Striving for Excellence in Health Care

Basic Science

Population Health

Clinical Research

Winthrop Professor Fiona Wood
Conflict of Interest

Fiona Wood is an inventor of the ReCell device used for harvesting autologous cells for clinical use and also a founder of Clinical Cell Culture, the company that developed the ReCell device, and is currently a director of Avita Medical Ltd (formerly Clinical Cell Culture).

Fiona Wood’s Intellectual Property is assigned to the McComb Foundation with no personal financial gain.

Ethics approvals for the research have been granted.
Burn Care of the Future?

**Assessment** is key in understanding the extent of injury. **Debridement** is focused on tissue salvage. **Reconstruction** balances repair with regeneration.

Investigation of multimodality, multiscale characterisation, including confocal microscopy and synchrotron technology will quantify **assessment**.

**Debridement** using autolytic inflammatory control techniques with image guided physical methods will ensure the vital tissue frameworks are retained.

Tissue guided regeneration afforded by self-assembly nano-particles will provide the framework to guide cells to express the appropriate phenotype in **reconstruction**.

To solve the clinical problem a multi-disciplinary scientific approach is needed to ensure the quality of the scar is worth the pain of survival.
Dream
Tissue Regeneration
every minute 30,000-40,000 dead skin cells fall from your body! In approximately a month's time, your body has made a whole new layer of skin cells!

‘There is no magician’s mantle to compare with the skin in its diverse roles of waterproof, overcoat, sunshade, suit of armour and refrigerator. Sensitive to the touch of a feather, to temperature and pain, withstanding the wear and tear of three score years and ten and executing its own running repairs’
Gold standard

NOT
Skin Graft Scar
BUT
Normal skin appropriate for the body site and age of the patient
Regenerative Medicine

“Regenerative medicine replaces or regenerates human cells, tissue or organs to restore and establish normal function.”

C Masom P Dunhill Futuremedicine 2009
Today, biomedicine sits on the cusp of a new revolution: the use of microbial and human cells as versatile therapeutic engines.

MA Fischbach JA Bluestone WA Lim Scietranslationalmedicine 2013
Autologous cells
A therapeutic engine for burn wound healing?

Patient needs

Experience knowledge

Outcome

Environment of care
Future of scar free healing

• Meticulous attention to detail
• Use what we know
• Optimise the system
• Push the boundaries
ReCell® and Integra®

- How can we progress to an insitu tissue guided regeneration solution of both the dermis and epidermis?
- Integra dermal template seeded with cell suspension harvested from the dermal epidermal junction
- Epidermal cells migrate through the Integra to develop an intact epidermal layer
What are the consequences of conservative wound care in paediatric burns?
Donor site

• Dermal transfer with SSG
• Risk of depth?
• Risk of take?
• Risk of scar?
Cells harvested from the DEJ for immediate use
Use of cell therapies in partial thickness wounds

• Diagnosis to understand healing potential
• Understanding the therapeutic opportunity of cell therapy
• Understanding the changes needed in techniques and thinking
Cell based therapies in PT Burns

• CEA relies on cell adherence to irradiated 3T3 fibroblasts
• Can cells of the DEJ adhere to dermis in the zone of stasis?

• Wound bed preparation focused on salvage
Topical single application C-Jun inhibitor PYC 35 b

Natalie Giles et al Wound Repair Regen. 2008 Jan-Feb;16(1):58-64.
AP-1 Inhibition and Cell Death

**AP-1 family of transcription factors:**

- involved in proliferation, transformation, inflammation and cell death

**c-Jun**

- member of the AP-1 family of transcription factors
- activates cell death pathways and inflammation
Impact of First Aid

Reduces:
- Length of stay by 21%
- Rate of infection 56%
- Need for surgery by 52%
Scald injury treated with autologous cell suspension
Todler burn injury from a camp fire treated with a combination of; Meshed dermis and glaberous cells harvested from the dermal epidermal junction to the palm. Meshed Split thickness skin graft on deeper areas of the dorsum of the hand with cells sprayed over all areas of viable dermis to reduce the time to healing and reduce the scar potential.
Future of cell Delivery

- With biologically active complexes for tissue salvage and cell adhesion
- With variable phase scaffold techniques
- With a static architecture known to influence cell behaviour
- An interactive composite cell scaffold with external trigger potential
Survival data of patients burn injury < 15 years old

Adjusting for confounders U15 yrs burn patients $\times 1.6$ times mortality than general population attributable risk 38%

Could 59 of the 154 deaths in this group been prevented if they had not been burnt?

96%<20%TBSA in this cohort
Scar is abnormal

- Architecture
- Chemistry
- Cell phenotype

Scar is an abnormal structure tolerated by the host immune system

What role does the change in the immune surveillance and response play in life long impact of burn?

What is the role of the stress of burn on cellular senesce?
Is the methylation pattern of the fibroblast key to phenotype expression?

- Heritable changes in gene expression
- Modification of DNA without changes in DNA sequence
- DNA methylation is a common mechanism
- DNA methylation influences genes expression
Results comparing keloid with normal scar fibroblasts

Integrated data

- Differentially methylated with cut-off p-value <5 x 10^{-8}
  - 552 genes
- Differentially expressed with fold change >2.0
  - 2,973 genes

Red box highlights 99 genes

- 55 genes down-regulated
- 44 genes up-regulated
- 552 genes
- 2,973 genes
Regeneration V Repair
Elements needed for healing

• Source of cells capable of differentiation

• A framework for cell migration

• 3D spatial information of the wound area

• A feedback mechanism to guide self organisation
Figure 1 Sensation and Nerve Density

**1A** Mean Light Touch Thresholds

![Graph showing mean light touch thresholds with stars (*) indicating significant differences between Control and Scar groups.](image)

**1B** Mean two point discrimination score

![Graph showing mean two point discrimination score with stars (*) indicating significant differences between Control and Scar groups.](image)

**1C** Mean Sharp Touch Score

![Graph showing mean sharp touch score with stars (*) indicating significant differences between Control and Scar groups.](image)

**1D**

![Image showing epidermis and dermis with arrows indicating specific areas.](image)

**1E** PGP 9.5 Nerve Density (Dermis)

![Graph showing PGP 9.5 nerve density with lines for different groups.](image)

**1F** CGRP Nerve Density (Dermis)

![Graph showing CGRP nerve density with lines for different groups.](image)
Figure 2 Nerve Density

Nerve Density vs Injury Severity

![Graph showing nerve density vs injury severity with data points for PGP, PGP control, and scar categories.]

Scar $R^2 = 0.4163$

Control $R^2 = 0.3804$

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- CONTROL
- SCAR

![Graph showing connectivity and nerve density for control and scar categories.]

PGP
CGRP

Mission Impossible
- Wound Care of the Future?
Cell based therapies of the future

- Genetic manipulation of keratinocytes to produce a therapeutic effect e.g. insulin producing cells
- Use of cells to manipulate immune responses
- Use of cells to deliver a biological payload with external triggers
- Cells with environmentally adaptive pigment e.g. UV light responsive biological tattoos
Scar post flame burn treated with dermabrasion and resurfacing using autologous cell suspension using a post auricular split thickness skin biopsy
Time frame for data collection

**Acute psychological distress**
- Physiological Parameters
  - Weight
  - Pain & Itch
  - CVS fitness
  - Joint mobility
  - Muscle power
  - Hand & upper limb

**Follow up psychological tests**
- FBC, LFT
- Weight
- Pain & Itch
- Joint mobility
- Muscle power
- Hand & upper limb

**Confounds**
- Burn severity
- Co-morbidities
- Substance abuse

**Lower limb**
- Wound infection
- Wound healing

**Acute**
- 1
- 3
- 6
- 12
- 24

**Lower limb**
- Wound infection
- Wound healing

**Scarring**
- Need for reconstructive surgery

**ADL**
- QOL
Community Responsibility

Preventable Pathology

Advancing Technology

Health Budget

Preventable Pathology
Clinical practice is the art of problem solving.

Research provides innovative solutions.
Striving for Excellence in Health Care

- Basic Science
- Clinical Research
- Population Health

Education and training program translating into improved patient outcomes
This is the true joy in life,  
The being used for a purpose  
Recognised by yourself as a mighty one.  
The being a force of nature  
instead of a feverish little clod of ailments and grievances,  
Complaining that the world will not devote itself to making you happy  
I am of the opinion that my life belongs to the whole community, and  
as long as I live it is my privilege to do for it whatever I can  
I want to be thoroughly used up when I die,  
For the harder I work the more I live.  
I rejoice in life for it own sake.  
Life is no “Brief Candle: to me. It is a sort of splendid torch  
Which I have got hold of for the moment,  
and I want to make it burn as brightly as possible  
before handing it on to future generations.
Acknowledgements

Picture courtesy of The West Australian Primary Intention, The Australian Journal of Wound Management