Dermatology Innovation Forum
Washington DC, USA 28 February 2019

CGskincare Ltd
Serènesse

Chris Griffiths

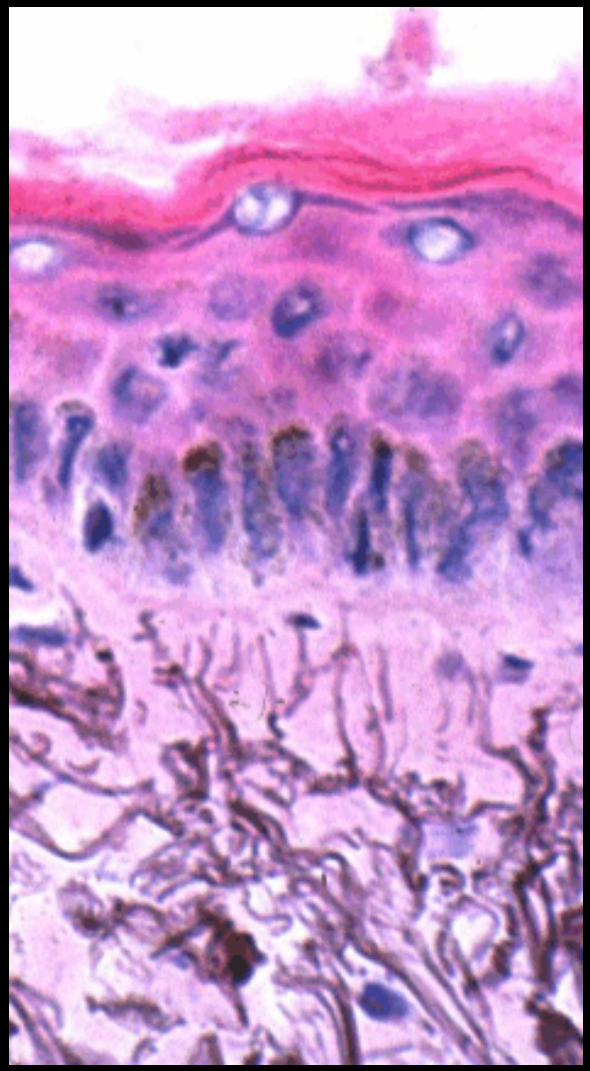
Manchester
Academic Health
Science Centre

Chronology

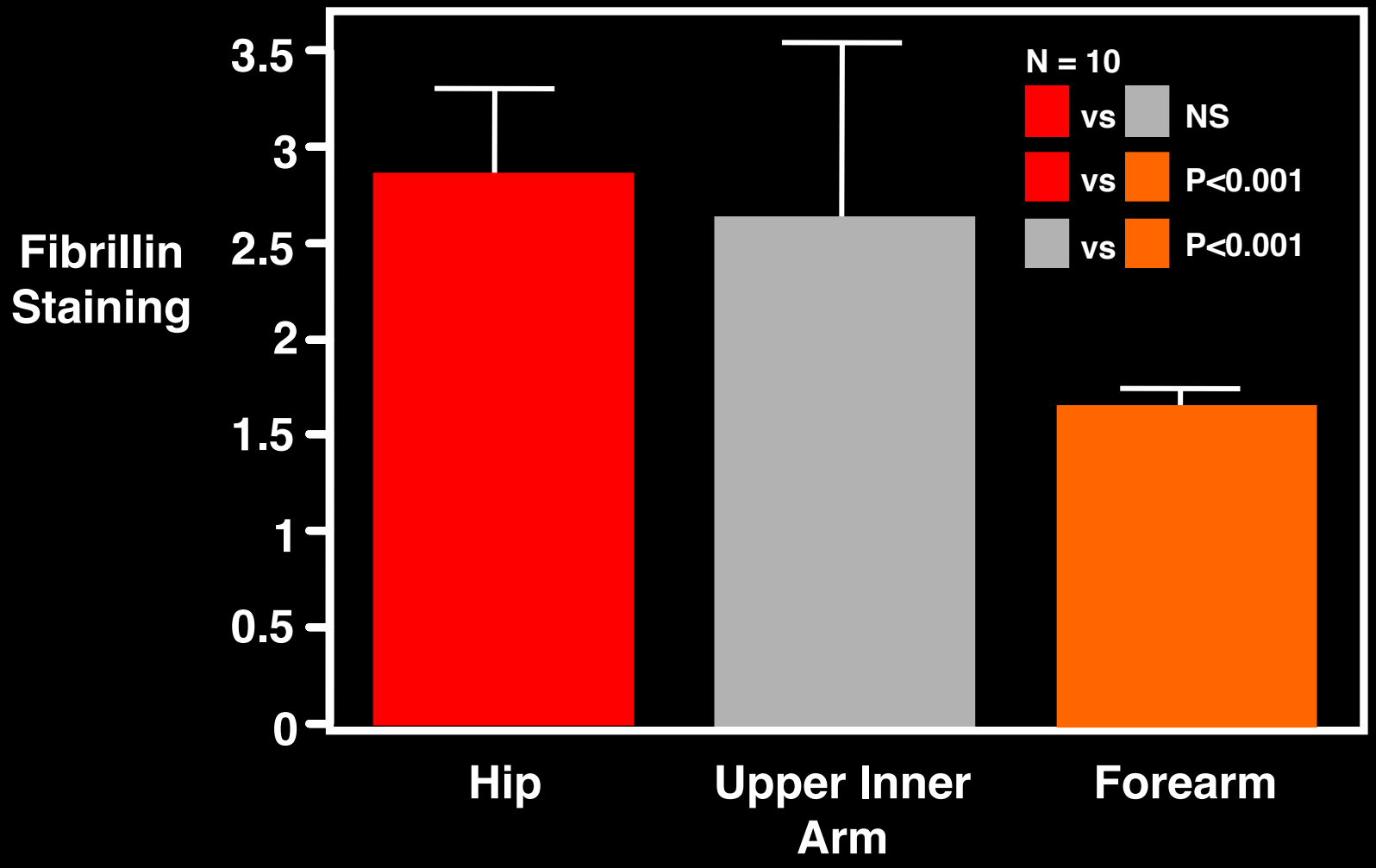
- Michigan - Worked on original studies of topical retinoids for photoaged skin J&J Renova 1992-3
  - Retinoids repair by stimulating collagen production
- Manchester – responsible for development and testing of Boots No7 Protect and Perfect 2007
  - Development of the Manchester Assay
- Formulated own product - formed company CGskincare Ltd

Elastic fibres
composed of elastin
and fibrillin
microfibrils

Microfibrils
strengthen elastic
fibre and transmit
forces between
dermis and epidermis

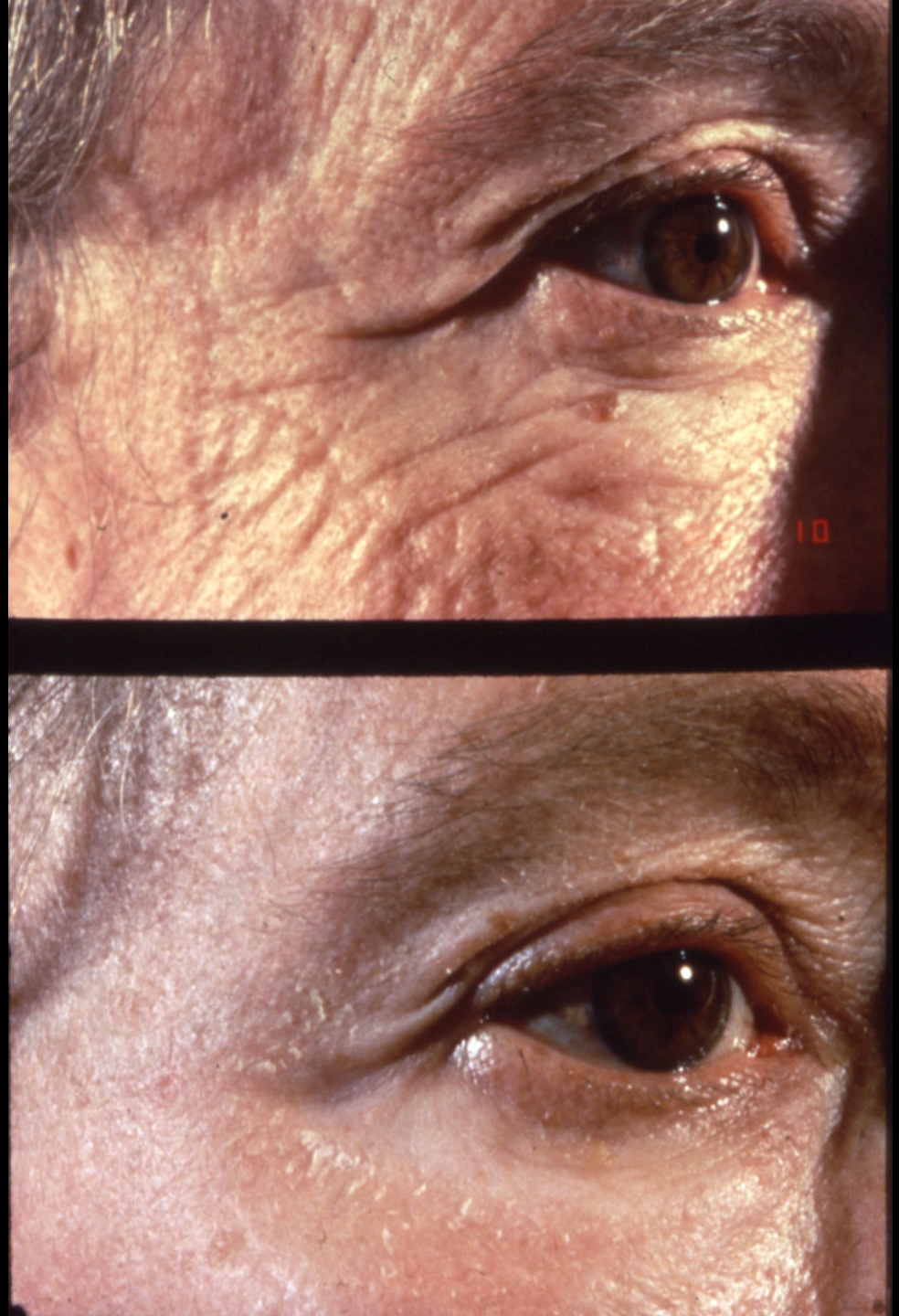


Fibrillin is Reduced in Papillary Dermis of Photoaged Skin



Watson, Griffiths, Craven et al J I D 1999 ; 112 : 782-7

Baseline

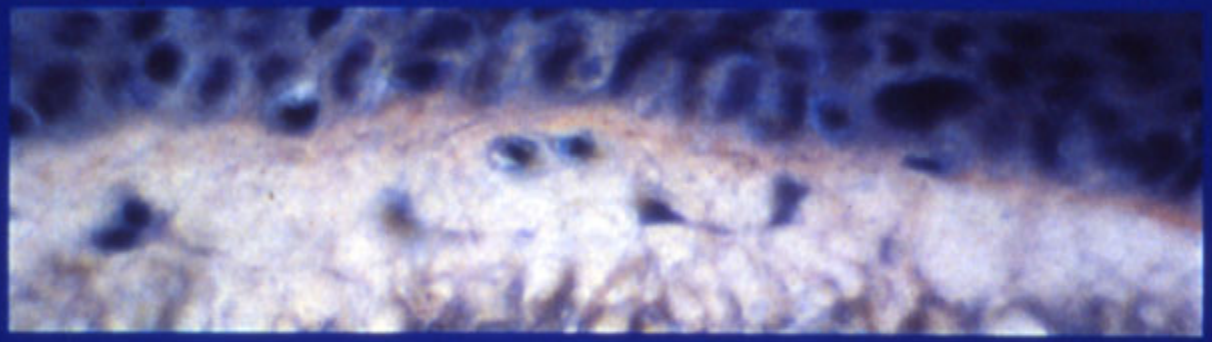


4 years

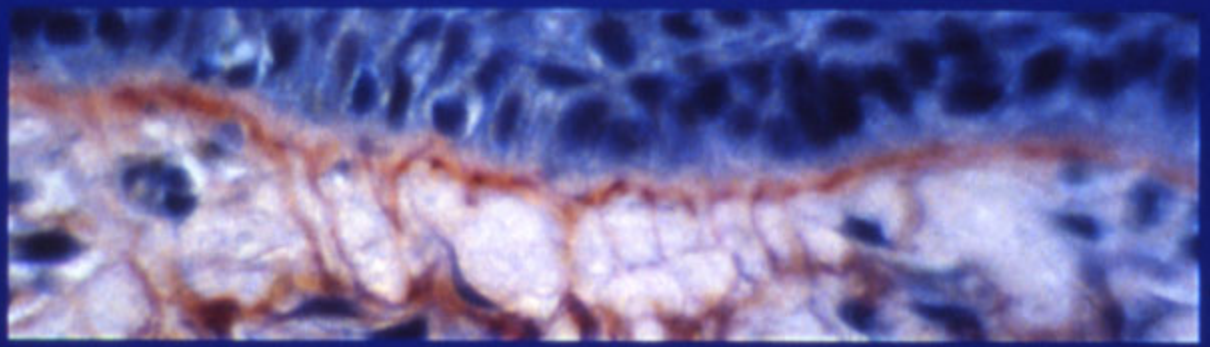
Retinoic Acid 0.1% Repairs Photoaged Skin

Long-term topical treatment with RA repairs the fibrillin-rich microfibrillar network in photoaged human facial skin

Baseline

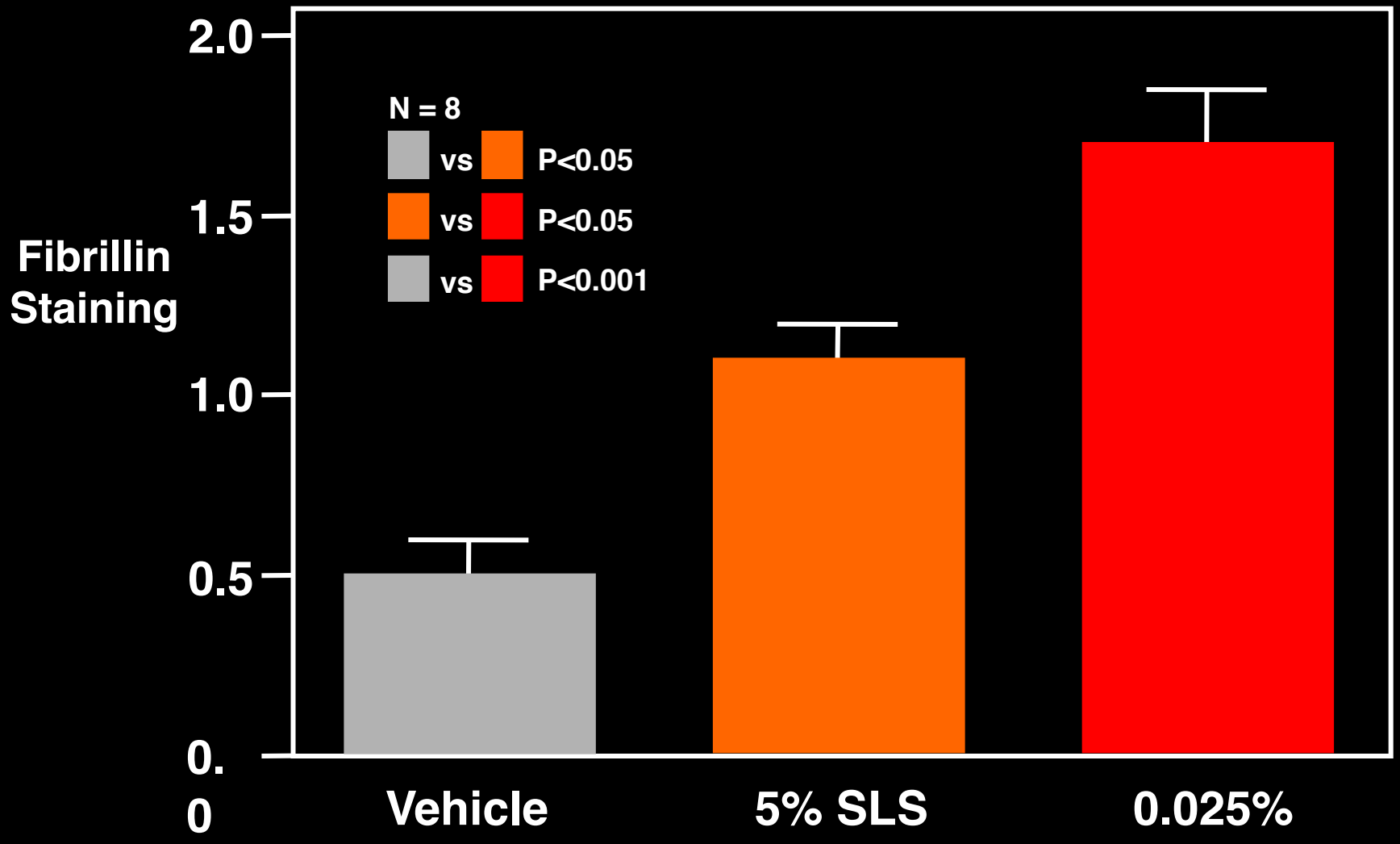


192 weeks treatment



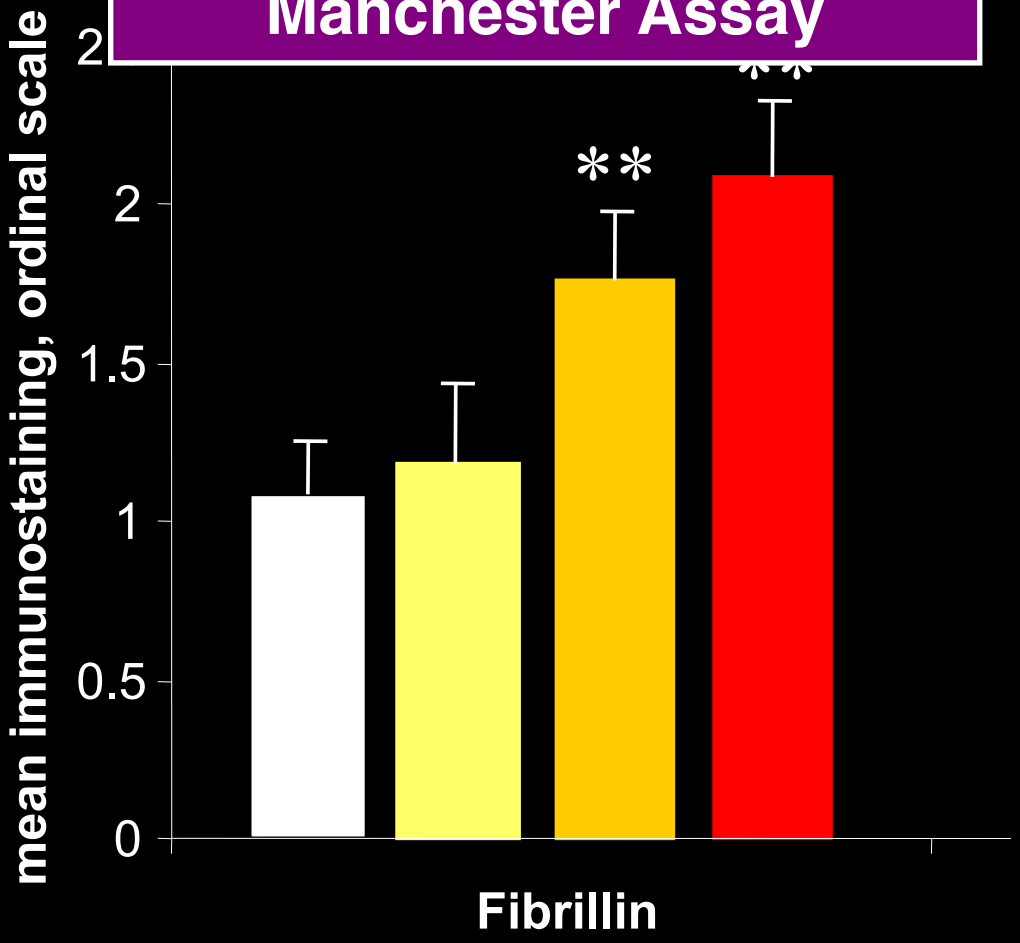
Watson,Craven,Kang,Jones,Kielty,Griffiths JID

Photoaged Skin Manchester Patch Test Assay - RA Increases Fibrillin-1



Watson et al JID 2001;116: 672

An Over-the-Counter Cosmetic Can Restore Fibrillin in 12 day Manchester Assay



baseline moisturiser

2% active serum

6% active serum

0.025% all-*trans* RA

**, p < 0.01

*, p < 0.05

Watson *et al*, *Br J Dermatol 2008; 58:472-7*

The Media

- Boots Company - No. 7 “Protect & Perfect”
- BBC flagship science programme “Horizon”
- Filmed Sept 2006; Broadcast March 2007
- Media frenzy!


United Kingdom
Country Boundary
Road
River
Sovereign State Capital
Country Capital
Norwegian Sea
SHETLAND ISLANDS
North Sea
Lerwick
NORTH ATLANTIC OCEAN
ORKNEY ISLANDS
Kirkwall
Thurso
Stornoway
Lewis with Harris
The Minch
North Uist
South Uist
Skye
Rum
HEBRIDES
Mull
Oban
Islay
Arran
NORTH ATLANTIC OCEAN
Londonderry
Belfast
NORTHERN IRELAND
Lough Neagh
Sligo
Lough Allen
Dundalk
Westport
Drogheda
Lough Ree
Galway
Dublin
IRELAND
Shannon
Lough Derg
Limerick
Tralee
Waterford
Wexford
Cork
Fishguard
Saint George's Channel
Irish
Penzance
ISLES OF SCILLY
(Crown Dependency)
FRANCE

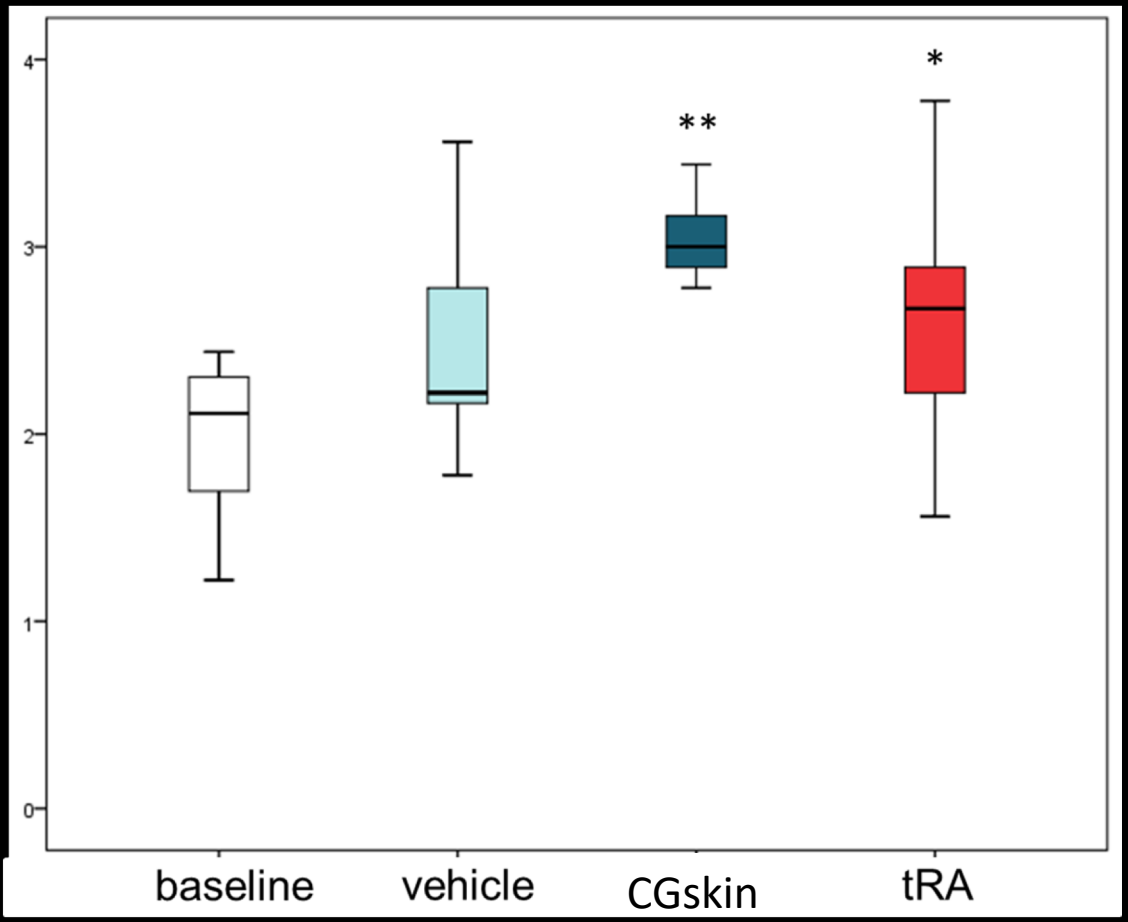
Bilberry

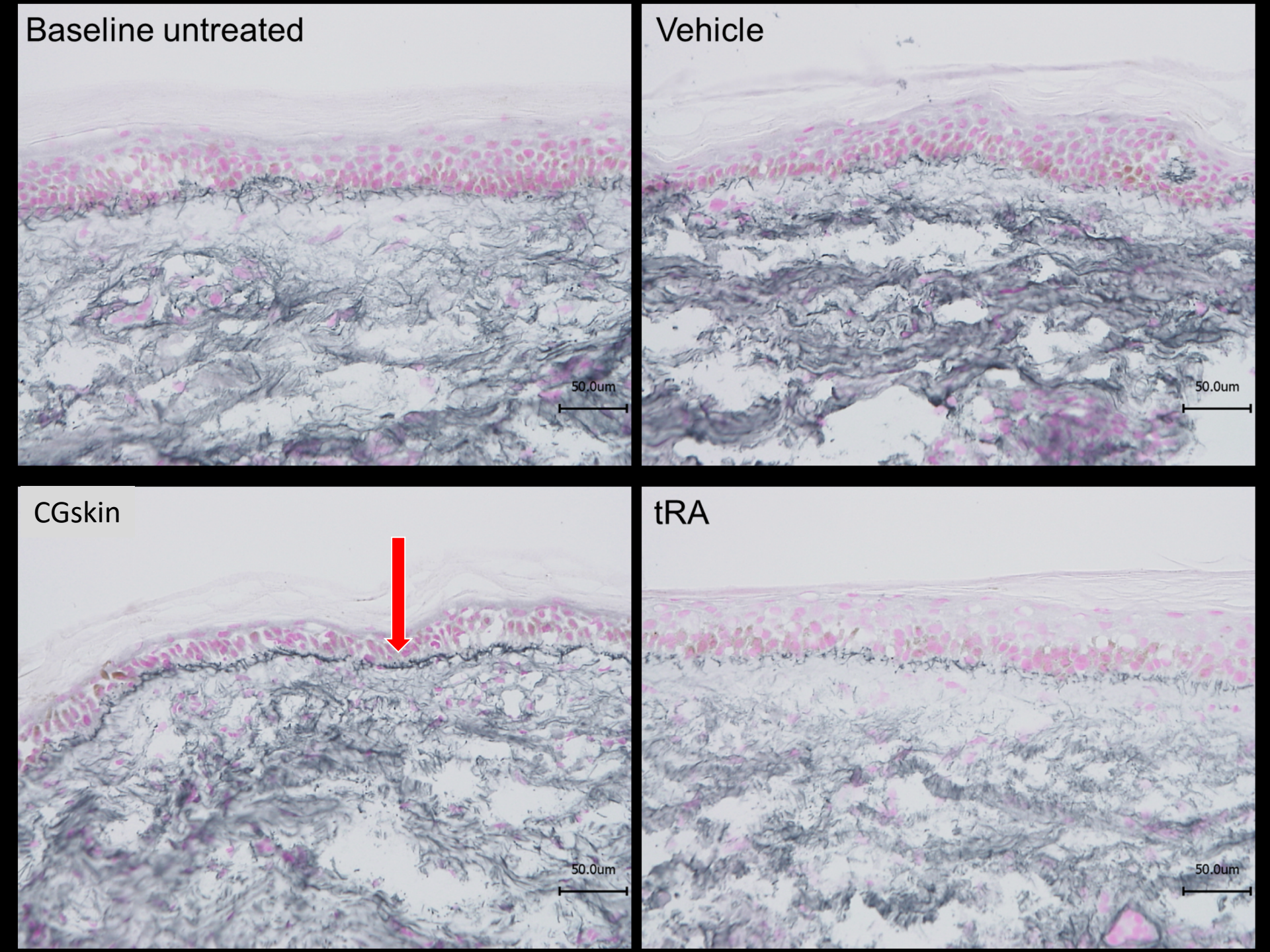
CGskincare

- Proof of Principle funding from UMIP (£90K)
- Formulation in Leicester Andy Juj
- Tested in Manchester Patch Test Assay for ability to repair photoaged skin
- Positive data for the night cream Serènesse
- Positive use test reports from consumer panel: Night Cream, Day Cream, Eye Gel and Cleanser
- University Spinout 2015
- £120K 2016 Clinical trials, manufacture, Internet selling

> *"I have loved using all four product when and where can I buy them?!"*
>
> *LB, Macclesfield*

Serènesse Stimulates More Fibrillin Than does Tretinoin in Manchester Assay




Baseline untreated
50.0um
Vehicle
50.0um
CGskin
50.0um
tRA
50.0um

Deposition of fibrillin-rich microfibrils in photoaged dermis following topical treatment with Erés – a novel anti-ageing product

LF Cotterell and REB Watson

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Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

INTRODUCTION & AIMS

Skin ageing is the result of both intrinsic, time-dependent ageing combined with the effects of extrinsic factors, such as chronic solar ultraviolet exposure; these extrinsic factors are thought to accelerate the natural ageing process.

We have previously shown that loss of fibrillin-rich microfibrils (FRM) from the papillary dermis is an early event in photoageing[1] and is a useful marker of outcome when studying potential repair agents using the Manchester patch test assay[2-5].

In the current study, we have examined whether a novel anti-ageing cosmetic, Erés (CG Skin, UK) shows utility in repairing photoaged skin.

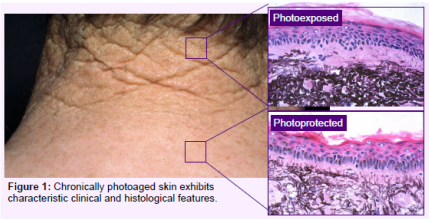

Figure 1: Chronically photoaged skin exhibits characteristic clinical and histological features.

Note the loss of fibrillin-rich microfibrils (FRM) from the papillary dermis in photoexposed skin (histological identification using Weigert's resorcin fuchsin).

from Tsoureli-Nikita et al. Photochem Photobiol Sci *5:160-4, 2006*

MATERIALS & METHODS

- 10 healthy photoaged volunteers were recruited (4M, 6F; 66 – 81 years);
- Each volunteer was treated on the affected dorsal aspect of their photoexposed, photoaged forearm with:
  - the novel formulation, Erés (active);
  - the component base minus active ingredients (vehicle);
  - occluded but untreated (negative control).
- Products (30µl) were applied to the skin via Finn chambers every 4-days for a 12-day period. On day 8, all-*trans* retinoic acid (tRA) was applied under a separate patch (positive control);
- Punch biopsies (3mm diameter) were taken on day 12 for histological analysis (measurement of epidermal thickness) and immunohistochemistry (FRM).
- Epidermal thickness was quantified by image analysis (ImageJ; NIH, Bethesda, MA, USA). Analysis of FRM was semi-quantitative, as previously described[1-5]. Statistical analyses employed repeated measures ANOVA with significance taken at the 95% confidence level (SPSS v22, IBM Corp.).

RESULTS

Following topical treatment of photoaged skin with these investigation formulations, only tRA induces significant epidermal thickening (*p*<0.05; *figure 2*)

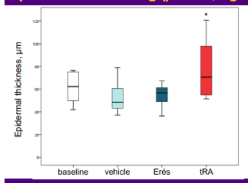

Figure 2: Quantification of epidermal thickness.

Image analysis reveals that only tRA treatment causes a significant thickening of the epidermis, *p<0.05.

Only subjects who had a positive response to tRA were included in the analysis. Both tRA and Erés were shown to induce FRM deposition (tRA, *p=0.002; Erés, **p=0.001; *figure 3, figure 4*).

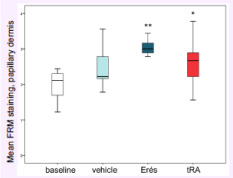

Figure 3: Quantification of FRM response.

Both tRA and Erés were found to induce a significant increase in the amount of FRM in treated skin, over that observed at baseline (tRA, *p=0.002; Erés **p=0.001).

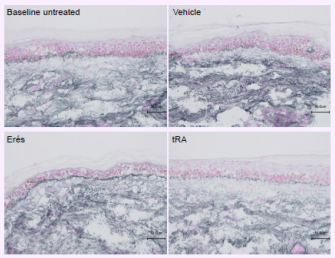

Figure 4: Representative photomicrographs of photoaged skin treated during the Erés Manchester patch test.

DISCUSSION

The novel, over-the-counter anti-ageing product, Erés, is capable of partially repairing the dermal extracellular matrix damage caused by chronic photoexposure;
Further research is required to ascertain whether this repair is specific to the elastic fibre system of skin, or whether benefit might also occur within the collagenous matrix.

References

1. Watson REB, Griffiths CEM, Craven NM, Shuttleworth CA, Kielty CM: Fibrillin microfibrils are reduced in photoaged skin: Distribution and abundance at the dermal-epidermal junction. *J Invest Dermatol* 112:782-7, 1999
2. Watson REB, Craven NM, Kang S, Jones CJP, Kielty CM, Griffiths CEM: A short-term screening assay, using fibrillin-1 as a reporter molecule, for photoaging repair agents. *J Invest Dermatol* 116:672-8, 2001
3. Farwick M, Watson REB, Rawlings AV, Wollenweber U, Lersch P, Bowden JJ, Bastrilles JY, Griffiths CEM: Salicyloyl-phytosphingosine: A novel agent for the repair of photoaged skin. *Int J Cos Sci* 29:319-29, 2007
4. Watson REB, Long SP, Bowden JJ, Bastrilles JY, Barton SP, Griffiths CEM: Repair of photoaged dermal matrix by topical application of cosmetic anti-ageing product. *Br J Dermatol* 158:472-7, 2008
5. Tran C, Michelet JF, Simonetti L, Fiat F, Garrigues A, Potter A, Bazin R, Segot E, Watson REB, Griffiths CEM, De Lacharriere O. *In vitro* and *in vivo* studies with tetra-hydro-jasmonic acid (JR2412) reveal its potential to correct signs of skin ageing. *J Eur Acad Derm Venereol* 28:415-23, 2014

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Salford Royal NHS Foundation Trust

Manchester Academic Health Science Centre

A novel topical anti-ageing product, Erés, induces the re-organisation of fibrillar collagens in photoaged human skin

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Manchester Academic Health Science Centre, Manchester, UK

INTRODUCTION & AIMS

Skin ageing is the result of both intrinsic, time-dependent ageing combined with the effects of extrinsic factors, such as chronic solar ultraviolet exposure (photoageing); these extrinsic factors are thought to accelerate the natural ageing process. As well as changes to the elastic fibre network of skin[1], photoageing also impacts on the fibrillar collagen matrix, reducing pro-collagen I synthesis and deposition (*figure 1*).

Figure 1: Chronically photoaged skin exhibits characteristic clinical and histological features Adapted from [2,3]

In the current study, we have examined whether a novel anti-ageing cosmetic, Erés (CG Skin, UK) shows utility in repairing photoaged skin.

MATERIALS & METHODS

- 8 healthy photoaged volunteers participated in this research (66–81 years);
- Each volunteer was treated on the affected dorsal aspect of their photoexposed, photoaged forearm with:
  - the novel formulation, Erés (active);
  - the component base minus active ingredients (vehicle);
  - occluded but untreated (negative control).
- Products (30µl) were applied to the skin via Finn chambers every 4-days for a 12-day period. On day 8, all-*trans* retinoic acid (tRA) was applied under a separate patch (positive control);
- Punch biopsies (3mm diameter) were taken on day 12 for histological analysis (picrosirius red staining for fibrillar collagens; PSR, *figure 2*) and atomic force microscopy (tissue AFM) to assess collagen organisation plus immunohistochemistry (pro-collagen I; *figure 3*) and qPCR (COL1) for collagen synthesis.
- Statistical analyses employed repeated measures ANOVA with significance taken at the 95% confidence level (SPSS v22, IBM Corp.).

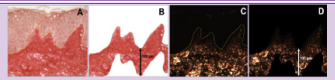

Figure 2: PSR staining for fibrillar collagens. Frozen sections were prepared and stained with PSR for collagen fibres; three areas from a PSR-stained section were captured by bright field (A, B) and polarised (C,D) microscopy (magnification x200). Positive stained fibres were quantified in pixels to a depth of 100µm and the area calculated (B, D).

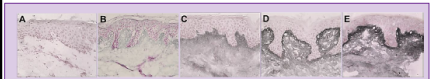

Figure 3: Representative images of pCI immunostaining. The scale was: 0 = no stain (A); 1 = diffuse with light grey stain at dermal-epidermal junction (DEJ; B); 2 = dark grey at DEJ (C); 3 = very dark grey at DEJ (D) and; 4 = maximal staining with very dark grey/black staining (E).

References

1. Watson *et al.* (1999) Fibrillin microfibrils are reduced in photoaged skin: Distribution and abundance at the dermal-epidermal junction. *J Invest Dermatol* **112**:782-787
2. Talwar *et al.* (1995) Reduced type I and type III procollagens in photodamaged adult human skin. *J Invest Dermatol* 105:285-290
3. Tsoureli-Nikita *et al.* (2006) Photoageing. *Photochem Photobiol Sci* 5:160-164

RESULTS

Treatment with a novel anti-ageing cosmetic increased the amount of fibrillar collagens in photoaged human skin

As observed in numerous other studies, tRA had no effect on the deposition of fibrillar collagens in treated skin. However, treatment with the novel anti-ageing formulation, Erés, significantly increased the amount of organised fibrillar collagens in the papillary dermis (mean % ± SD: occluded, untreated baseline, 34.5±2.1; vehicle, 46.9±1.8; Erés, 47.8±1.4; tRA, 31.2±2.0; P<0.05; *figure 4*).

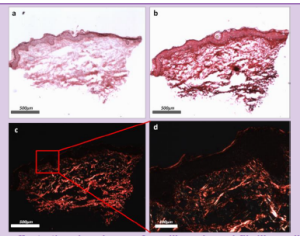

Figure 4: Erés effects the abundance of papillary dermal fibrillar collagens. A-B PSR-stained sections observed under brightfield (A) untreated baseline, (B) Erés. C-D Erés -treated section viewed under polarised light microscopy (C) low magnification, scale bar, 500µm, (D) high magnification, scale bar, 200µm.

Erés treatment resulted in significantly decreased collagen periodicity

Sharp tip AFM identified re-organisation of the fibrillar collagens in the papillary dermis. The mean periodicity of collagen fibres in untreated baseline skin (A 64nm ±1.2) and vehicle treated skin (B, 60 nm ±1.9) were significantly longer than those in Erés -treated skin (50nm ±1.8, P<0.05; *figure 5*).

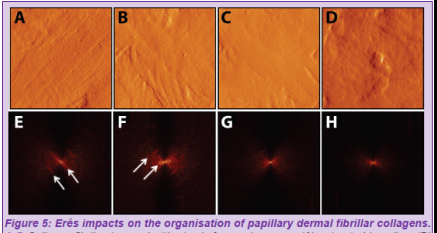

Figure 5: Erés impacts on the organisation of papillary dermal fibrillar collagens. A-D Collagen fibrils observed with atomic force microscopy (A) untreated baseline, (B) vehicle, (C) Erés, (D) tRA (magnification x200). E-H Fourier transform of images to allow discernment of periodicity (E) untreated baseline, (F) vehicle, (G) Erés, (H) tRA.

IHC and qPCR do not identify significant alterations in gene expression of COL1 or deposition of pro-collagen I

Neither qPCR or immunohistochemistry for the amino-propeptide of collagen altered following treatment with any formulation (data not shown).

CONCLUSIONS

Treatment of photoaged skin with the novel anti-ageing treatment increased the amount of fibrillar collagens in the papillary dermis; however, synthesis and deposition of collagen I was not stimulated. This implies that the treatment induced a reorganisation of the collagen matrix as further evidence by the alternations in collagen periodicity we have observed.

Further study is required to assess whether this is mediated by influencing the expression of matrix organising molecules such as members of the small leucine-rich protein family.

We are grateful to CG Skin Ltd. for financial support of this project

Serènesse Repairs Photoaged Skin

- **Serènesse is capable of partially repairing the dermal extracellular matrix damage caused by chronic sun exposure;**
- **Serènesse increased deposition of fibrillin-rich microfibrils and the amount of fibrillar collagens in the papillary dermis.**
- **Previous work has shown that such data in the Manchester Patch Test Assay equate to clinical repair in real-wold use tests**
- **Product to be launched in May 2019**