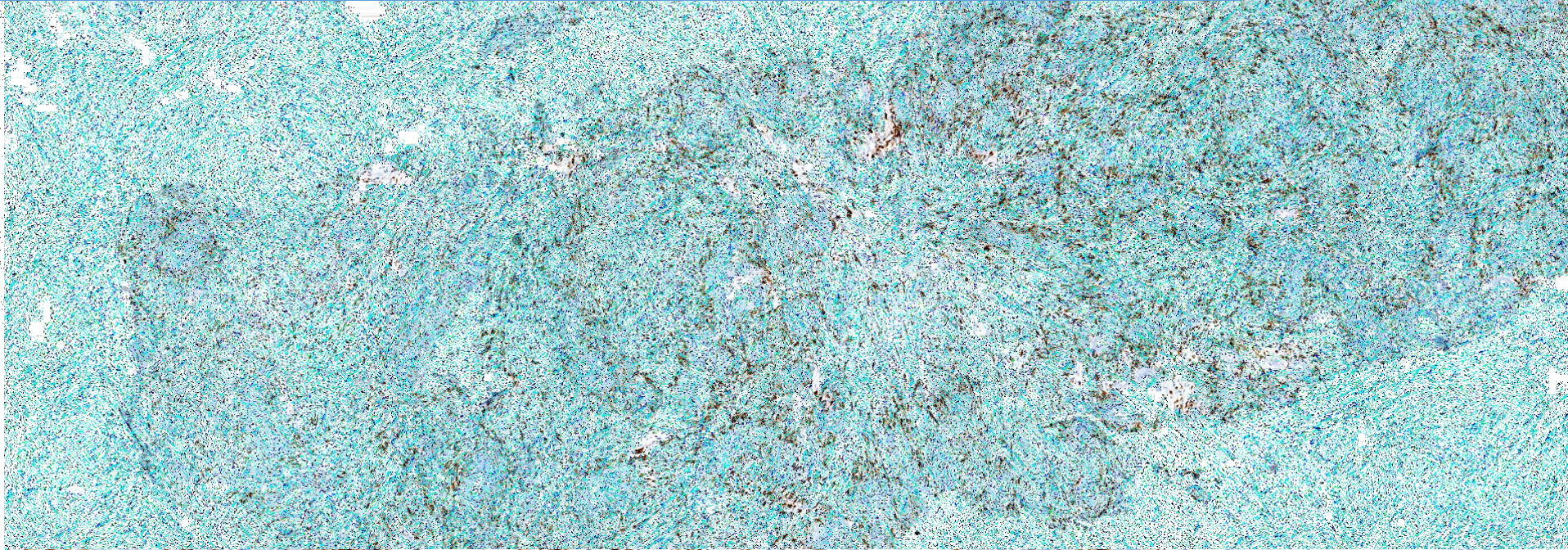
Immunostaining CD 38 (M1 Monocytes) Time 0



Immunostaining CD 38 (M1 Monocytes) Time 30d



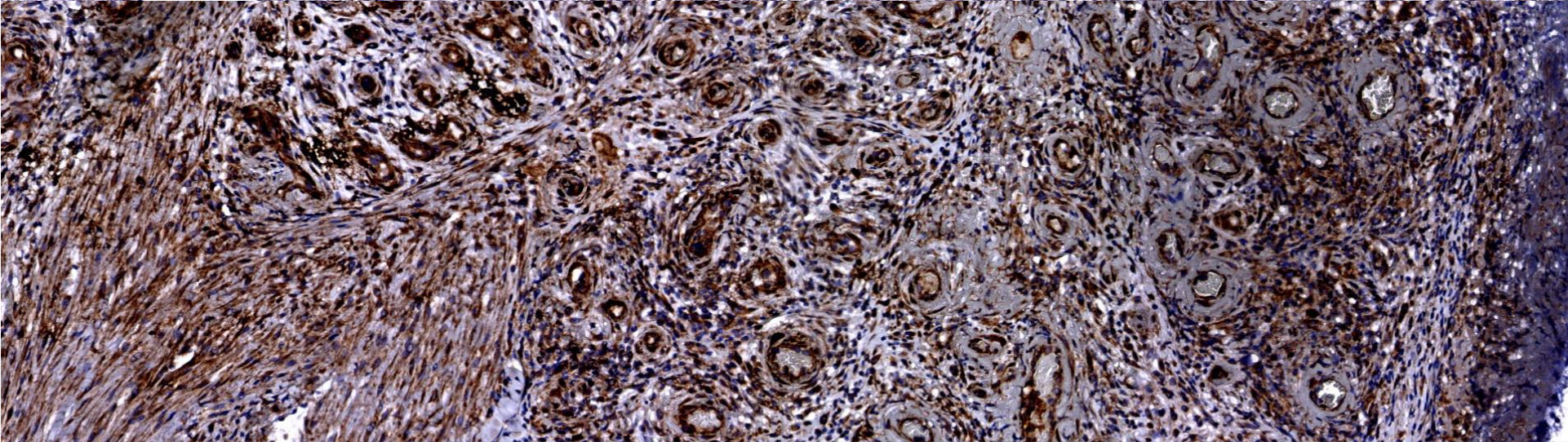
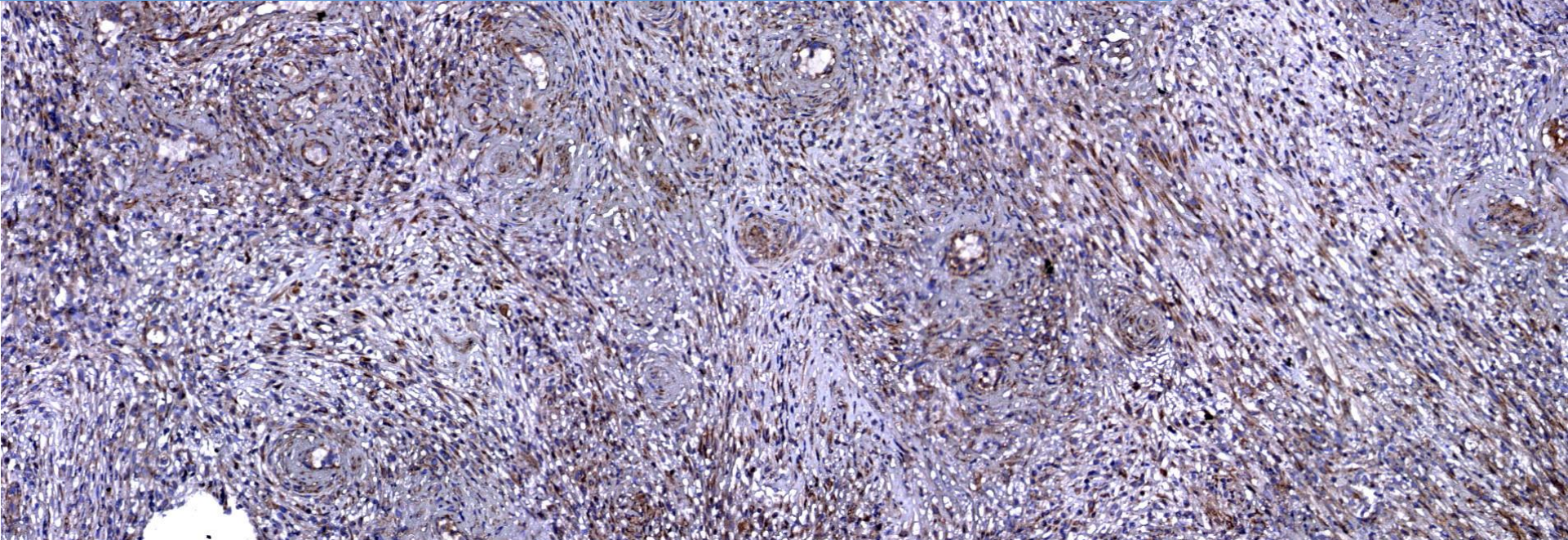
Immunostaining CD 163 (M2 Monocytes) Time 0



Immunostaining CD 163 (M2 Monocytes) Time 30d



Immunostaining *egr2* (M2 Monocytes) Time 0



Immunostaining *egr2* (M2 Monocytes) Time 30d



# Conclusioni ad Interim

- Il sostituto dermale utilizzato ha promosso una guarigione nel 32% dei pazienti e una riduzione delle dimensioni dell'ulcera >50% nel 44% dei pazienti in follow-up medio di 7 mesi
- Il pattern immunologico-istologico ha mostrato uno shift della polarizzazione monocitaria da M1 (infiammatorio) a M2 (rigenerativo)
- Il sostituto dermale è stato capace di promuovere la rigenerazione dermale ed epidermica attraverso l' «one step approach» guidata dal monocita

# COMMENTI

- Le raccomandazioni derivano da review sistematiche di pubblicazioni rilevanti ma il **processo ha le sue limitazioni**..(IWGDF)
- Le raccomandazioni sono fatte **per supportare un intervento**, ma anche **contro l'uso di particolari interventi** se non c'è una forte evidenza per giustificarne il suo uso..
- **..il processo di guarigione è altamente complesso**, includendo l'interazione di numerosi e diversi tipi cellulari e segnali, per cui il beneficio della maggior parte degli interventi è limitato a un **particolare tipo di ulcera o a una fase particolare** nel processo di guarigione..

# NUOVI ELEMENTI

- **Le nuove tecnologie** aprono **un nuovo percorso** e potrebbero essere utili o suggerite in specifici casi in relazioni alle disponibilità cliniche e dei pazienti e basate sul costo-beneficio
- Possibilità di medicazioni/devices di supporto **nell'approccio integrato** alle lesioni croniche e post-chirurgiche
- **Prime evidenze** cliniche nel trattamento delle ulcere neuro-ischemiche
- **Maggior conoscenza dei bias** negli studi clinici e degli elementi ostacolanti la guarigione dell'ulcera

# CRITICITA' ATTUALI-PUNTI NON DEFINITI

## ✓ WOUND CARE

C'è un **chiaro bisogno di evidenza** per supportare l'uso di un particolare intervento nella gestione delle DFUs e per giustificare l'uso di una particolare terapia

## ✓ MISURE DI OUTCOMES PER GLI STUDI DI INTERVENTO

C'è la necessità di aumentare la **qualità della metodologia degli studi e dei trials clinici**. La carenza di evidenze è spesso legata alla **scelta delle misure di esito** negli studi di intervento (es. Fase dell'ulcera, regressione, guarigione, qualità di vita, costo beneficio) e **popolazione** (ulcere neuropatiche, ischemiche, superficiali o profonde, comorbidità, real life)

## ✓ LETTO DELL'ULCERA, MICROAMBIENTE, TERAPIA RIGENERATIVA

Nell'applicazione dello Standard of Care, **il letto dell'ulcera** dovrebbe essere valutato specificamente nelle ulcere croniche (attività proteasica, stato infiammatorio, etc) e le medicazioni/devices più idonei a creare un pathway di guarigione dovrebbero essere identificate; **il ruolo potenziale del monocita** dovrebbe essere approfondito per un nuovo approccio alle ulcere croniche con l'utilizzo della "terapia rigenerativa"