

Summary and Innovation in Wound Care

Keith Harding CBE, FRCGP, FRCP, FRCS, FLSW

*Professor of Wound Healing Research
School of Medicine Cardiff University
Clinical Director Wound Healing Cardiff & Vale UHB
Medical Director Welsh Wound Innovation Centre
Ynysmaerdy, Pontyclun, Rhondda Cynon Taf
Senior Clinical Research Director
A*STAR Singapore
Visiting Professor LKC Medical School
Hon. Consultant National Skin Centre
Singapore*

Summary and Innovation in Wound Care

Keith Harding CBE, FRCGP, FRCP, FRCS, FLSW

*Professor of Wound Healing Research (**Academic Fraud**)
School of Medicine Cardiff University*

*Clinical Director Wound Healing Cardiff & Vale UHB (**Failed Clinician**)*

*Medical Director Welsh Wound Innovation Centre (**Commercial wide boy**)
Ynysmaerdy, Pontyclun, Rhondda Cynon Taf*

*Senior Clinical Research Director (**Global Traveller**)
A*STAR Singapore
Visiting Professor LKC Medical School
Hon. Consultant National Skin Centre
Singapore*



Potential Conflicts of Interest

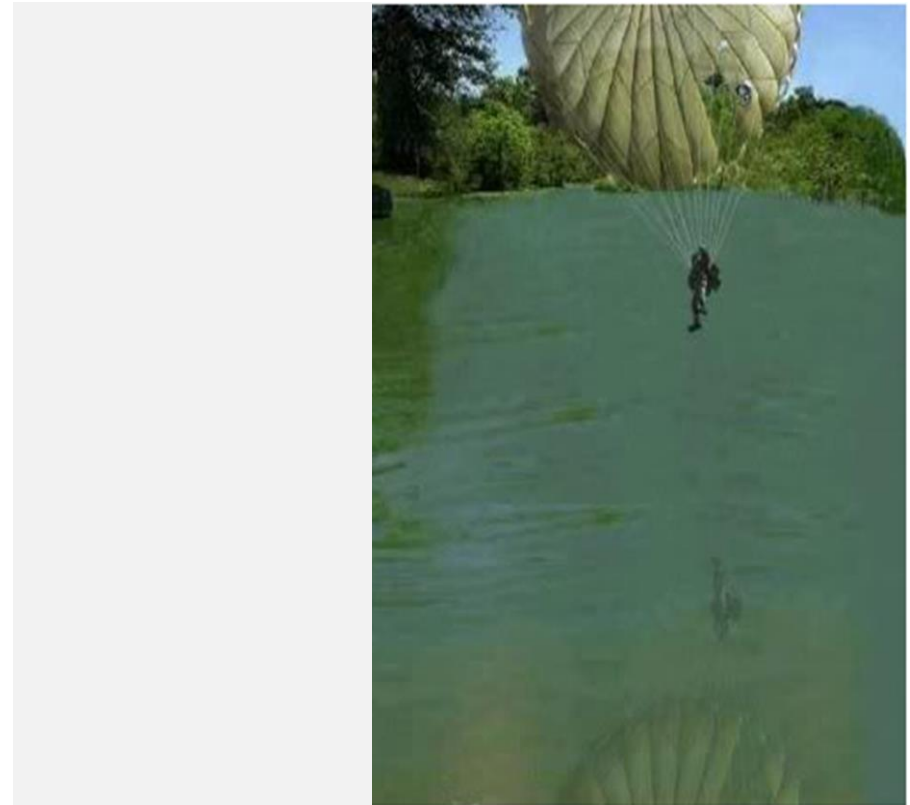
- ...are many & varied
- I have received funding from more than 70 companies involved in this subject over the past 30 years
- I have undertaken more than 200 evaluations of products
- I have no personal vested interest in any established commercial concern making products to treat wounds
- I am one of the inventors named on series of patents in areas of wound prognostics and therapeutics

NZWCS Conference Dunedin 2019

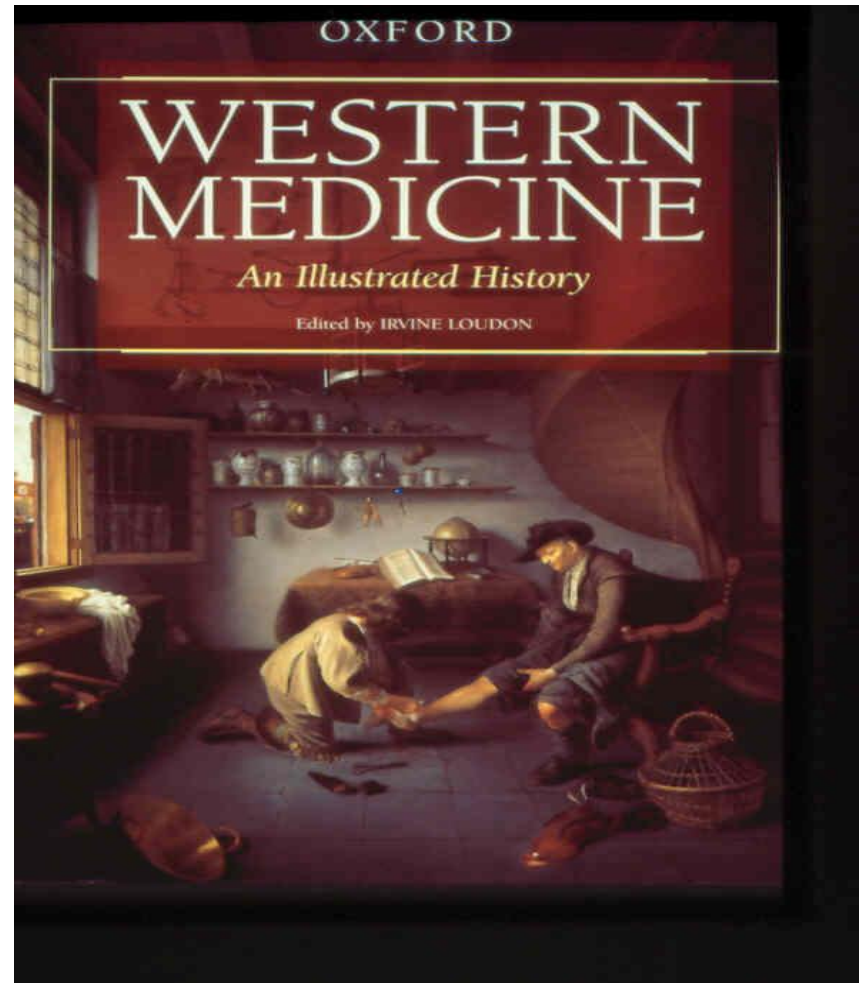
Themes

- **Choices**
- **Changes**
- **Challenges**

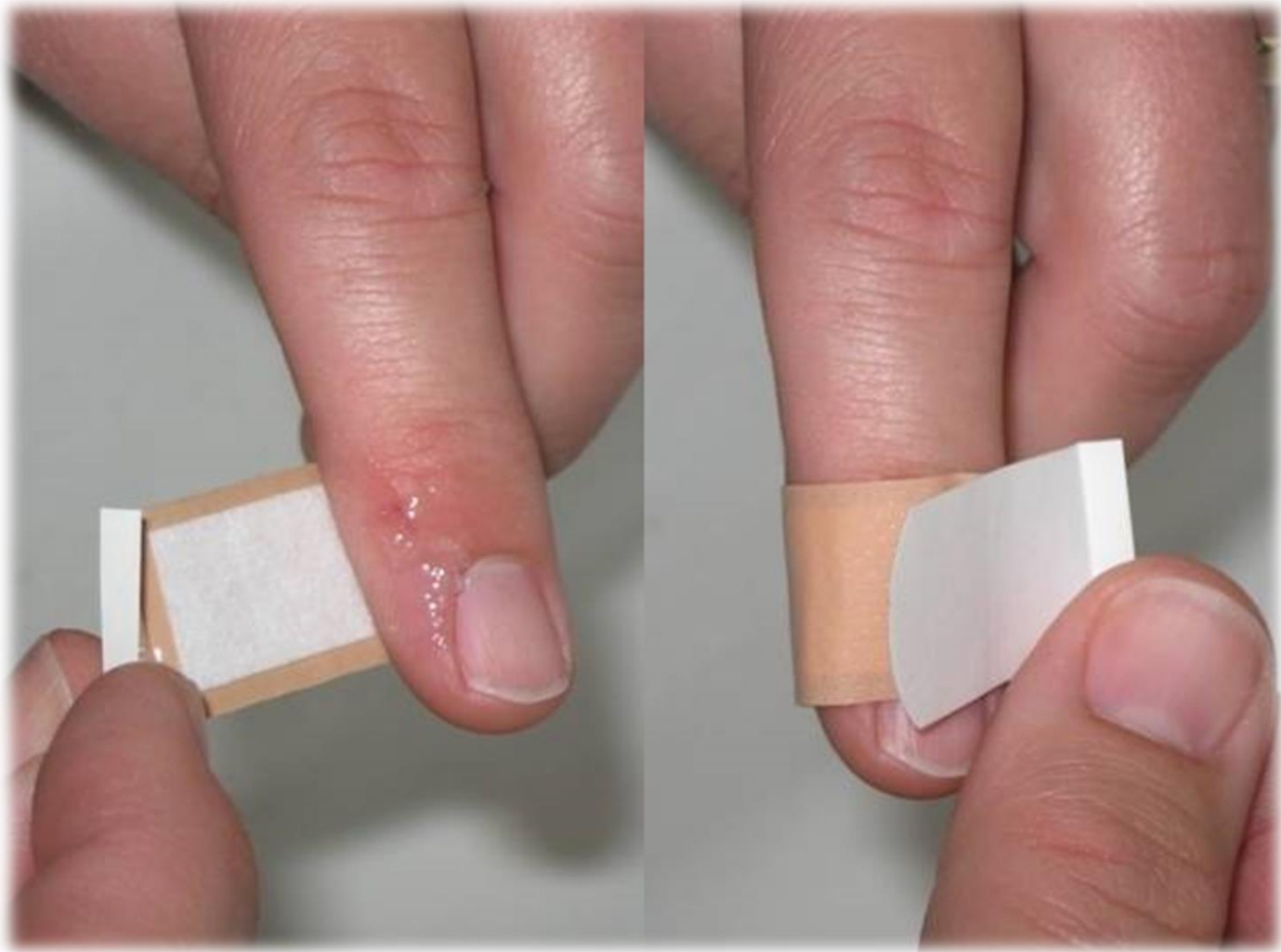
Personal reflections



Are we focused on Dressing, Managing or Healing Wounds ?



Public View of Wounds



The Reality of Clinical Practice



Burden of diabetic foot ulceration (DFU)

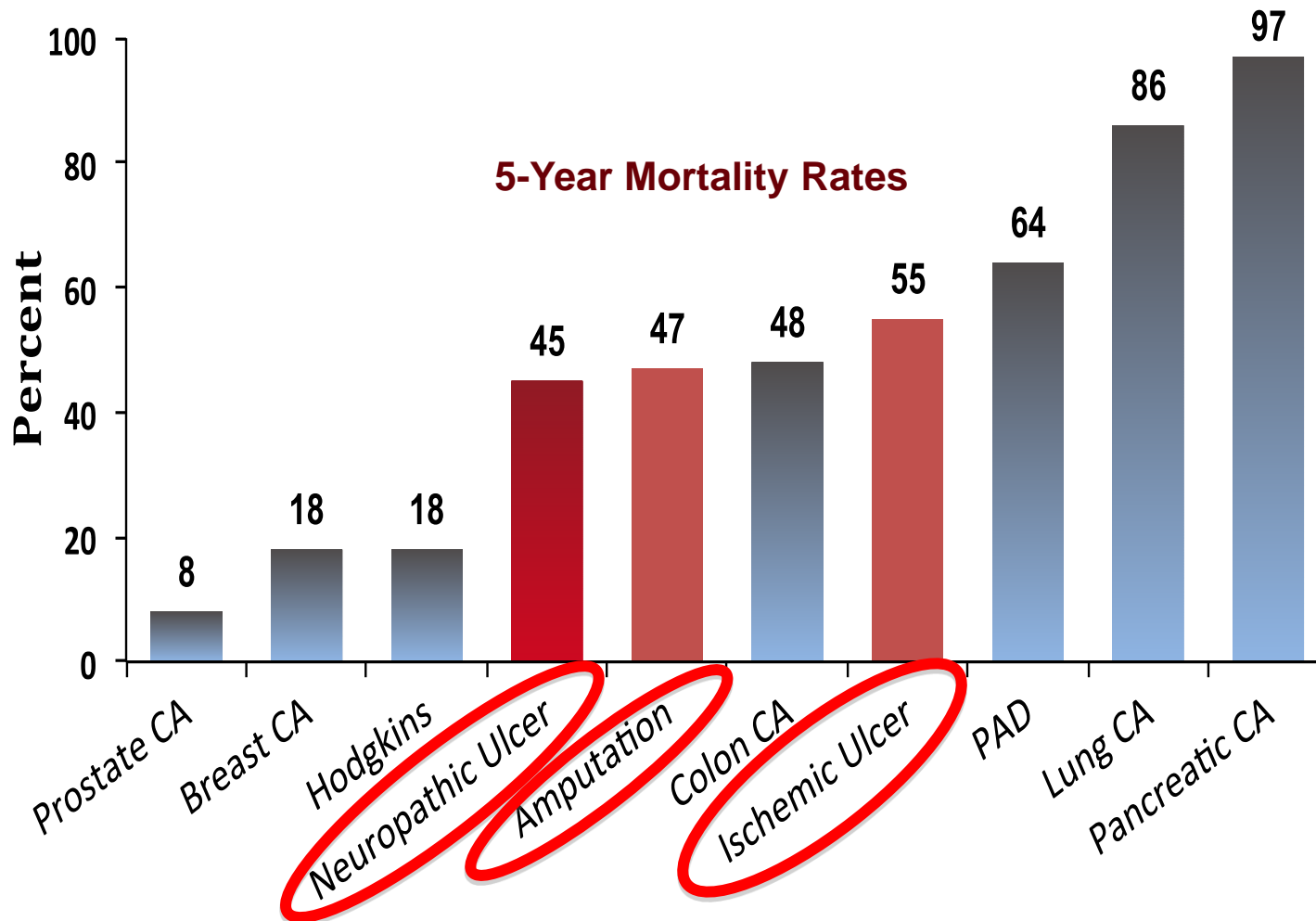
- Estimated 2.5% of 415 million adults worldwide with diabetes have DFU¹
- Equates to approximately 86,000 with DFU in the United Kingdom²
- Person with diabetes has 25% chance of developing a DFU³
- Most common cause of non-traumatic lower limb amputation (85%)⁴
- Diabetic foot account for approximately £1 in every £150 spending in the NHS⁵
- Approximately 25% of diabetes-related admissions due to DFU infections²

1. Kerr M. *Foot care for people with diabetes: The economic case for change*. Available at <https://www.diabetes.org.uk/Documents/nhs-diabetes/footcare/footcare-for-people-with-diabetes.pdf>. 2012. NHS Diabetes. Last accessed 12 December 2016.
2. Boulton AJ, Meneses P, Ennis WJ. *Diabetic foot ulcers: A framework for prevention and care*. *Wound Rep Reg* 1999; 7:7 – 16.
3. Singh N, Armstrong DG, Lipsky BA. *Preventing foot ulcers in patients with diabetes*. *JAMA* 2005; 293: 217–228
4. Clokie M, Greenway AL, Harding KG, Jones NJ, Vedhara K, Game F, Dhatariya KK. *New horizons in the understanding of the causes and management of diabetic foot disease*. *Diabetic Medicine* 2017; 34: 305-315
5. Kerr M, Rayman G, Jeffcoate WJ. *Cost of diabetic foot disease to the National Health Service in England*. *Diabetic Med* 2014; 32: 1498–1504.

The reality of Diabetic foot disease



Wounds Have Consequences



Armstrong et al. *Int Wound J.* 2007;Dec;4(4):286.

CA = Carcinoma.
PAD = Peripheral artery disease.

Prevalence of surgical site infection in Europe

- Infected wounds are a serious complication and add significantly to overall costs
- Surgical infection affects 30-40 patients per 1000 operations
- Mean additional length of stay = 11 days
- Mean cost per episode €5800
- Attributable mortality rate = 5%

Wounds in the USA

- Chronic wounds 6.5 million
- In excess \$25billion spent annually
- Sharp rise in diabetes and obesity
- Product spend \$15.3billion 2010
- Surgical procedures 40 million in 2000
- Outpatient surgical procedures 31.5 million
- Scarring costs \$12billion
- Need to allocate higher level of attention and resources to wound care

Sen et al (2009)

The Financial Cost of Wounds in Units of Management in England

*In 2013, the average NHS Clinical Commissioning Group/Health Board was managing **11,200** wounds, of which **48%** were chronic. For these chronic wounds they were...*

- ...paying for **22,000** GP visits.
 - **£1,131,000**
- ...paying for **38,000** community nurse visits.
 - **£2,340,000**
- ...paying for **9,000** hospital outpatient visits.
 - **£1,138,000**

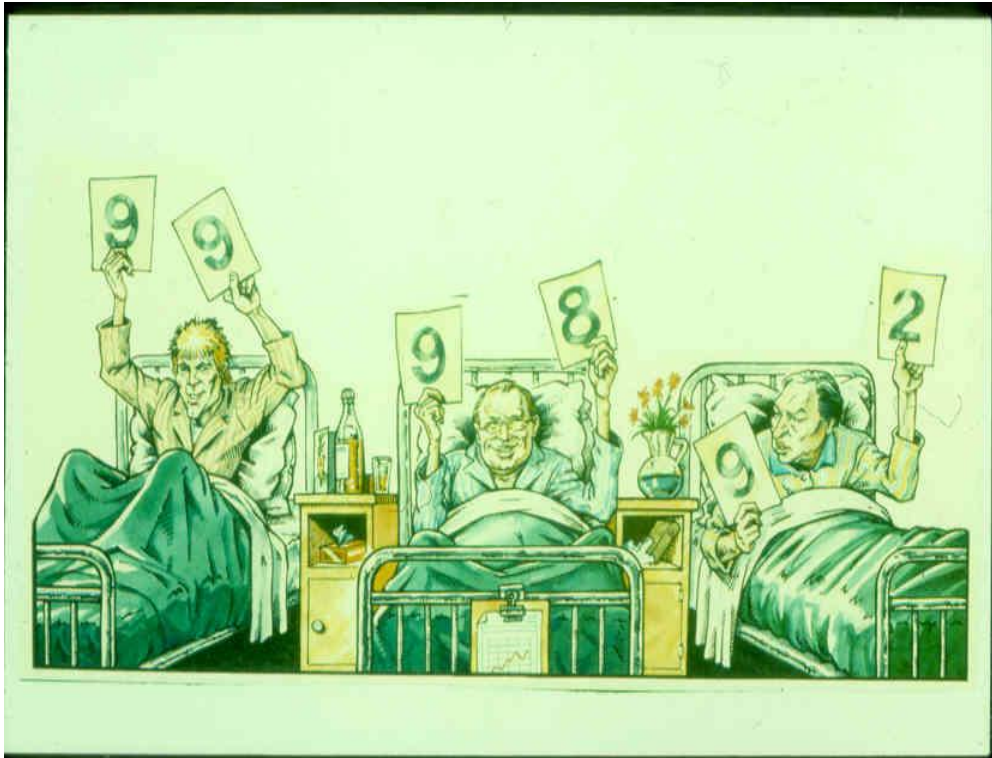
The Financial Cost of Wounds in Units of management in England

- ...ordering **113,000** investigations.
 - **£550,000**
- ...prescribing **307,000** drugs.
 - **£4,227,000**
- ...using **1,267,000** wound care products.
 - **£2,307,000**

(Guest, Vowden, Vowden, 2017)

Current Situation in Practice

- We cannot guarantee that any patient with a wound will be seen by an appropriate health care professional and receive a high standard of care including treatment that may benefit the patient



How it all started for us in Cardiff



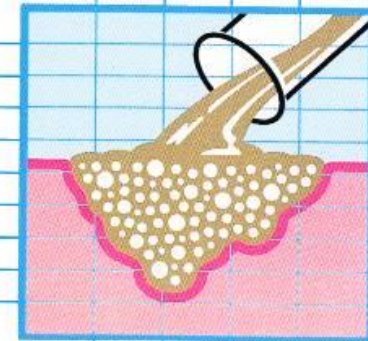
BRITISH MEDICAL JOURNAL 18 OCTOBER 1975

Silicone foam sponge for pilonidal sinus: a new technique for dressing open granulating wounds

R A B WOOD, L E HUGHES

British Medical Journal, 1975, 4, 131-133

A GUIDE TO THE PRACTICAL MANAGEMENT OF GRANULATING WOUNDS



131

Normal Development of a Clinical Specialty

The Extent of the Problem

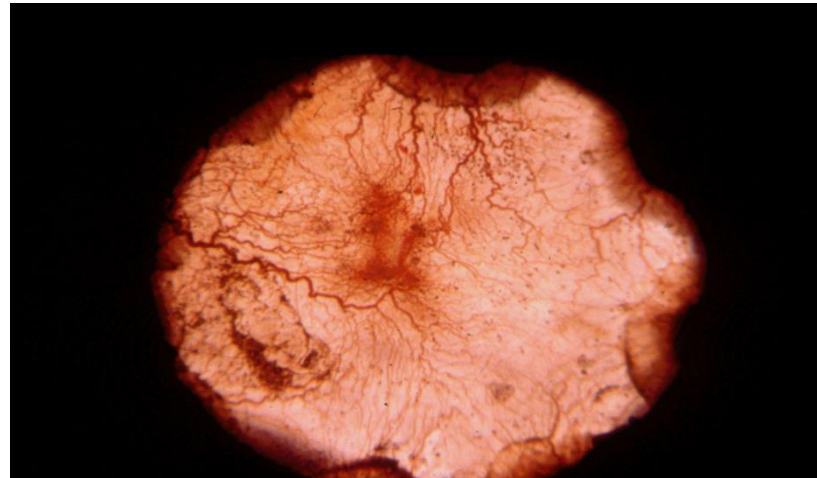
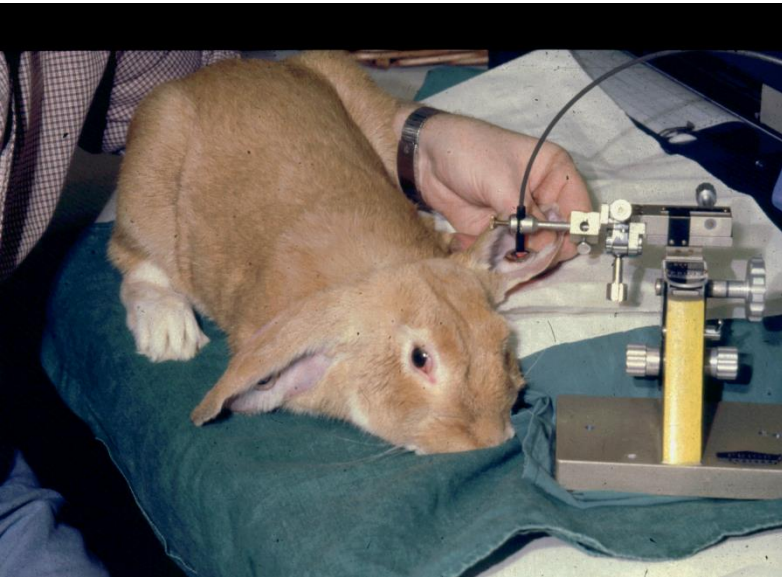
Starting to be recognised Need Increased Profile-
Convince 3 P's....Politicians, Professionals and Patients



Normal Development of a Clinical Specialty

Pathophysiology of the Disease

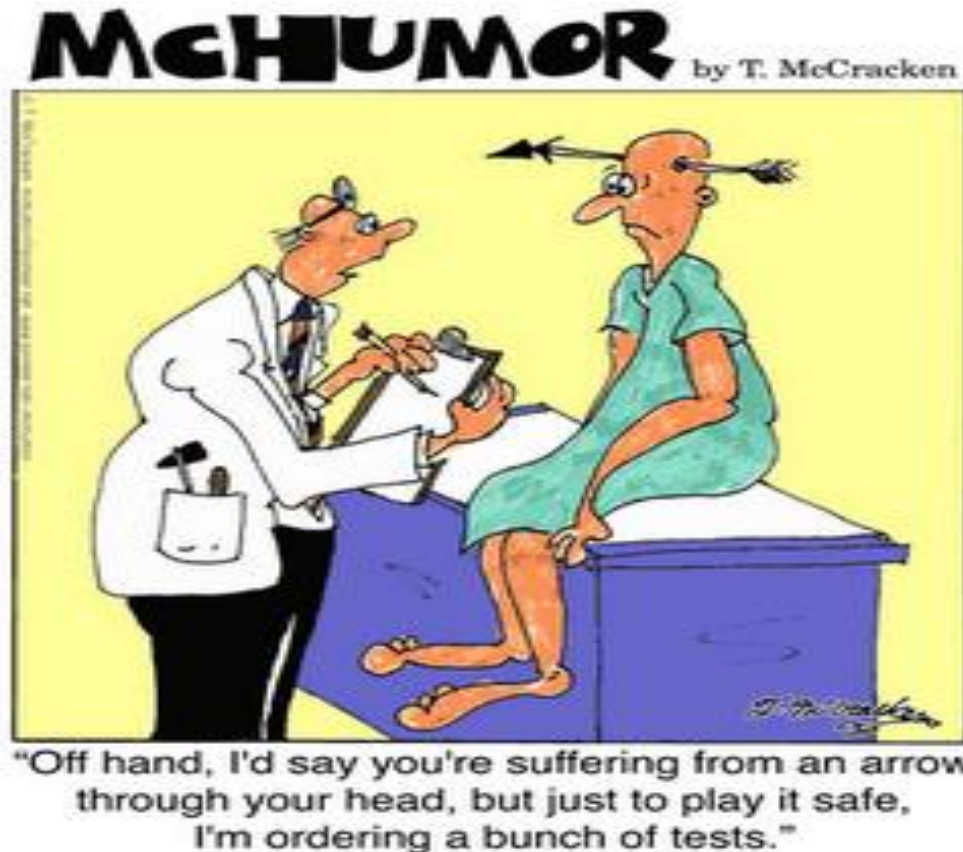
Limitations of animal models of Chronic wounds and difficulties of clinical trials in this area



Normal Development of a Clinical Specialty

Assessment & Diagnosis

We are very immature in the use of such tools currently and there is an urgent need for clinically useful methods to be developed



MDT working is essential for treating/healing patients with wounds



- Diverse problem
- Broad range of Medical/Surgical skills
- Nursing is essential
- Therapists are undervalued
- No single individual/Professional group can manage in isolation
- This is the way forward for many complex clinical conditions

Normal Development of a Clinical Specialty

Treatment Options

We are currently awash with treatments ...but how selective are we in their prescription ?.. is it the fault of Industry or the Clinician ?



Normal Development of a Clinical Specialty

Evidence of Effective interventions...

Is it the lack of Evidence or the interpretation of EBM that leads to difficulties in knowing how to offer best treatment to individual patients ?



Wound Care – What works- Is there any evidence?

- **Goal**

Wound Care?

Wound Management?

Wound Dressing?

Wound Healing?

- **Works for**

Healing?

Symptoms?

Infection?

- **Evidence of**

Healing

Cost

Effectiveness/Efficiency

Prevention 1ary/2ary



- **Evidence**

Levels

Experience

Availability

Cochrane reviews - DFU

Topic	Year	Trials	Patients	Problems	Evidence
Pressure relieving interventions for treating DFU	2013	14	709	Various	<p>Non-removable, pressure-relieving casts are more effective in healing diabetes related plantar foot ulcers than removable casts, or dressings alone.</p> <p>Non-removable devices, when combined with Achilles tendon lengthening were more successful in one forefoot ulcer study than the use of a non-removable cast alone.</p>
Patient education for preventing DFU	2014	12	Over 3546	Conflicting	<p>Foot care knowledge and self reported patient behaviour seem to be positively influenced by education in the short term. In conclusion there is insufficient robust evidence that limited patient education alone is effective in achieving clinically relevant reductions in ulcer and amputation incidence.</p>
NPWT for DFU	2018	11	972	Potential conflict of interest. Variable follow-up	<p>Low certainty evidence to suggest NPWT may be effective in healing post-operative foot wounds and ulcers in people with diabetes compared with wound dressings. Further trials required.</p>

Accessed 9/May/19

Lewis J. Lipp A.. Pressure relieving interventions for treating diabetic foot ulcers. Cochrane Database of Systematic Reviews 2013, Issue 1.

Dorresteijn JA N, Kriegsman DM W, Assendelft WJJ, Valk GD. Patient education for preventing diabetic foot ulceration. Cochrane Database of Systematic Reviews 2014, Issue 12.

Liu Z et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database of Systematic Reviews 2018. Issue 10.

Cochrane reviews - DFU

Topic	Year	Trials	Patients	Problems	Evidence
Debridement of diabetic foot ulcers	2010	6	602	Various methods of debridement	There is evidence to suggest that hydrogel increases the healing rate of diabetic foot ulcers compared with gauze dressings or standard care. There is insufficient evidence of the effects of larval therapy on diabetic foot ulcers.
Growth factors for treating diabetic foot ulceration	2015	28	2365	High risk of bias	Growth factors may increase the likelihood that people will have complete healing of foot ulcers in people with diabetes. However, this conclusion is based on RCTs with high risk of systematic errors.
Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections	2013	5	167	Trials were underpowered	Adjunctive G-CSF treatment in people with a diabetic foot infection does not appear to increase the likelihood of resolution of infection or healing of the foot ulcer. However, may reduce the need for surgical interventions, amputations and duration of hospitalisation.

Edwards J, Stapley S. Debridement of diabetic foot ulcers . Cochrane Database of Systematic Reviews 2010, Issue 1.
 Martí-Carvajal AJ, Gluud C, Nicola S, Simancas-Racines D, Reveiz L, Oliva P, Cedeño-Taborda J. Growth factors for treating diabetic foot ulcers. Cochrane Database of Systematic Reviews 2015, Issue 10.
 Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database of Systematic Reviews 2013, Issue 8

**Accessed
9/May/19**

Cochrane reviews - DFU

Topic	Year	Trials	Patients	Problems	Evidence
Complex interventions for preventing diabetic foot ulceration	2015	6	Over 2084	Significant heterogeneity	There is no high-quality research evidence evaluating complex interventions for preventing diabetic foot ulceration and insufficient evidence of benefit.
Systemic antibiotics for treating diabetic foot infections	2015	20	3791	Heterogeneous and high risk of bias	Unclear if any one systemic antibiotic treatment is better than others in resolving infection or in terms of safety. One non-inferiority trial suggested that ertapenem with or without vancomycin is more effective in achieving clinical resolution of infection than tigecycline. Otherwise the relative effects of different antibiotics are unclear.
Topical antimicrobial agents for treating DFU	2017	22	2310	Small numbers Poor design Low quality	Some types of antimicrobial dressing may increase the numbers of ulcers healed in medium-term follow-up vs. non-antimicrobial dressing (low certainty evidence).

Accessed 9/May/19

Hoogveen RC, Dorresteyn JAN, Kriegsman DMW, Valk GD. Complex interventions for preventing diabetic foot ulceration. Database of Systematic Reviews 2015, Issue 8.

Selva Olid A, Solà I, Barajas-Nava LA, Gianneo OD, Bonfill Cosp X, Lipsky BA. Systemic antibiotics for treating diabetic foot infections

Cochrane Database of Systematic Reviews 2015, Issue 9.

Dumville JC et al. Topical antimicrobial agents for treating foot ulcers in people with diabetes. Cochrane Database of Systematic Reviews 2017, Issue 6.

Cochrane reviews - DFU

Topic	Year	Trials	Patients	Problems	Evidence
Dressings to treat foot ulcers in people with diabetes	2015	13 systematic reviews	N/A	Low quality evidence Different methodologies Small numbers	No clear evidence that advanced wound dressings were better than basic wound contact dressings for healing DFU.
Negative pressure to treat DFU	2018	11 RCTs	972	Evidence is low certainty	Negative pressure therapy when compared with wound dressings, may increase the proportion of wounds healed and reduce the time to healing for postoperative foot wounds and ulcers of the foot in people with DM.

Wu L et al. Dressings for treating foot ulcers in people with diabetes. Cochrane Database of Systematic Reviews 2015, Issue 7.

Zhenmi L et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database of Systematic Reviews 2018

Accessed 9/May/19

Conventional Management of Diabetic Foot Wounds - Experience

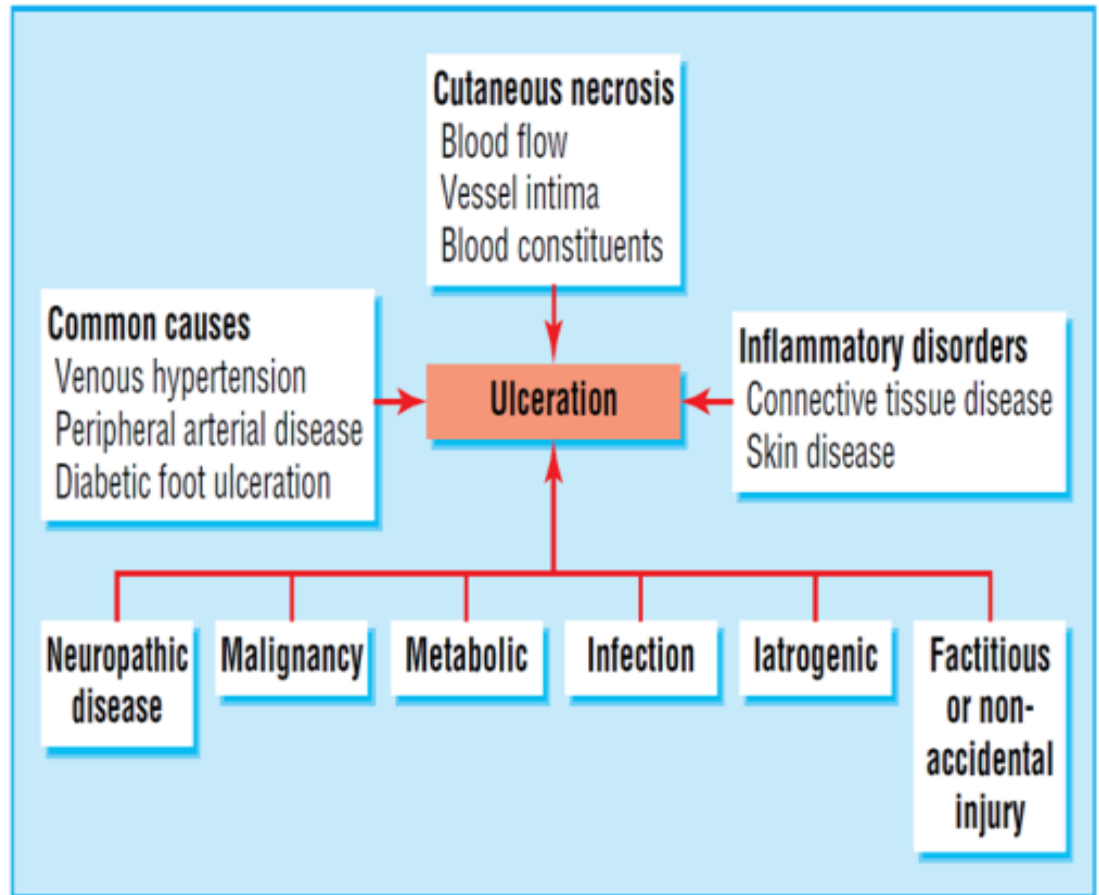
- Keep it clean.
- Keep moisture levels correct.
- Support the stages of wound healing.
- Off load areas of pressure
- Treat infection.
- Debride non viable tissue.
- Revascularise if arterial.
- Optimise glycaemic control



*...but this isn't
always enough...*

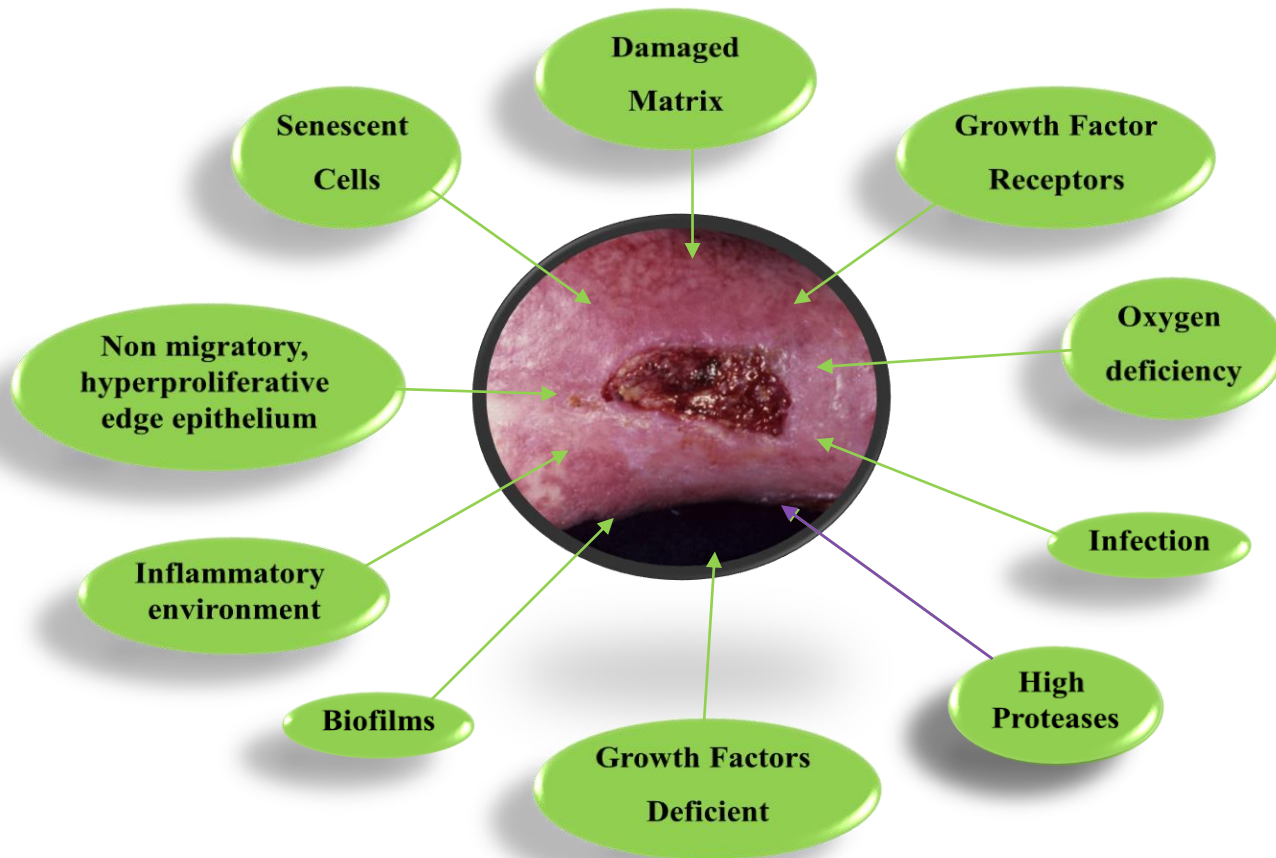
Causes of Chronic Wounds

- Chronic wounds are usually a manifestation of underlying disease process
- Comprehensive assessment is the key to successful management



From Patel, Grey & Harding 2006

Local factors influencing healing



Therapeutic Armamentarium for Wound Healing

- Dressings
- Devices
- Drugs
- Surgery
- Biologics
- Combination Therapy
- Search of PubMed & Cochrane
- In past 12 months 573 papers published on wound treatments
- Only 47 seemed relevant or of a reasonable standard
- Research Fellow with 2 months experience in wounds

Is there potential for a single magic bullet ?

NO not in my opinion

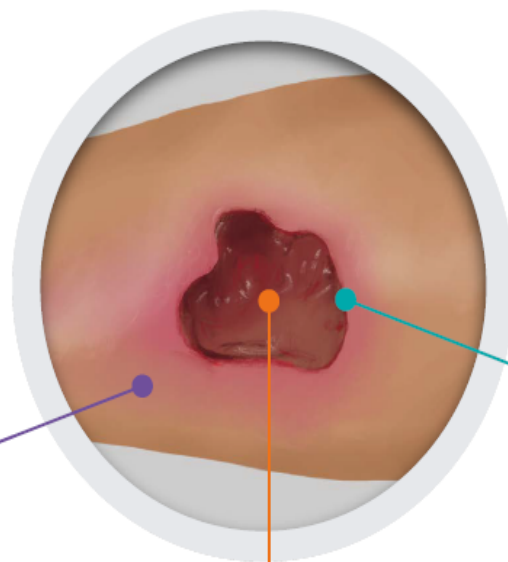
Dressings alone don't heal wounds




Wound healing is a complex process;

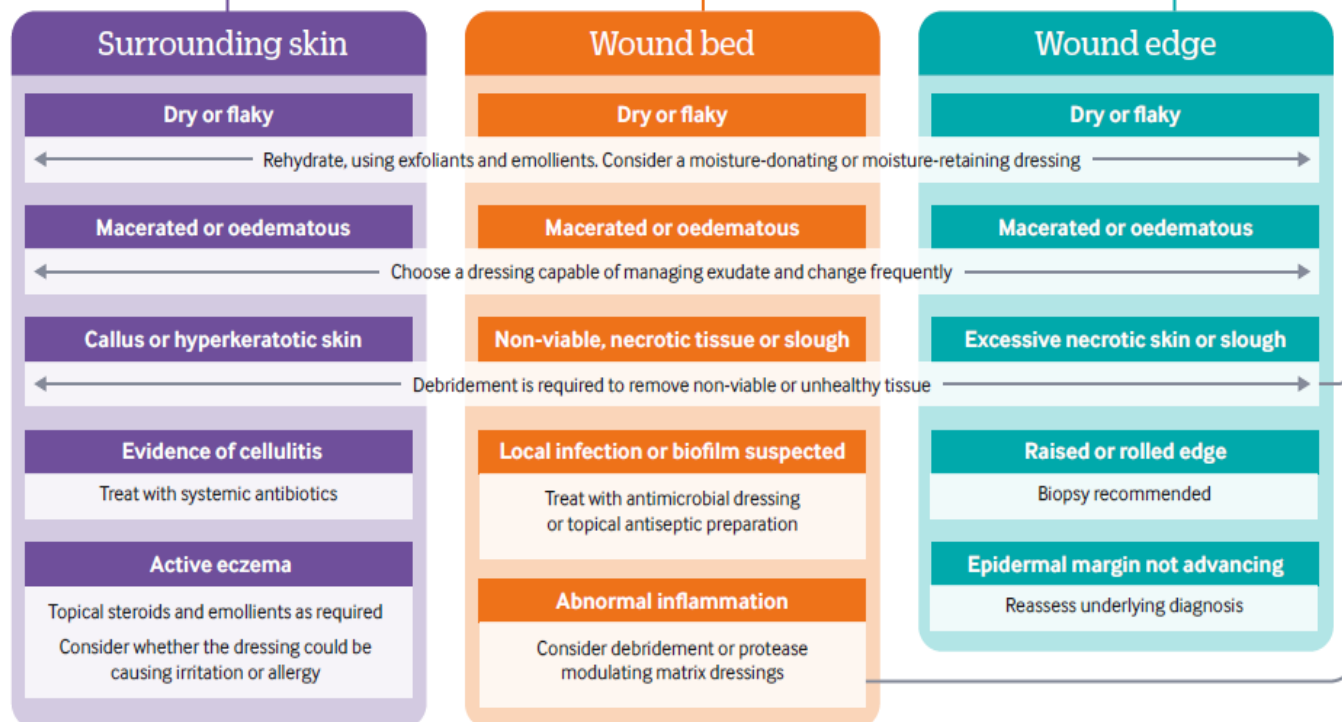
- Assess + Address underlying systemic/ metabolic factors
- Assess + Address local factors
- Get the factors corrected and in balance and maintain them until the wound heals and then consider influencing scarring

Wound assessment and dressing choice for venous ulcers

Dressings should be selected based on the properties of the wound and surrounding skin. Consider the wound location, size, depth, exudate level, and presence of infections. Dressings can help symptom control and promote healing. However, compression therapy remains the cornerstone of treatment.



Debridement methods	
	Surgical or sharp
	Autolytic with hydrocolloid, hydrogels or honey dressings
	Larvae



Structured Approach for selecting dressings in leg ulcers

BMJ April 2018

Choice of dressing

Exudate level



Dry



Low



Moderate



High

Flat wounds

Shallow wounds

Deep wounds

Locally infected wounds

Hydrogel sheets —

Soft polymer dressings —

Hydrocolloid fibrous —

Alginates —

Low-adherent dressings

Semipermeable films

Hydrocolloid sheets —

Foam dressings —

Chronic wound with prolonged inflammatory phase

Protease modulating matrix dressings

Many kinds of dressing are available impregnated with antimicrobial agents, such as:

Iodine

Chlorhexidine

Silver

Honey

Dialkylcarbonyl chloride

Polyhexamethylene biguanide (PHMB)

Structured Approach for selecting dressings in leg ulcers

BMJ April 2018

thebmj

Read the full article online



<http://bit.ly/BMJvlu>

© 2018 BMJ Publishing group Ltd.

Disclaimer: This infographic is not a validated clinical decision aid. This information is provided without any representations, conditions, or warranties that it is accurate or up to date. BMJ and its licensors assume no responsibility for any aspect of treatment administered with the aid of this information. Any reliance placed on this information is strictly at the user's own risk. For the full disclaimer wording see BMJ's terms and conditions: <http://www.bmj.com/company/legal-information/>



See more visual summaries



<http://www.bmj.com/infographics>



Types of dressings

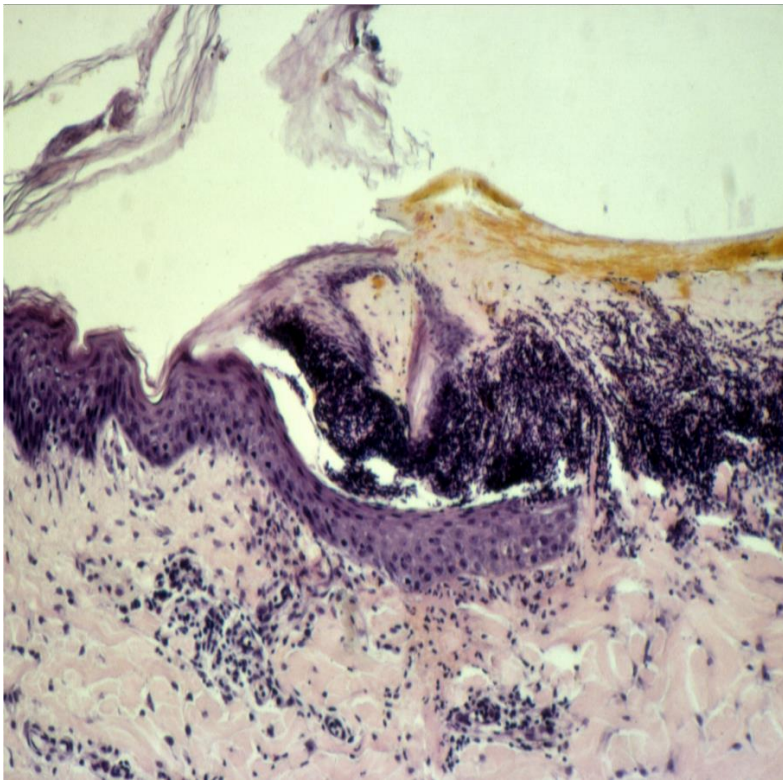
- **Passive:** ordinary dressing (e.g. gauze) that cover and conceal the wound
- **Interactive:** capable of modifying the physiology of the wound environment to optimize healing by promoting debridement, enhancing granulation/re-epithelialization, reducing exudate levels and bacterial load
- **Bioactive:** deliver active substances such as antimicrobials/ antibiotics which have a direct role in changing the chemical and cellular environment of the local wound, stimulating the healing



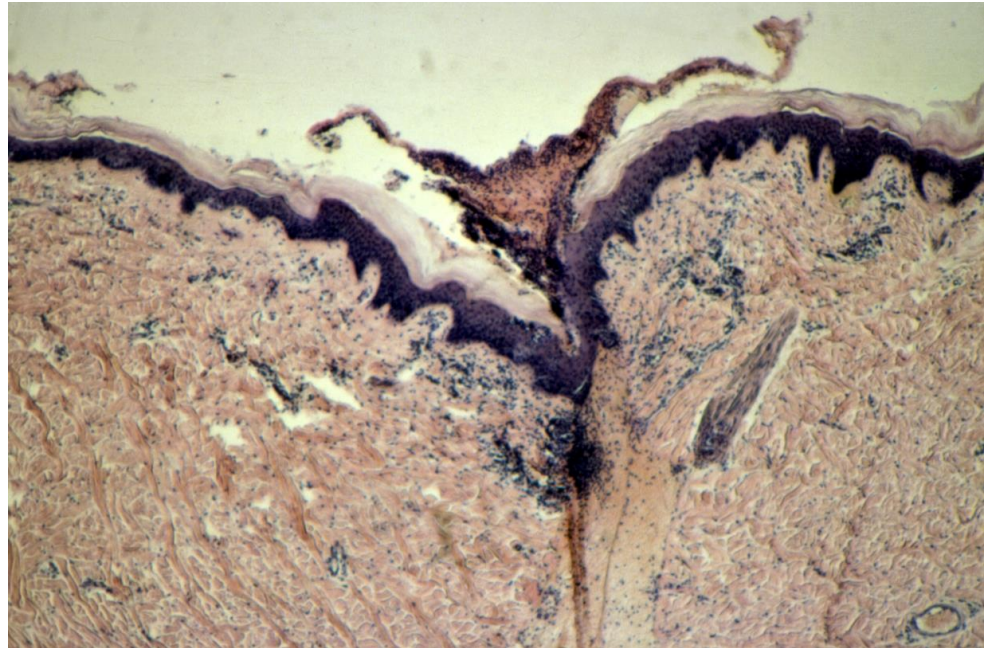
George Winter's original slides



Winter G (1962). Nature 193: 293-294



**Acute partial
thickness wounds
that demonstrated
epithelialisation
increased by 50%**



Winter G (1962). Nature 193: 293-294

Current Dressing Categories

- Basic Dressings
- Absorbent Dressings
- Alginates
- Antimicrobials
- Films
- Foams
- Honey Dressings
- Hydrocolloids
- Hydrogels
- Odour Control
- Protease Modulators
- Scar Management
- Skin Protection
- Wound Contact Layers
- Other dressings

See BNF.org

<http://www.bnf.org/bnf/index.htm>

Wound Care Handbook

<http://www.woundcarehandbook.com>

Modern Dressing Types and their Problems

- Semi permeable films
- Hydrocolloids
- Foams
- Alginates
- Hydrogels
- Hydrofibres
- Antimicrobial
- Anti MMP
- Matrix replacements
- Adhesion/Semi permeable
- Gel and Smell/ Occlusive
- Absorbent/ Variable
- Haemostatic/ Gel
- Water donating/Debriding
- Gel/Retain Structure
- Iodine/Silver/Biofilms
- 25% all wounds/Proof
- Dressing/Implant

New kids on the block- Chitosan

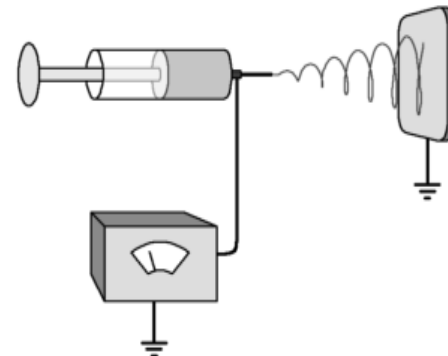
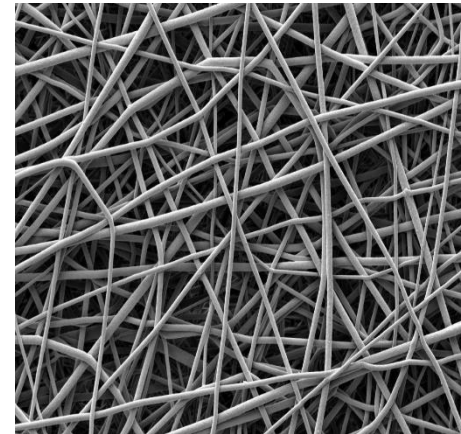
- Chitosan: second most abundant naturally occurring carbohydrate polymer derived from chitin present in the shells of crustaceans
- Chitosan has the following properties
- Potentially developed into forms of dressings that can deliver inflammation regulatory peptides such as neurotensin.⁴⁷



- biocompatible
- biodegradable
- non-toxic
- antimicrobial
- hydrating
- retain fibroblast growth factors
- stimulate dermal fibroblasts, cell adhesion
- promote collagen deposition

Nano Fibres

- Electrospun scaffold made from bioresorbable “suture” polymer. Nano/micron scale fibres
- Scaffold is attractive to healthy cells from adjacent tissue following creation of an acute wound
- Fibroblasts migrate into the scaffold, *along the fibres* to repair the wound
- Considerable know-how built into our electrospinning process making this a platform technology



No-contact dressing for all clinical settings

SpinCare is applied 20 cm from the wound and offers **excellent adherence** to wound bed

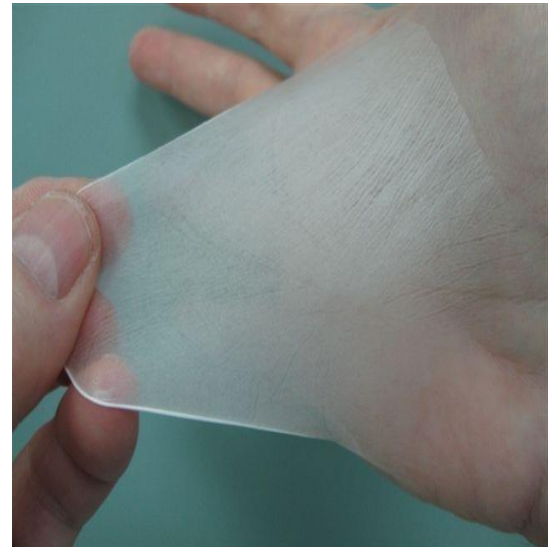
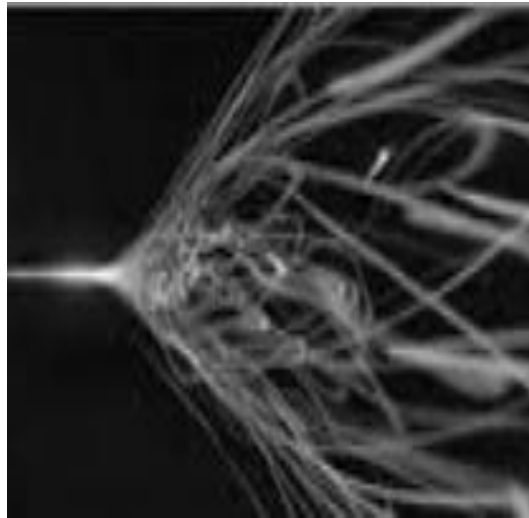
SpinCare
Device



Nano-fibers
Generated

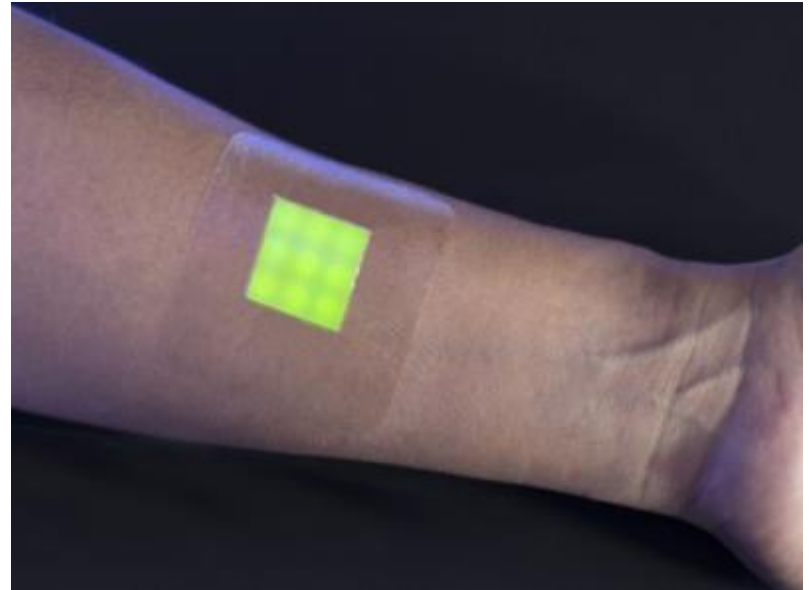


Dressing
Created



Colour changing dressing in presence of infection

- Dressing releases a fluorescent dye from nano-capsules triggered by toxins secreted by disease causing bacteria within a wound.
- The nano-capsules only break open when toxic bacteria are present
- Allows treatment of only patients with an infection avoiding the unnecessary use of antibiotics.



Link:

<http://www.bath.ac.uk/news/2015/11/16/burns-dressing-mrc/>

Epidermal Cell Grafting

Microdomes applied to wound



Donor Site





Full thickness multiple small biopsies

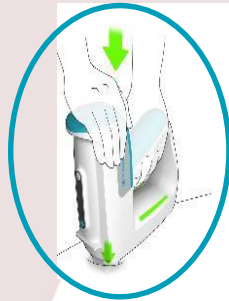


ARTTM

Total procedure time is 10 minutes or less with no disruption to patient/clinic flow



1. Prepare donor site
Numb the top of thigh
5 mins



2. Harvest Skin
MicroColumns
60 seconds



3. Scatter Skin
MicroColumns
directly into wound
60 seconds



4. Dress wound
2 minutes



Cartridge
(sterile)



Handheld
(reusable)

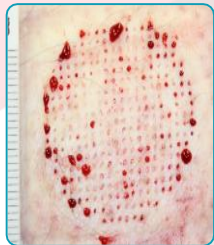


Skin MicroColumns



ART™

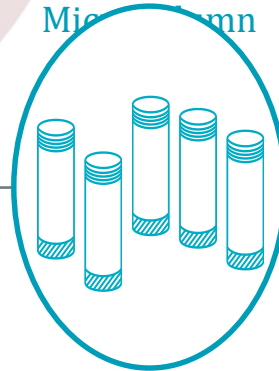
Harvest Skin MicroColumns
Many **microscopic holes**
created



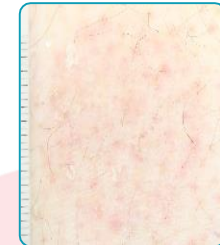
Harvest

Creates > 300 MicroColumns to
cover 6.5 cm²

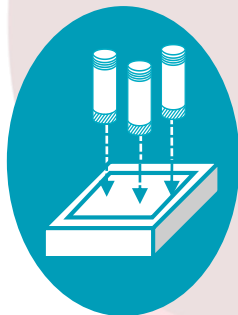
Full-thickness Skin
MicroColumn



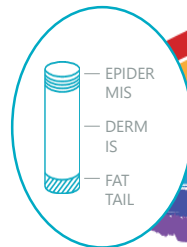
Rapid Donor Site Healing
Holes close in days;
barely visible in months



Scatter



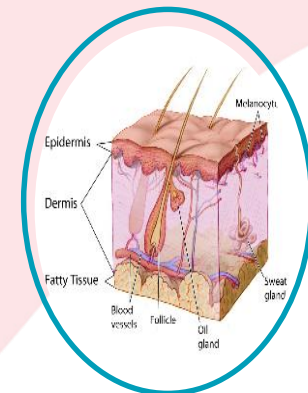
Scattered into Recipient Wound
10x expansion; orientation
doesn't matter



FIBROBLASTS (INCL. DEEP
DERMAL)
KERATINOCYTES
MELANOCYTES
STEM CELLS,
LANGERHANS CELLS
CYTOKINES
GROWTH FACTORS
ADnexal COMPONENTS

Full thickness
skin components

MicroColumns transfer Healing Factors to
Recipient Wound
Contains **all key elements** of full-
thickness skin



Full Benefits of Autologous Skin
No bioengineering downsides



Evidence to support TO therapy

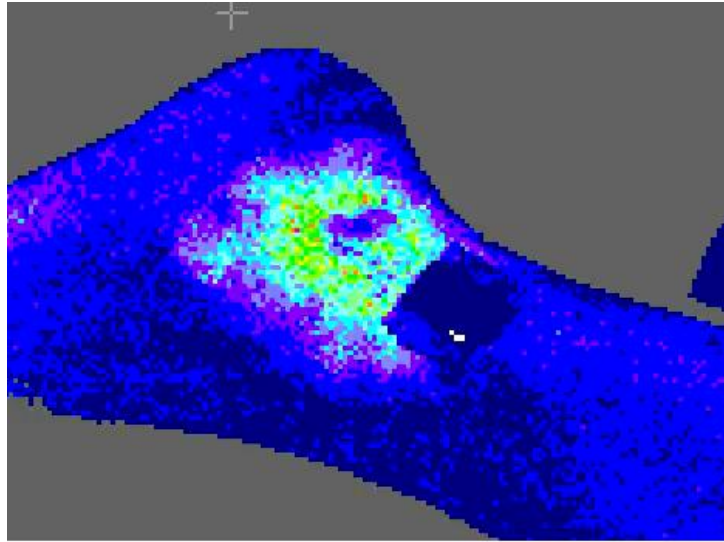
- Oxygen is a nutrient and has antibiotic properties
- Oxygen drives redox signalling
- TO therapy induces vascular endothelial growth factor (VEGF165) expression.
- Improved wound closure with TO therapy

Geko

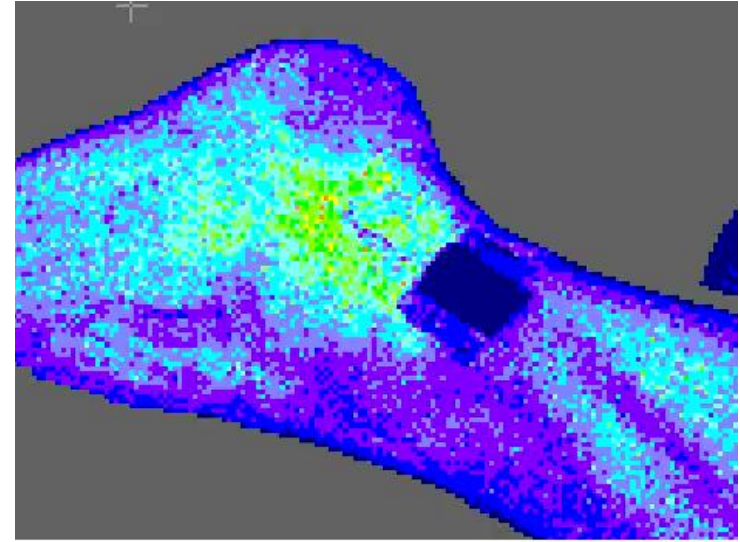
- Useful for a range of lower limb applications as well as VLUs, e.g.:
 - Mixed ulcers.
 - Post op oedema.
 - VTE prophylaxis.
- Has effect on:
 - Venous flow.
 - Arterial flow.
 - Microcirculation.



Laser speckle contrast imaging



Baseline



geko™

Wound bed – 225% increase in flux ($p < 0.001$)
Peri-wound – 67% increase in flux ($p < 0.001$) –
patient had active infection, this area therefore
had more flux than usual so this figure is lower
than expected

Electrical stimulation (ES)

- Low-intensity direct current (LIDC)
- High-voltage pulsed current (HVPC)
- Transcutaneous electric neural stimulation (TENS)
- Pulsed electromagnetic energy (PEM)



Cold Plasma Application in Ulcers

- Wound decontamination.
 - “Prototype devices have been shown to kill micro-organisms without necessarily affecting mammalian cells, destroy bacterial spores, and control biofilm generation.”
- Wound healing.
 - “NTGPs have been shown to increase proliferation of fibroblasts and other cells, produce nitric oxide, which in itself is bactericidal and also may have oxygenation and angiogenesis properties, reduce the prolongation of the inflammatory phase of wound healing, and reduce wound odors.”

(Lloyd, Friedman, Jafri, Schultz, Fridman, Harding, 2010)

Recent data using Sucrose Octasulfate on DFU

- | | | | | |
|----------------------------------|-------------|--------|---------|---------|
| • DFU Texas 1C or 2C | | Active | | Control |
| • 2 week run in | • Healed | 48% | p=0.002 | 30% |
| • 20 week study | • Infection | 20% | | 28% |
| • 126 patients active | • Died | 2% | | 4% |
| • 114 patients control | | | | |
| • Sucrose Octasulfate binds MMPs | | | | |

(*Edmonds et al Lancet Diabetes & Endocrinology 2018*)

Biological Therapy for DFU

- Conc'n of patients leucocytes/platelets/fibrin
- 269 patients
- 32 specialist centres
- **Healing rate 34% vs 22%**
at 20 weeks $p=0.0235$

SAE's Infection 24% and 27%

Conclusion has potential to enhance healing of DFU

Game, Jeffcoate et al Lancet Diabetes-endocrinology 2018

Topical application of platelet-rich plasma for diabetic foot ulcers: A systematic review

One thousand two hundred and seventeen articles were screened. Eleven articles (322 PRP subjects, 126 controls, PRP subject mean age 58.4 ± 7.2 years, control mean age 58.7 ± 5.9 years) were analyzed. Six articles were level II evidence, four were level III, and one article was level IV. The mean MCMS was 61.8 ± 7.3 . **Healing rate was significantly faster with PRP application compared to controls (0.68 ± 0.56 cm²/wk vs 0.39 ± 0.09 cm²/wk; $P < 0.001$).** Mean heal time to $> 90\%$ of the original ulcer area was 7.8 ± 2.7 wk and 8.3 ± 3.7 wk for patients in the PRP group and control groups, respectively ($P = 0.115$). There were significantly lower adverse effects reported with PRP application compared to controls (7 wound infections, 1 contact dermatitis vs 14 wound infections, 1 maceration; $P < 0.001$).

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

135 participants were recruited with 148 ulcers (EDX110-75; control-73), 0% of which were clinically infected at baseline. **EDX110 achieved its primary endpoint by attaining a median percentage area reduction of 88.6% compared to 46.9% for the control group ($p=0.016$) at 12 weeks in the intention-to-treat population.** There was no significant difference between wound size reduction achieved by EDX110 after 4 weeks and the wound size reduction achieved in the control group after 12 weeks. EDX110 was well tolerated.

Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients

After a 2-week screening period, during which patients with DFUs were unsuccessfully treated with SOC, patients were randomised to either SOC alone or SOC with dHACA applied weekly for up to 12 weeks. **At 12 weeks, 85% (34/40) of the dHACA-treated DFUs healed, compared with 33% (13/40) treated with SOC alone.** Mean time to heal within 12 weeks was significantly faster for the dHACA- treated group compared with SOC, 37 days vs 67 days in the SOC group ($P = .000006$). **Mean number of grafts used per healed wound during the same time period was 4.0, and mean cost of the tissue to heal a DFU was \$1771.** The authors concluded that aseptically processed dHACA heals DFUs significantly faster than SOC at 12 weeks.

Drugs and Wound Healing

- **Drugs that delay healing**

- Non selective β blockers
- Steroids
- Immune suppression
- NSAID's
- Anticoagulants
- Cytotoxic agents
- Hydroxyurea
- Nicorandil

- **Drugs that enhance healing**

- Antibiotics
- Pro inflammatory agents
- Anti inflammatory agents
- MMP binding agents
- Antidepressants
- Analgesics
- GTN
- Sildenafil

Wound Care – What works- Is there any evidence?

- **Goal**

Wound Care?
Wound Management?
Wound Dressing?
Wound Healing?

- **Works for**
Healing?
Symptoms?
Infection?



- **Evidence of**
Healing
Cost Effectiveness/Efficiency
Prevention 1ary/2ary

- **Evidence**
Levels
Experience
Availability

How to Measure Success here?



Options of how to measure success in wound patients

- Wounds healed?
- 'Wound free days'?
- Decrease in pain, odour or exudate?
- Eradication of infection?
- Increase in patients quality of life?
- Changes in Patients/ Care givers Experience ?
- Improved Cost Effectiveness ?

Unrealistic to use complete healing as primary outcome measure more appropriate to adopt broader based approach

*Grey, Leaper, Harding
Editorial BMJ 24 April 2009*

Clinical Innovation - Definitions

Clinical Innovation is "stuff " that we do that makes a difference and benefits patients and society

Harding 2014

It consists of

Technological Innovation

Service, System and Process Innovation

Social Innovation

Spectrum runs from Continuous Quality Improvement through to Transformative/Disruptive Innovation

Welsh Wound Innovation Centre

WWIC was Formally launched in September 2014 as a Centre of Excellence in Skin Health, Wound Prevention and Treatment.

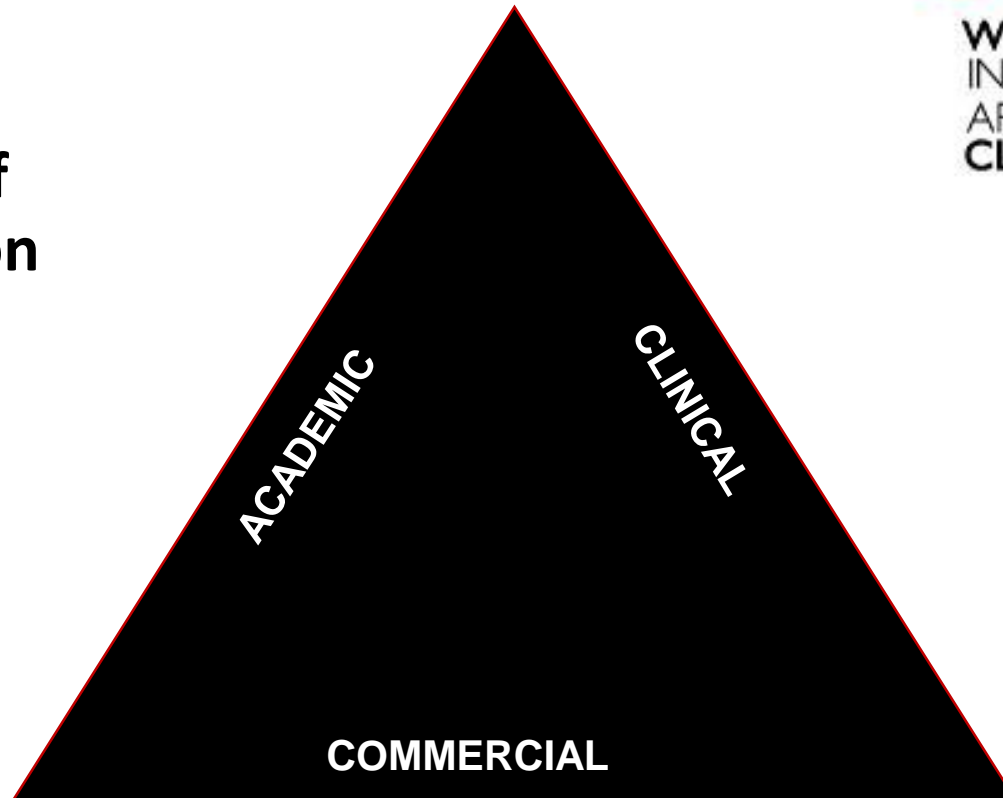
Funded by £4.2 M Government grant



WWIC – What is it?

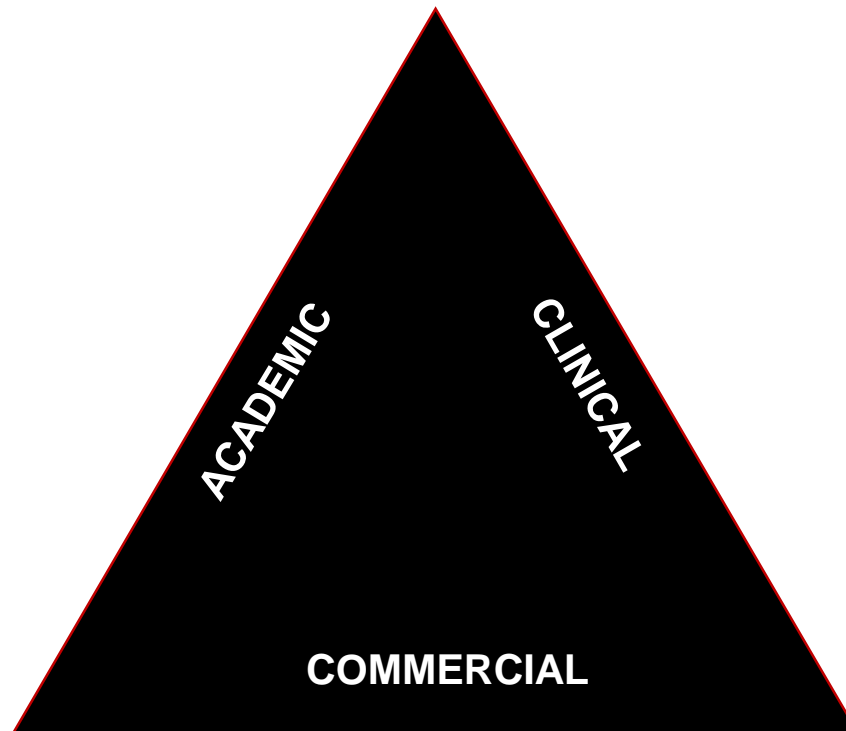


A New Model of Clinical Innovation



Set up as a company limited by guarantee so it can operate without the constraints of a public body or a charity but enable interaction with NHS and Universities to have confidence no one is taking profits for personal gain. It also allows the team in WWIC to act as academic, clinical or commercial partner in projects as appropriate

What have we achieved since 2015?



Similar model now being developed for
Respiratory Disease and other clinical areas

Academic activity 2015-8



- **Translational funding from MRC/ Wellcome trust**
- **5 MD/PhD degrees awarded, 1 further PhD submission pending**
- 41 students enrolled onto the MSc programme
- **5 International students - clinical attachments**
- 81 Posters and Presentations at International meetings
- **30+ papers published**
- **Commissioned by BMJ, Nature Reviews and Lancet to write material**
- **Involved with others in ACCELERATE £24M grant for Team Wales !!!!!**
- **Living lab of Clinical Innovation**
 - **2018 NHS Budget announcement 'Extra £70m for the NHS, including £9m for health innovation centres modelled on the Welsh Wound Innovation Centre'**
- **Additional Universities and NHS bodies joined WWIC**

Resource utilisation in Wales SAIL database

IWJ 2016

Resource utilised	Number in cohort	Unit cost (£)	Cost (£)	Cost at all-Wales level (£)
Initial GP visit	78,090	45	3,514,050	8,570,854
Subsequent GP visits	1,249,809	13	16,247,517	39,628,090
Number of dressings	2,344,930		3,964,537	9,669,602
Number of district nurse attendances	703,479	35	24,621,765	60,053,085
Number of out-patient attendances	68,662	120	8,271,711	20,174,905
Number of in-patient episodes	14,697		78,204,577	190,742,871
Total expenditure			134,824,157	328,839,408
Average cost per patient				1726.53

National Wound Audit

BMJ Open 2017;7:e015616. doi:10.1136/bmjopen-2016-015616

8365 patients

66 hospitals

748 with pressure ulcers (8.9%)

18.2% were not documented

18% were documented inaccurately

50% developed in hospital

30% of all In Patients had a wound

Problem of use of inappropriate mattresses

In Partnership with



**All Wales Tissue
Viability Nurse Forum**

Fforwm Nyrsys Hyfywedd
Meinwe Cymru Gyfan

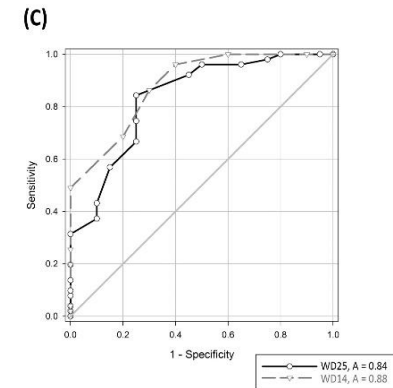
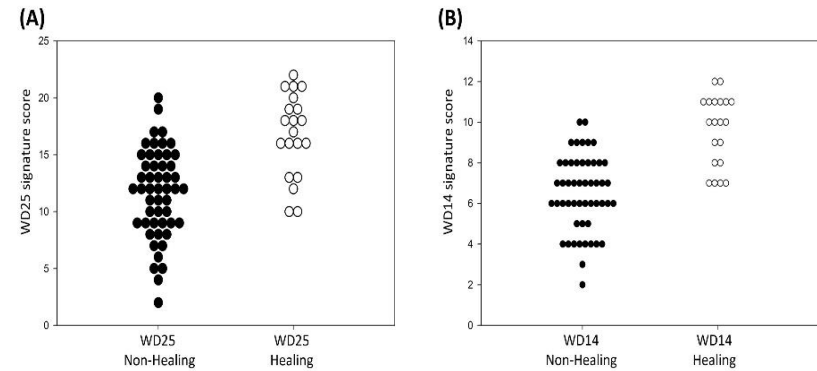
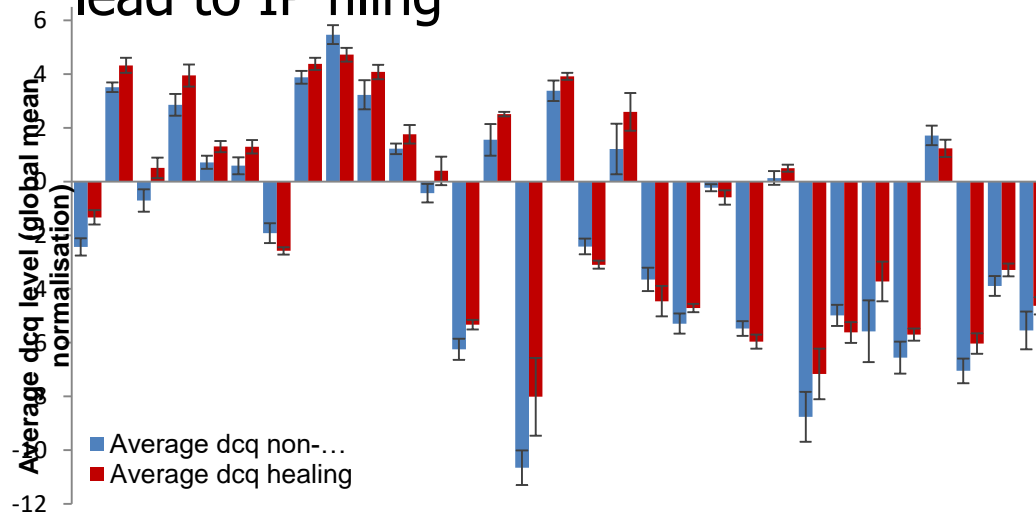
IP developments and Partnerships

- Wound genetic and wound therapy patents awarded in partnership with **Prof Jiang**

New method of delivery of old treatment patent filing with

Dr Houston

- Work on identifying new approach to diagnostic markers with **Prof Weeks** that is likely to lead to IP filing



Wounds and Cancer

Is There a link?

Tumours: Wounds that do not heal. Similarities between
Tumour and Stroma generation in Wound Healing

Dvorak HF NEJM 1986 315: 1650-9

Cancer as an Overhealing Wound. An old hypothesis revisited

Schafer M Werner S Nat Rev Mol Cell Biol 2008 9 628-38

Cardiff Gene Signature Development

Jiang & Harding et al *BJS May 2019*

- **Study 1 Retrospective (Screening Cohort)**
 - 10 Acute and 14 Chronic Wounds
 - Identification of 121 genes from set of 2000
 - Resulted in 25 Gene Signature
- **Study 2 Retrospective (Validation Cohort)**
 - 71 patients VLU
 - 20 Healers and 51 Non healers at 12 weeks
 - Resulted in 14 Gene Signature

Results of the WD25 signature analysed in the screening cohort. Each gene was classified as either a promoter or inhibitor of wound healing, and assigned a score of one if a promoter was present or an inhibitor absent. Synthesis of the individual scoring elements of the WD25 signature into an overall genotype of either healing or non-healing resulted in a highly significant predictive model, (sensitivity 92·9 (66·1-99·8)%; specificity 90·0 (55·5-99·8)%, $p=0·00017$).

Genotype	Non-healing	Healing	Total
Chronic wounds	13	1	14
Acute wounds	1	9	10

The 25 gene signature list, comprising genes significantly different between acute and chronic wounds. Based on their differential expression, genes were termed either ‘promoting’ of wound healing (elevated in acute wounds, reduced in chronic wounds) or ‘inhibiting’ (reduced in acute wounds, elevated in chronic).

Molecule name	Expressional differences between wound and normal tissues
AMFR	Promoting
ARP2	Promoting
β-Catenin	Promoting
BMP15	Promoting
CAR1	Promoting
Claudin-5	Promoting
CREB1I	Promoting
Endomucin-2	Promoting
IL17BR	Promoting
IL17C	Promoting
IL22R	Promoting
IL8RB	Promoting
KAI1	Inhibiting
N-WASP	Promoting
Par4	Promoting
PEDF	Promoting
Psoriasin	Promoting
PTPRK	Promoting
RhoGDI-G	Inhibiting
RON	Promoting
TEM4	Promoting
TEM7R	Promoting
VEGF-C	Promoting
VEGF-D	Promoting
WAVE2	Promoting

Stratification of wound outcome from the validation cohort according to WD25 score. WD25 predicted for wound healing outcomes (sensitivity: 98·0 (89·6-99·9)%, specificity: 40·0 (19·1-64·0)%, $p<0·00001$)

Genotype	Non-healing	Healing	Total
Chronic non-healed wounds	50	1	51
Chronic healed wounds	12	8	20

Composition of the WD14 gene signature. Significant genetic markers were divided into two groups depending on their relationship to the threshold in healing wounds (group 1; same or higher, group 2; lower).

	Gene	Level in healing wounds relative to threshold	Role
Group 1	ARP2	same or higher	Cellular migration via actin polymerisation [44]
	VEGF-C	same or higher	Lymphangiogenesis [45]
	Psoriasin	same or higher	Tumour progression [46]
	IL22R	same or higher	Unclear, but IL22 acts by causing increased cellular motility and enhanced antimicrobial defence [47]
	TEM4	same or higher	Cellular migration [48]
	IL8RB	same or higher	Immune response [49], angiogenesis [50]
	Claudin-5	same or higher	Cellular adhesion and tumorigenesis [51]
	PTPRK (Protein-tyrosine phosphatase- κ)	same or higher	Cellular migration [52], tumour suppressor [53]
	CAR1	same or higher	Unknown
	TEM7R	same or higher	Precise function on TEM7R unclear, although TEM4 is thought to be a regulator of angiogenesis [54]
Group 2	Endomucin-2	lower	Unknown
	IL17RB	lower	Tumour suppressor [55]
	KAI1	lower	Metastasis suppressor [56]
	CREB1I1	lower	Cancer promoter (CREB 2) [57] Unclear (CREB1=Cancer promoter) [58]

Cardiff Gene Signature Development

- **Study 3 Prospective Study (Study Cohort)**
- 85 patients VLU
- 45 Healing at 12 weeks
- 40 Non Healing at 12 weeks
- **Follow up Longitudinal study**
- 13/15 correct at first biopsy
- 14/15 correct at second biopsy
- 3 patients who changed status were correctly identified
- 1 incorrectly identified non healing to healing

The WD14 gene signature was significantly predictive of healing outcomes on multivariate analysis. A greater wound duration was associated with a reduced likelihood of subsequent healing. NA: Not applicable.

Factor	Univariate		Multivariate	
	P value	Odds ratio (95% C.I.)	P value	Odds ratio (95% C.I.)
Wound duration	0·053	0·985 (0·970-1·000)	0·44	0·983 (0·966-0·999)
WD14 gene signature score	<0·001	9·529 (3·315-27·396)	<0·001	12·166 (3·800-38·949)
Age	0·284	0·985 (0·959-1·012)	NA	
Smoking	0·119	0·317 (0·075-1·344)	NA	
Use of antibiotics or antimicrobials	0·146	2·153 (0·766 - 6·054)	NA	

Clinical Activity 2015-8



- 60% of Community nurse time spent on wounds
- **Community nurse project improved outcomes by 45%**
- **Practice nurse project improved outcomes by 85%**
- First National Wound Audit 8500 patients and 400 staff over a week
- **Links with Charities in Wales including Lindsey Leg Clubs**
- **630 nursing and social care staff receiving wound care education to include legal study days**
- **Flynn report- PU integrated reporting across the Care Home sector**
- Led a significant service improvement project on wound care in an English CCG
- **Build of National Wound Registry supported by CMO/CNO/CEO NHS Wales**
- Exploring National TBM contract
- **Compulsory on line education for clinical staff developed**

Overview of Commercial Activity 2015-8

- Interactions with over 400 companies
 - 32 signed contracts
 - 5 Welsh based companies have signed contracts
- **Patent submission awarded**
- 5 inward investments in Wales
- **Created 82 new jobs in companies**
- **Helped protect the 2000+ jobs already based in Wales in Wound Healing**

Drives	Measures	Unit	2015/16	YTD	month/Dec	Rating	Comments
Research & Development/Innovation & Improvement	SSD/PM		21,911	4,297	478	G	Reports/Articles: Clark M, Young T, Fallon M. Systematic review of the use of Statistical Process Control methods to measure the success of pressure ulcer prevention. <i>International Wound Journal</i> 16(1):1-10; 2017. Young, T., Moisture management in wound care: A review of the literature. <i>Wound Management and Practice</i> 20(1):1-10; 2017. Clark M, Jones N, Harries R, Owen S, Moore M, Li J, Zhang Z, Harding K, Yorkington J, Jiang W, G. et al. Impact of patient epithelium-derived factor on colorectal cancer. <i>Journal of Clinical Investigation</i> 127(1):1-10; 2017. Van Netten J, Lazzarini D, Moore M, Li J, Zhang Z, Harding K, Yorkington J, Jiang W, G. et al. Impact of patient epithelium-derived factor on colorectal cancer. <i>Journal of Clinical Investigation</i> 127(1):1-10; 2017. Prentice J, Scott K-P, Verhaegh M, Li J, Zhang Z, Harding K, Yorkington J, Jiang W, G. et al. Impact of patient epithelium-derived factor on colorectal cancer. <i>Journal of Clinical Investigation</i> 127(1):1-10; 2017. Research 2018 accepted. Clinical Pharmacy and Therapeutics – 6th Edition (eds) R Walker, C Whittlesea. Wounds, S Holloway, K Harding. Accepted Dec 2017. Pan European Network for Wound Healing – national wound healing centre worldwide. Clark, M, Accepted Dec 2017. Final reports. Evaluation of static and powered hybrid mattresses. Report for Drive DeVilbiss, November 2017. Audit of Swindon Clinical Commissioning Group. Fallon, M; Ivins N and Clark, M. Presentations: Keith (Verity 1; Miles 4; Trudie 6 presentations and 1 workshop for St. Mary's Hospital, Hong Kong Award Submission 2017.
	No of publications			55	20	10	
	No of presentations/workshops	EMT		101	31	21	G
	Award Submissions				2	1	
	No of new ideas/patents and pathways developed	EMT		1			G
	No of jobs created	EMT		50	30		G
	Compliance with R&D process	MD/CRD					G
	No of new ideas/patents and pathways developed			140	61	2	G
	No of joint PhDs with commercial/academic partners	MD		3	1	1	G
	Number of customers with contractual agreements; NDA's and Memorandum of Understanding	EMT		41	10	6	G
Engaged Customers	Number of social media contacts	EMT		1,160	1,268	15	G

- **2 successful joint ventures signed in 2017 – licencing agreement and R&D lab**
- UKTI/DIT have focus on wound industry – hosted National and International events
- **Relaunched website and social media platform – significant increase in reach**
- **Delivery of Internal financial and savings plan**

Examples of Commercial partnership

- **Direct Health Care Group**
Caerphilly

- Relocation of new acquisition to Caerphilly
- Expansion space 100,000 sq.ft.
- Expansion staff 17 in 2017
45 in 2018

Queens award for innovation 2015

Laboratory evaluation of products

- **Frontier Medical Group**
Blackwood

- Increased head count
60% 2014-2017

Majority based in Wales

New acquisition in 2016

New posts in Blackwood

Future Direction export markets

Germany and USA

New Export Manager

Examples of Commercial Partnership

- **Huntleigh Diagnostics
Cardiff**

- Long standing relationship
- Supported evaluation of new technology
- Worked on
vascular assessment
Intermittent Pneumatic compression
New forms of vascular assistance
- Potential new Clinical study
application for grant funding
submitted

- **Neem Biotech
Abertillery**

- A Welsh R&D biotech that is fully owned by the Swiss-based Zaluvida organisation
- More than 10 publications produced that demonstrate the effect of NX-AS-911, a candidate molecule for wound healing, as a biofilm disruptor
- Research agreement in place to access WWIC's world-leading understanding and expertise in the field of wound healing

Comfort	Patients numbers	Ease of application	Patients numbers	Ease of removal	Patients numbers
Very comfortable	13	Very easy	10	Very easy	12
Comfortable	4	Easy	6	Easy	6
Fair/unsure	1	Fair/unsure	2	Fair/unsure	2
Uncomfortable	0	Difficult	0	Difficult	0
Very uncomfortable	0	Very difficult	0	Very difficult	0
Total	18*		18*	Total	18*

*Missing data are those patients who were either withdrawn or healed.



Examples of Commercial Partnership

New foreign investments

- **Medical Ethics**

- Australian company
- Veterinary focus
- Pain and infection prevention
- WWIC helped convince company to set up European and Clinical business in Wales despite experience of Dragons Den at earlier BioWales!!!
- Funding from

UK Government
Innovate UK

Welsh Government

First in man application March 2019

- **Solascure**

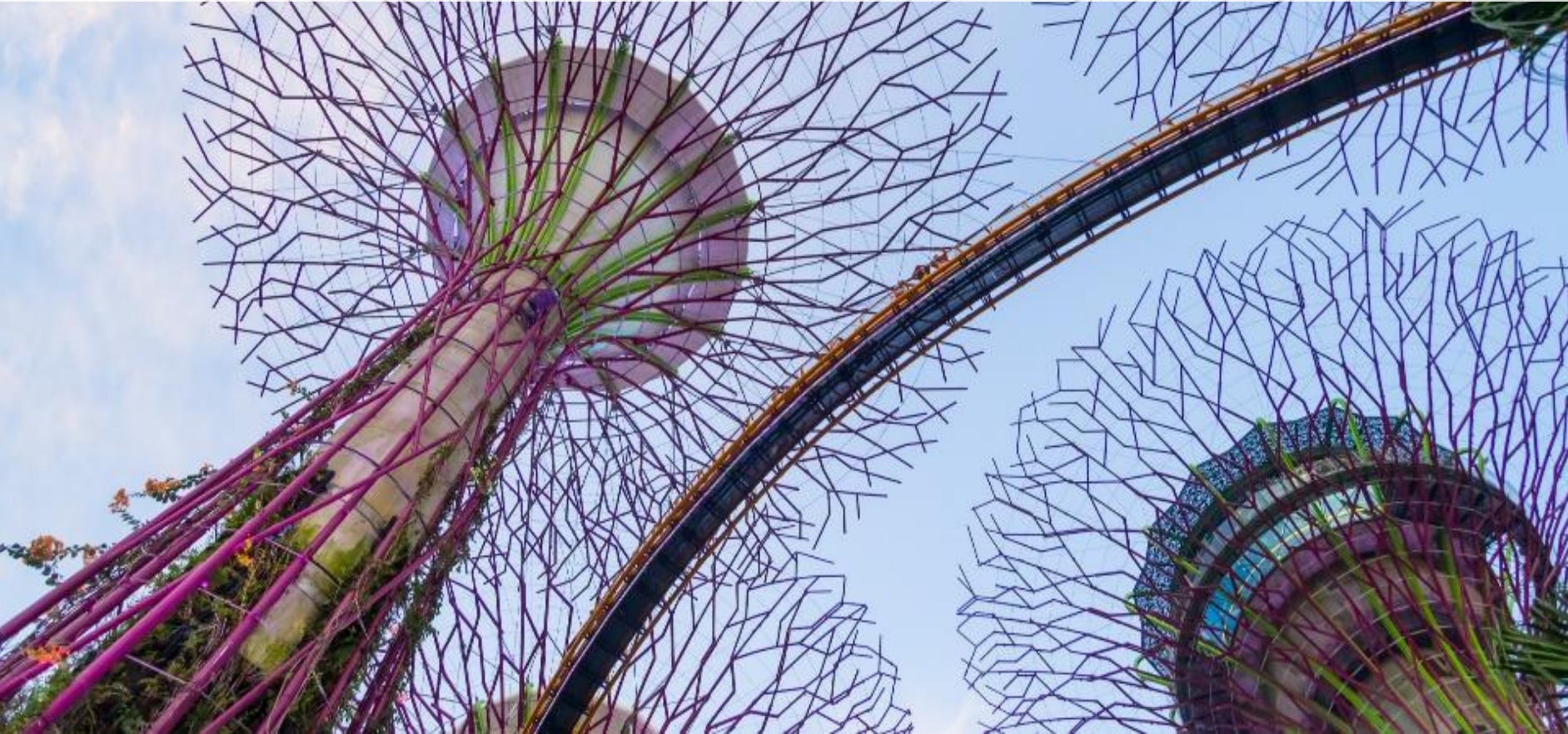
- Parent German public company
- Support from UK Global Entrepreneurs programme
- Advice regarding clinical studies
- Linked to Swansea University
- WWIC to undertake clinical studies
- Company to set up operations in Wales

International Collaborations



Wound Care Innovation for the Tropics

Global Influence, Asian Impact



- SG\$28Million wound programme grant

NZWCS Conference Dunedin 2019

Themes

- **Choices**
- **Changes**
- **Challenges**

Personal reflections



