

# Research

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**A** wide variety of topics were presented in the Research Stream, providing Congress attendees with an opportunity to hear about the latest research. In many cases, it will be a long time before the results of this research can be translated into bedside practice. In other cases, the results should enhance thinking about our current practice and whether it is based on the latest evidence. Here are the highlights of the Research stream.

## Gene Therapy and Related Genetic Approaches

There were several oral presentations about gene, cellular or animal studies that, while having results that had no immediate relevance to clinical practice, may be previews of future therapies.

### Farshad Forouzandeh

Laboratory research in development of non-rejectable cultured skin substitute.

*In vitro* and *in vivo* results demonstrate a decreased chance of rejection, improved angiogenesis and healing in immune-compromised rats. This is preliminary work, and the presenter is aiming to find a local immune-suppressive agent in a slow-releasing system, i.e., graft.

### José Bonilla

Human papilloma virus E6/E7 oncogenes promote mouse ear regeneration in the transgenic model Tg (K6b-E6/E7).

This may be a model for hair growth and wound healing; wounded mouse ears showed increased healing without scarring compared with controls.

### Feung-Kyu Han

This presentation outlined the use of uncultured lipoaspirate cell autograft for the treatment of diabetic ulcers. *In vitro*, fibroblast production and collagen synthesis were identified. Aspirate from liposuction

was applied to diabetic foot ulcers and demonstrated healing within four to six weeks. These were case studies with no controls.

### Marjana Tomic-Canic

Gene transcription patterns may be able to guide the extent of excisional debridement of chronic wounds. In the study cited, biopsies were taken before and after debridement of chronic wounds such as diabetic foot ulcers and venous leg ulcers. The samples were analyzed at the cellular and gene level and compared with normal skin. Fibroblasts in the pre-debridement biopsy were enlarged and demonstrated a slower growth rate. They did not migrate. Fibroblasts in the post-debridement biopsy were closer to those in normal skin. Using the results so far, the researchers want to determine which genes may be predictors of wound healing. They are currently using this technology to investigate squamous cell carcinoma (SCC), psoriasis and chronic wounds.

### Rachel Clarke

In a study on infection in chronic wounds and the correlation to wound cytokine levels, diagnosis by clinician, and bioburden, the researchers found only 50 per cent concordance between clinical diagnosis and swabs. Correlation between cytokine levels and infection depended on wound type.

### Liping Jiang

Results from an experimental animal model for pressure ulcer by persistent stress in local ischemia-reperfusion suggest that at least six hours of pressure relief is required.

### C. Yhan Yeong Hoo

Vitamin C may increase flap survival rates (in rat studies), perhaps because of reactive oxygen species.

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### David Bates

In a discussion on the current advances of vascular endothelial growth factor (VEGF)/angiogenesis, David Bates suggested that while all VEGF has the same molecular weight and composition, molecular structure may vary.

VEGF can both stimulate or inhibit angiogenesis depending on the molecular structure, which may explain poor results to date with the application of isolated VEGF.

### Aging, Scars and Wound Healing

#### Madhuri Reddy

The aim of this session was to review the skills, knowledge and attitude required for providing the highest level of care for the elderly. Healing in the elderly is slower due to two major factors: normal aging and photo aging. Normal aging causes increased dryness and subsequently increased wrinkling and decreased immunologic and sensory responses. Photo aging enhances wrinkling and increases elasticity and matrix metalloproteinase (MMP) levels. Nutrition and aging were also discussed. More than 10 per cent of body loss in the elderly is unintentional. The goals of care should be discussed with patients and their families. Decrease of dressing changes, pain and odour should be emphasized in elderly patients.

### Mark Ferguson

This session focused on the role of an exogenous substance derived from human recombinant transforming growth factor- $\beta$ 3 (TGF- $\beta$ 3) in the treatment of scars. Studies indicate it reduces fibronectin and collagen type I and III deposition in the early stages of cutaneous wound healing and overall wound scarring.

Scars not only have aesthetic effect. Over joints, scars may cause functional problems, growth retardation and have a negative psychological impact.

This new medication has shown promise in a phase 1 trial and two phase 2 trials completed in the United Kingdom. In three clinical trials, wounds treated with the substance (via intra-dermal injection) showed a statistically significant improvement in scar appearance, with a response rate of greater than 70 per cent. In more than 1,500 human subjects, it does not seem to have safety or tolerability issues for use in the prevention or reduction of scarring and it has large therapeutic index.

### What's new in pharmacological agents?

#### Marco Romanelli

This session reviewed new biologic therapies, including anti-tumor necrosis factor (TNF)- $\alpha$ , infliximab, etanercept and adalimumab.

- TNF- $\alpha$  is a pro-inflammatory cytokine that induces interleukin 1, 6 and 8. Anti-TNF- $\alpha$  is effective therapy in treating acute inflammatory response, rheumatic fever and vasculitides.
- Infliximab is a humanized monoclonal antibody against CD20 and a treatment option for ulcerative pyoderma gangrenosum.
- Etanercept is an immunosuppressive agent, so the indications and safety information should be checked before starting treatment.
- A case report for the treatment of systemic pyoderma gangrenosum (PG) with adalimumab was addressed. Side effects were hypersensitivity reactions, urticaria, positive antinuclear antibody, positive anti-double-stranded DNA, clinical lupus (rare), symptoms and/or radiological evidence of demyelinating disease, histoplasmosis and an increase risk of tuberculosis. The risk of malignancy was not increased.

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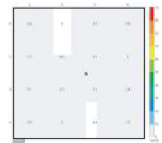
Using a 16-sensor, force sensing pad carefully affixed to the left heel of two subjects, pressure was "mapped" while the patients were lying supine and also with the knee flexed 30 degrees. Pressure mapping readings were done separately with the patient using various pressure reduction mattresses and numerous foot positioners, and heel protectors.

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### Pressure Mapping of the Heel - Supine

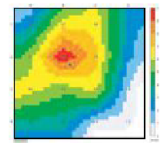
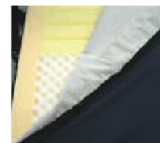
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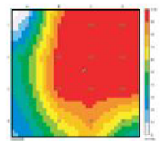
#### Pressure Reduction Mattress

Sensors included	16
Variation coefficient	59.7%
Standard deviation	26.8
Average pressure	44.8
Maximum pressure	100
Center of pressure	2.2, 2.2



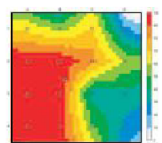
#### Heel Protector

Sensors included	16
Variation coefficient	36.4%
Standard deviation	28.2
Average pressure	77.5
Maximum pressure	100
Center of pressure	2.8, 2.4



#### Heel Pillow

Sensors included	16
Variation coefficient	40.5%
Standard deviation	28.1
Average pressure	69.4
Maximum pressure	100
Center of pressure	2.1, 2.5



The choice of treatment is based on the severity of the disease and rate of infection.

#### **Geoff Sussman**

The aim of this session was to review medications that have a negative impact on wound healing.

- Steroids decrease macrophage activity, collagen production, chemotaxis, protein synthesis and wound closure and will increase susceptibility to infection. Topical steroid application in peri-wound skin should be out of wound edges, and the edges should be separated by a barrier first.
- Cytotoxic drugs are neurotoxic, cause myelosuppression and decrease replication of wound repair cells such as fibroblasts.
- Hydroxyurea causes leg ulcers (commonly on the malleolar area). Lichenoid eruption with hydroxyurea is called hydroxyurea dermatopathy.
- Nicotine is a vasoconstrictor agent that causes platelet aggregation and decreased collagen synthesis. Each cigarette decreases blood circulation by five times for one hour.
- Colchicine decreases fibrinogen, granulocyte migration and cytokines.
- Anticoagulants are vasoconstrictors. Dapsone interferes with neutrophilic expression.
- Beta-blockers have negative effects on wound healing, but their effects vary depending on individual patients.
- Penicillin interferes with the tensile strength of the wound and decomposes in contact with tissue.

Medications have an important role in healing, but you need to know the medications that your patient is taking because this may be a factor in delayed wound healing. Consult with a pharmacist when necessary.

#### **Tania Phillips**

This session reviewed medications that have a positive impact on wound healing. Note: The numbers of randomized controlled trials (RCTs) in this subject are very limited.

- Pentoxifylline has variety of effects on red blood cells (RBCs) and tissue oxygenation, and modulates white blood cell (WBC) behaviour. It is an effective adjuvant to compression therapy in the treatment of VLU.
- Micronized purified flavonoid fraction (MPFF, Daflon)

is an antioxidant that reduces capillary re-permeability. It increases venous tone and capillary permeability. It can be used as conventional treatment for venous leg ulcers and, overall, the chance of healing is 30 per cent more with MPFF. Healing time is shorter (six to 12 months). Daflon is not FDA approved but diosmin, the most active component of Daflon is available as a dietary supplement.

- Becaplermin, platelet-derived growth factor (PDGF), is the only FDA-approved treatment for diabetic foot ulcers. It is effective in treating diabetic foot ulcers, but there are not enough data.
- Based on seven double-blind RCTs, cilostazol improved distance claudication in the management of arterial disease. In patients with ischemic ulcers who are not good candidates for revascularization, cilostazol may be a good choice, but more clinical trials are needed.
- Endothelin-1 is a potent vasoconstrictor that stimulates fibroblast and smooth-muscle proliferation.
- Bosentan is an anti endothelin receptor. Trials have shown there is evidence with good results in scleroderma.
- Hormone therapy reduces the risk for venous ulcer or pressure ulcers. Topical estrogen accelerates healing.

#### **Zee Upton**

In this session, on new topical pharmacological therapies, the presenter indicated that growth factors have variable efficacy. The necessity for high doses and corresponding high costs hampered their use. Vitronectin promotes migration of intracellular fluid (ICF) to the cell surface.


#### **Bench to Bedside**

##### **Lars Steinstrasser**

In those with damage to the epithelial barrier, infection can occur at the site of trauma. The presenter discussed a study based on an attempt to create an effective antimicrobial wound dressing against gram-negative bacteria using an occlusive silk membrane with a tiny pore size (<100 nm). Natural silk is allergenic. This bioactive silk is not. It is non-adhesive, occlusive and is loaded with slow-release colistin. The study indicated that the slow release of a topical antimicrobial is feasible and effective with silk dressings using this technology.

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### Robert Diegelmann

This session focused on mechanisms and new developments in local wound care. New strategies involve neutralizing or removing proteases, as well as restoring tissue and growth factors. None of the new technologies will work without proper wound bed preparation; the bacterial bioburden must be reduced.

### Gregory Schultz

In this session the presenter discussed the role of biofilms in wound healing. The main points of the presentation were:

- Biofilms may play a very important role in non-healing wounds.
- Biofilms cannot be seen with the naked eye, but their products may be seen.
- Bacteria in biofilms have changed their gene expression, and many are in a dormant stage.
- Antibiotics and antiseptics are relatively ineffective at killing bacteria in biofilms.
- Biofilms may create a chronic state of inflammation due to an off-target effect of the proteases produced by mast cells, neutrophils and lymphocytes as they attempt to kill the bacteria in the biofilms.

In the presence of biofilms, the most effective treatment appears to be debridement.

### Honey

Several presenters discussed the role of honey in wound healing. Their conclusions are summarized below.

### Rose Cooper

The role of honey in wound management.

How does honey work in the management of wounds? Honey produces hydrogen peroxide. It promotes anti-bacterial activity through increasing osmolality, acidity (its pH is acidic) and additional phytochemical factors. Honey inhibits more than 80 microbial species. It is effective on bacteria, dermatophytes, yeast, protozoa and viruses. But not all honeys have the same effectiveness. Manuka honey appears to stimulate rapid healing in wounds; it sanitizes the wound, and can eliminate odours. MSSA, MRSA, VSE and VRE are sensitive to Manuka honey. Honey inhibits the biofilm of *Pseudomonas*. It has immunomodulatory effect on monocytes and causes spontaneous release of TNF, IL1 and IL6. Honey has anti-inflammatory properties, decreases edema, enhances debridement and provides a moist wound healing environment. However, wound healing might be inhibited by lack of oxygen.

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## CAWC 2008 Theme Meetings

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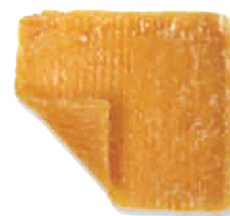
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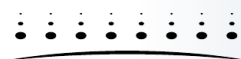
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