

An interdisciplinary approach to the development of new skin technologies: *initial focus on wounds*

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Wounds

A silent epidemic.....

Significant impact.....





Non-healing diabetic wounds account for most amputations - one every 20 seconds globally



Wound care accounts for ~ half of community nursing care time



Infection rates for acute surgical wounds are between 6% and 10%



More than 15% of hospital in-patients have a preventable hospital-acquired wound



More than 25% of residents in aged care facilities have a wound



Wound care is the second most frequently billed item in general practice in many jurisdictions

Innovation is overdue

- Wounds are a major & escalating problem
 - Ageing population
 - We are living longer
 - Increased incidence with age
 - Higher expectations for quality of life
 - Wound repair is impeded with age & chronic diseases such as diabetes, obesity, cardiovascular disease



Innovation is overdue

- Affects people in all settings
- It is not managed well
- No-one is addressing it
 - No medical speciality
 - Fragmented care
 - No coordinated initiatives
 - No public profile
- We can't sustain this



Current Treatment?

- Hippocrates (460 – 377 BC)
 - Avoid standing or hanging the feet down, and abandon horse riding
 - Wash the ulcer, if necessary cut it out, and compress it to squeeze out the blood and humours



<http://students.ou.edu/K/Christina.L.Kay-1/hippocrates-5.jpg>

What we need to help people with wounds?

- Wound diagnostic tests
 - Active treatments that improve wound healing
 - Best practice treatment
 - Cost effective approaches
- more research



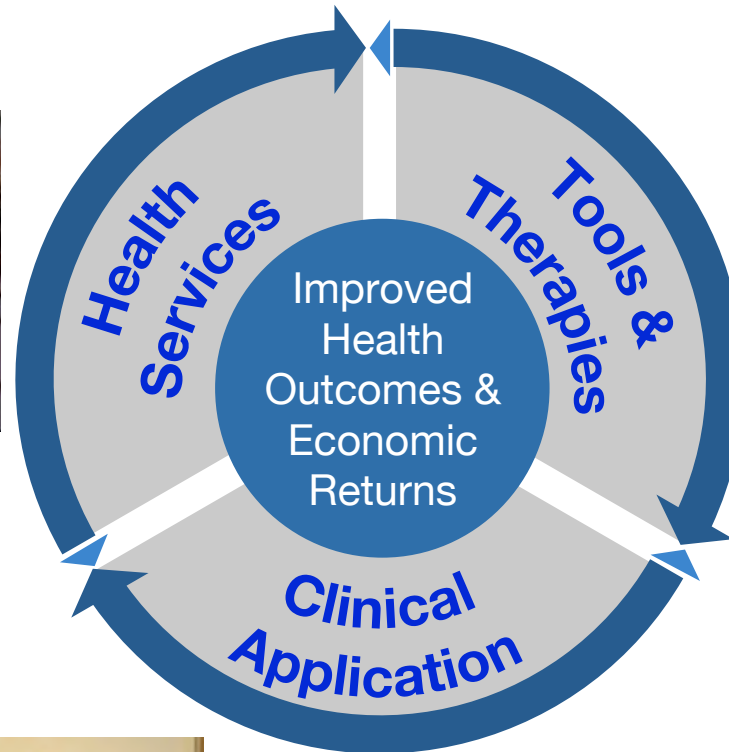
Why an Interdisciplinary Collaborative Approach is Required

- A national collaborative initiative is needed to address a nationally significant challenge
- Enables us to undertake the research that is necessary for us to tackle the whole problem:
 - Needs a whole of care approach
 - Requires input from researchers from diverse disciplines, clinicians and health care providers responsible for funding and delivering the care
 - Plus industry partners and new business models
 - None can address this challenge in an isolated approach
- It is a global problem, hence will have global reach and impact, particularly in tropical climates

Have Proposed 3 Integrated & Interdependent Themes in a pending TCR Programme Application



Prof Josip Car
Health Services Theme Leader



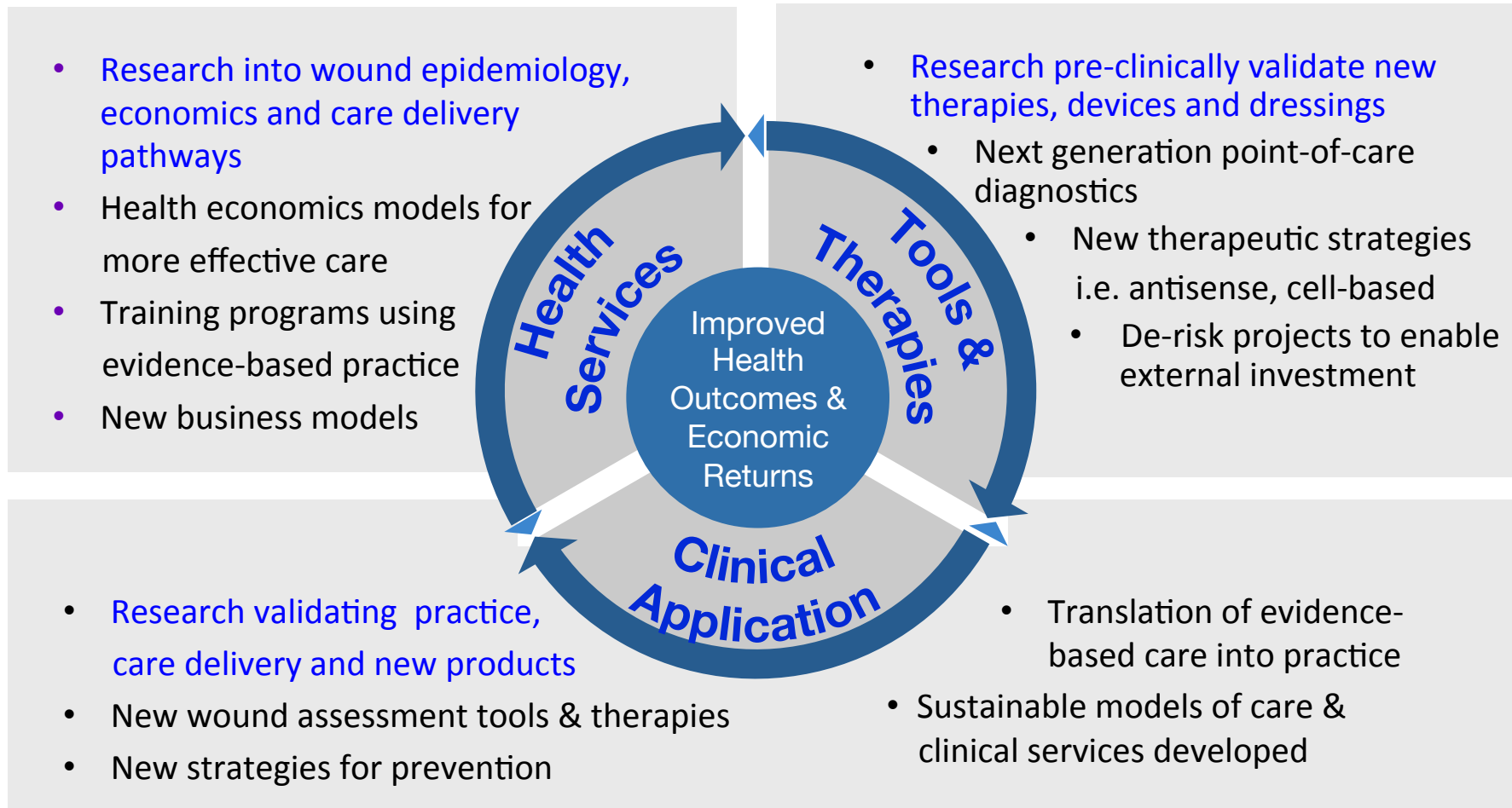
Prof David Becker
Tools & Therapies Theme Leader



Prof Artur Schmidtchen
Programme Leader
Clinical Application Theme Leader

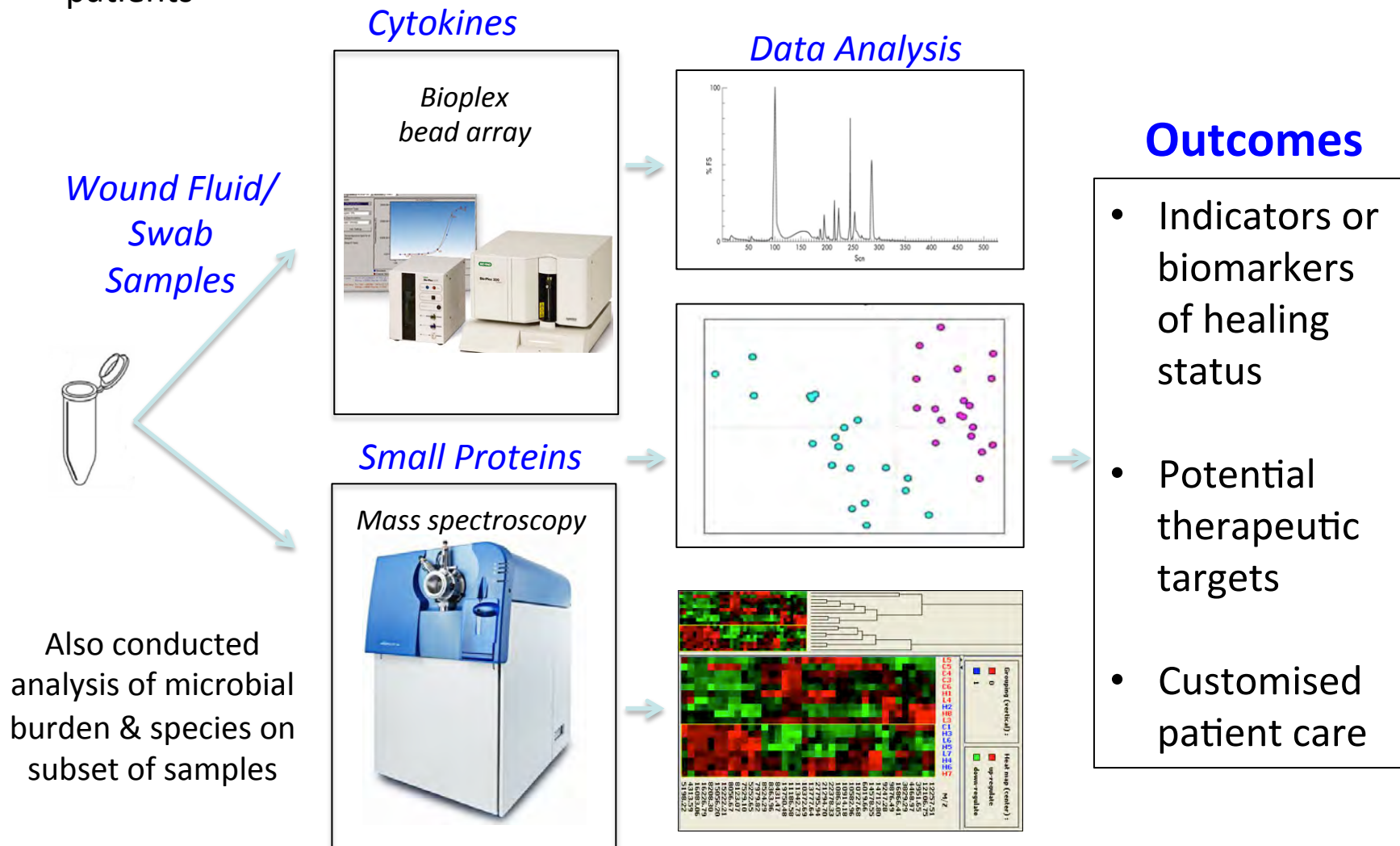
Programme involves 22 Co-Is and Collaborators from Health Care Organisations, A*STAR, NUS and NTU and overseas

Proposed Research & Outputs



Example: Biochemical profiling of chronic wound fluid

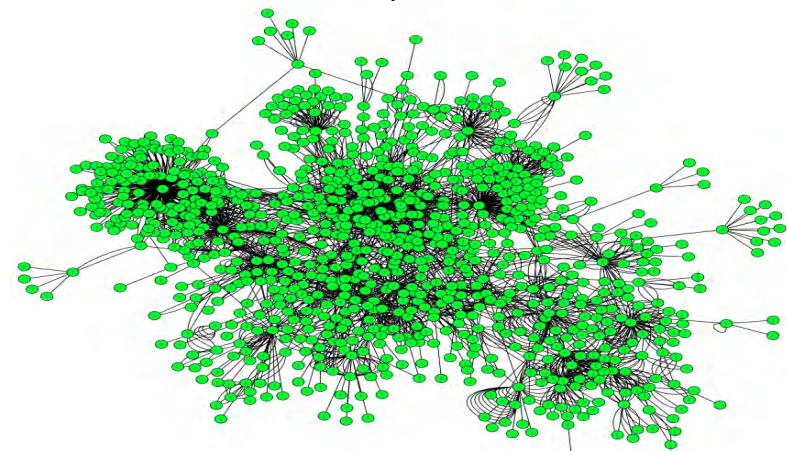
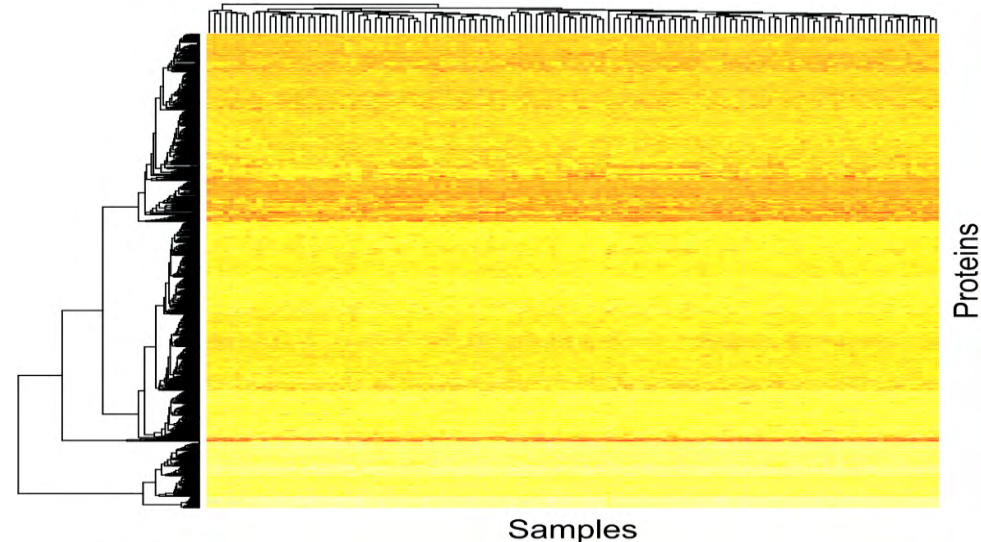
- **Objective:** Longitudinal study of how proteins, peptides, metabolites and breakdown products change/influence healing in order to develop diagnostic and prognostic tools
- Dynamic changes monitored in wound fluid samples in both healing and non-healing patients



Protein Biomarkers for Predicting Venous Ulcer Healing Outcome?

- Total patients recruited: 176
- Used SWATH Acquisition
- Ulcers analysed to date: 42
- Proteome depth: 916 proteins
 - *quantified by up to 25 individual measurements with a minimum false discovery rate of 1%*
- Proteomes measured to date: 240
 - *122 from healing wounds, 118 non-healing wounds*
- 91 proteins with significantly higher abundance in healing wounds and 111 proteins with significantly higher abundance in non-healing wounds
- 6 best proteins have a combined AUROC of 0.86.

➔ = Large, information rich data set

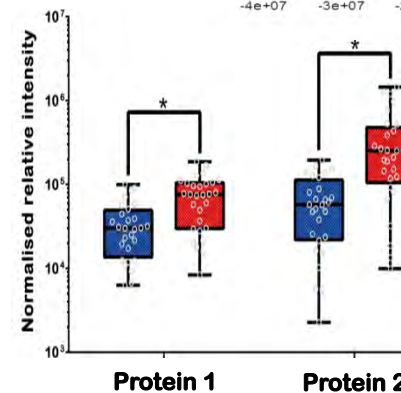
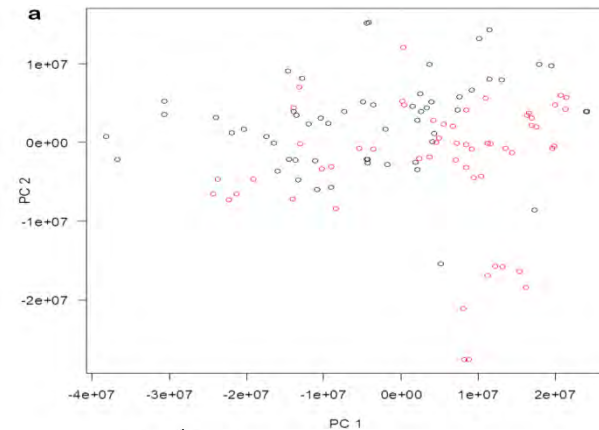


Protein interaction network of the 916 wound fluid proteins

Protein Biomarkers for Predicting Venous Ulcer Healing Outcome?

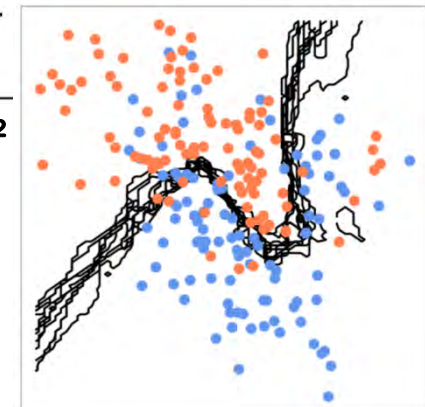
- Variance was measured in the proteome data to examine the contribution of protein abundance to the stratification of healing and non-healing cohorts
- Individual proteins were examined for differences in abundance between the healing outcome groups
- Proteins abundance data were then investigated in a “greedy iterative fashion” to identify an optimised suite of proteins as a final wound healing biomarker coordinate (**AUROC 0.86**)
- **Next steps: samples from second patient population being analysed**
- **Validation in an Asian Cohort**
- **Development of diagnostic tool**

PCA plot of variance between H vs NH



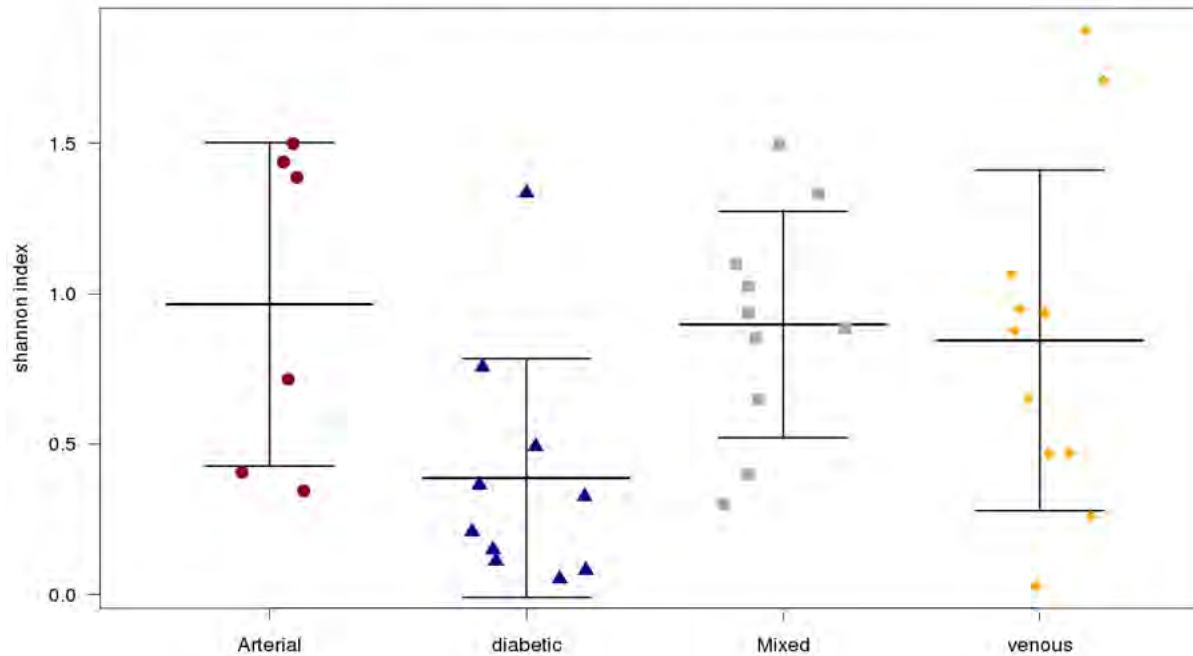
Univariate test of H vs NH

Machine learning algorithm reveals 6 biomarker candidates



Community Diversity Class $p=0.051966$ (anova)

$p < 0.05$ (anova)

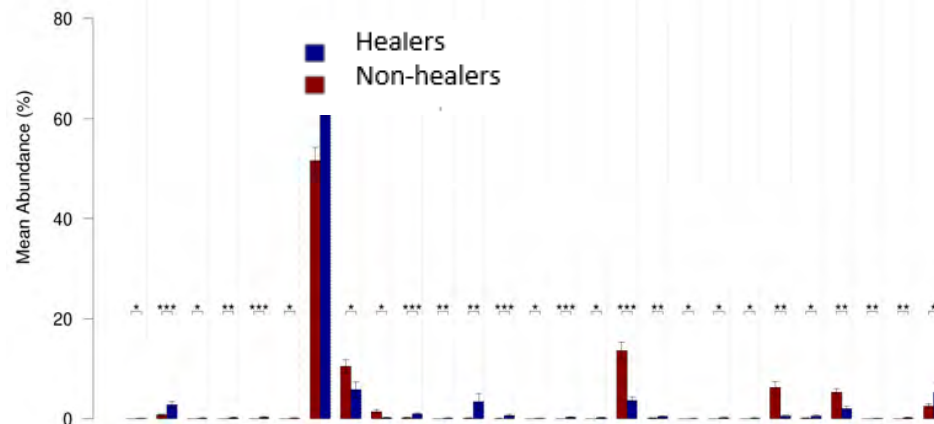


Microbiome of chronic wounds

- 30 healing and 30 non-healing wound samples analysed over 12 weeks of sampling, two-group comparison
- Largest known **temporal** dataset of wound microbiome (56 million valid DNA sequences)
- Clear association of bacterial species with healing wounds
- Clear association of bacterial species with non-healing wounds
- Distinct bacterial infective “biomarkers” indicative of healing vs non-healing wounds

Overall Abundance

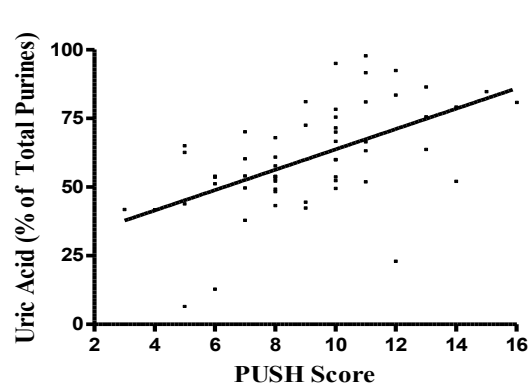
Genus ($p < 0.05$, anova)



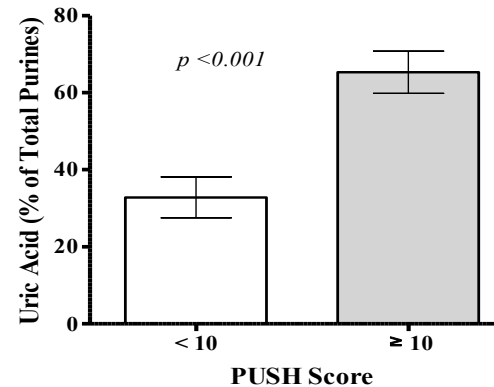
A/Prof Flavia Huygens, QUT



Other Profiling Activities → Revealed that Xanthine Oxidase Activity Related to Wound Severity

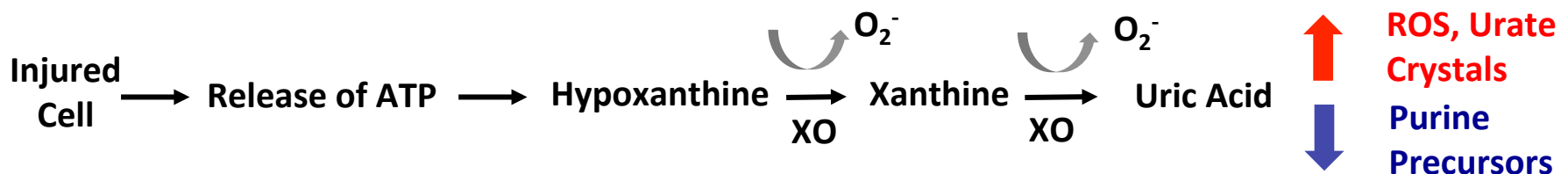


(a)



(b)

- Purine profiling revealed elevated levels of Uric Acid in clinically worse ulcers
- Xanthine Oxidase (XO) is active in the wound site generating free radicals
- Impaired clearance + sustained production of Uric Acid → urate crystals → further stimulating the inflammatory process
- Also decreased levels of Uric Acid Precursors in wound fluid from severe wounds
- Topical application of Purine Precursors → accelerate wound healing in animal and cell culture models
- **Proposed use of topical allopurinol (inhibits XOR) as therapy for venous ulcers**



Progress Towards Clinical Trial of Allopurinol

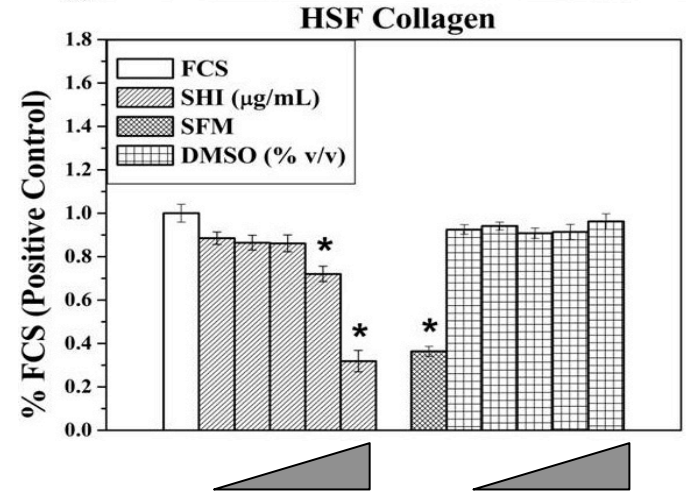
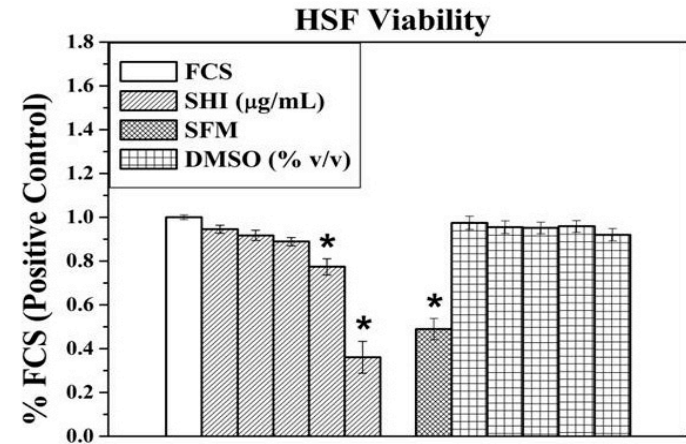
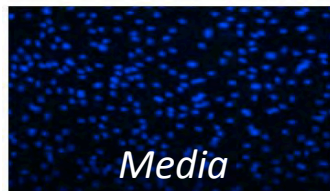
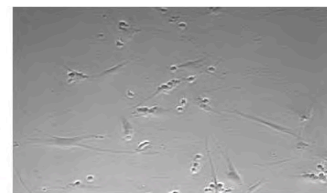
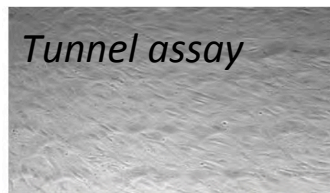
- Allopurinol – XO inhibitor, is cheap and well tolerated drug
- Orally prescribed for Gout treatment – 300-600 mg
- Breaks down to oxypurinol, which is also active XO inhibitor
- Previously used topically with no adverse effects
- Formulation:
 - Active – 20 mg Allopurinol in 5 g Solosite
 - Placebo – 5 g of Solosite
 - Stability Studies and Drug Release Experiments
- Hypersensitivity study (15 min exposure) recently completed → no adverse effects, increased granulation tissue ($p=0.034$), decreased slough tissue ($n=0.011$)
- **Next steps = pilot trial assessing efficacy (70 patients)**



Dr. Melissa Fernandez, Senior Research Fellow

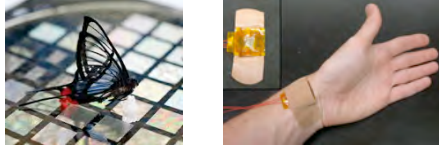
Learning from Other Cultures

- **Shikonin, a TCM used anecdotally for centuries to remediate scars**
- Used normal and hypertrophic scar-derived skin cells to investigate underlying mechanisms:
 - Induced apoptosis
 - Reduced cell viability and collagen production
 - Greater effects on fibroblasts
 - Reduced collagen I, II and α -smooth muscle actin gene expression, and TGF-beta signalling
 - **Next Steps = formulation & pre-clinical studies in porcine model**



Learning from Other Disciplines

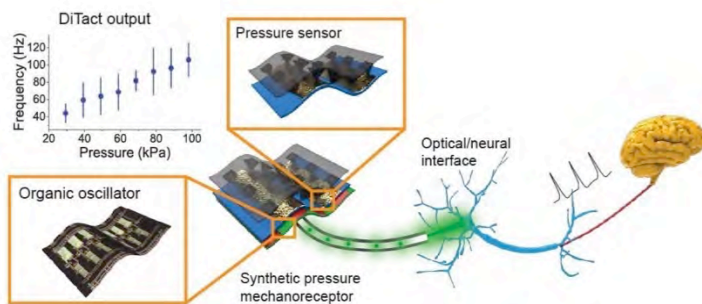
Ultra-high sensitivity e-skin & Smart pressure monitoring bandages



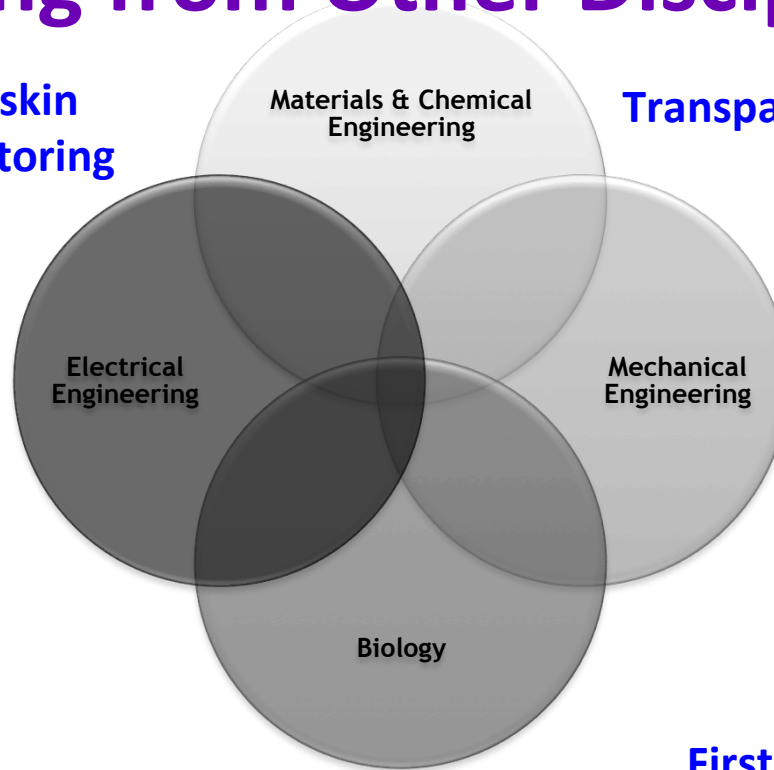
S. Mannsfeld, **B. C-K. Tee**, et al. Nature Materials 9 (2010).

G. Schwartz, **B. C-K. Tee**, J. Mei et al., Nature Communications 2013

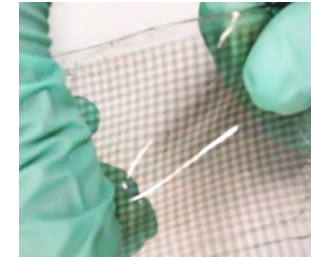
Bioinspired artificial mechanoreceptor



B. C.K. Tee*, A. Chorto*, A. Berndt* et al., Science, in press, Oct 2015

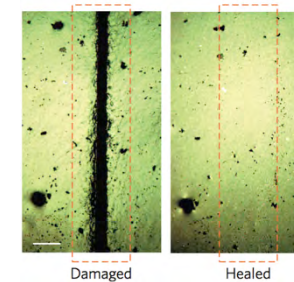


Transparent stretchable eskin



DJ Lipomi*, M. Vosgueritchian*, **B. C-K. Tee***, et al. Nature Nanotechnology 6 (2011). *equal contribution

First self-healing e-skin



B. C-K. Tee*, C. Wang*, R. Allen et al. Nature Nanotech, 7 825-832 (2012).

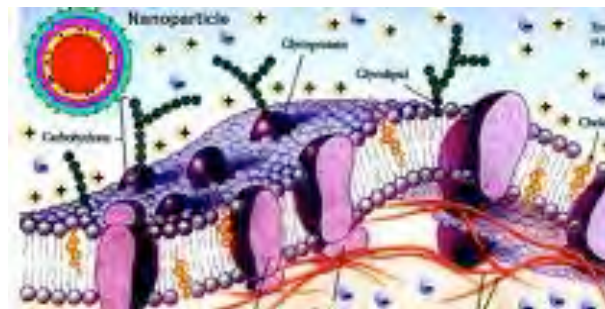
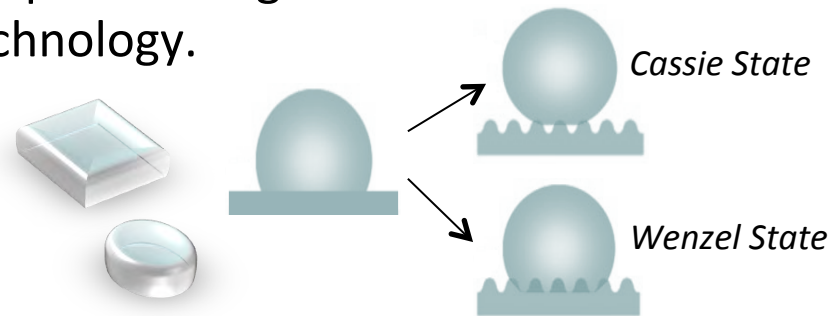
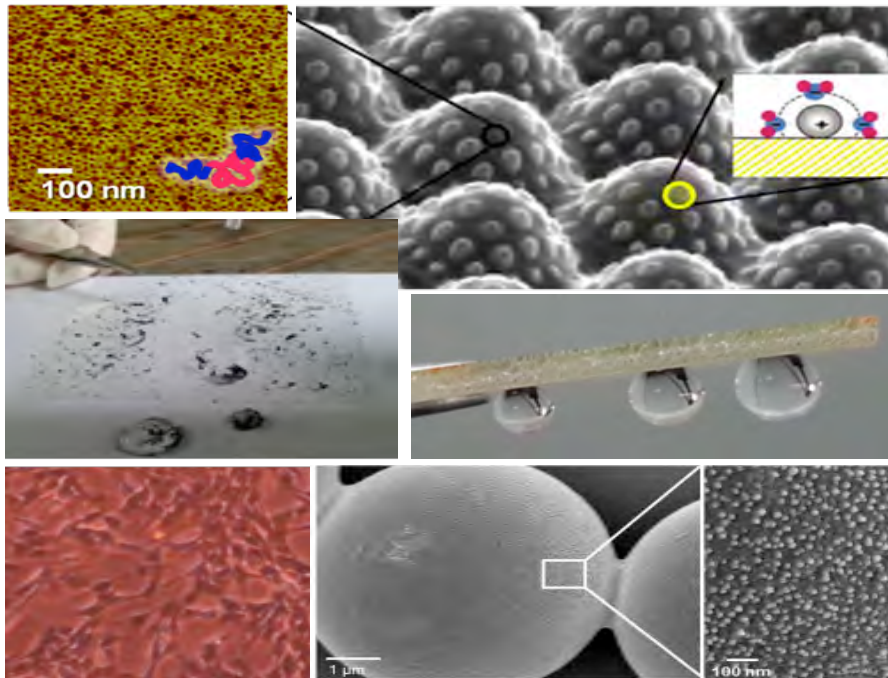
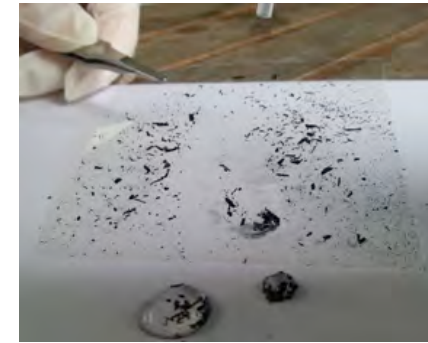


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Learning from Other Disciplines

Functional Surfaces:

- Customized surface wetting
- Surface protein interactions
- Smart, responsive surfaces (pH, T)
- Low fouling surfaces
- Material & surface technologies for improved diagnostics and biomedical applications, tissue culture and biotechnology.



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- **And patients with wounds**

