

limits cell spreading<sup>5</sup>, and prompts adhesion sites to align and provide signals that must be distinct from those received from a non-confined ligand<sup>2</sup>. Cell collectives also sense open edges via the reduced impact of auto-inhibitory activity, such as the release of the cytokine TGF- $\beta$  between cells<sup>6</sup>, or via the lack of cell–cell junctions mediated by cadherins or other adhesion systems towards the free edge<sup>7</sup>. The relevance of the curvature — in addition to the influence of free edges — demonstrated by Kilian and co-authors implies that multiple, possibly additive variables are integrated in the cell, balancing decisions such as those leading to the development of stem-cell-like properties. As also shown by the authors, the cells sense curved-edge topologies through  $\alpha_5\beta_1$  integrins (which bind fibronectin) and through mitogen-activated protein kinase (MAPK; which integrates multiple upstream signals from integrin and growth-factor receptors) signalling. Thus, geometry sensing overlaps, or integrates, with central-adhesion and growth-factor-receptor pathways involved in stemness regulation in normal and neoplastic cells<sup>3,8</sup>.

Stresses present at the edge may vary, depending on curvature, and support different types of focalized adhesions and their role in mediating different levels of actomyosin contractility and Rho/ROCK signalling, not unlike the machinery underlying cell sensing of substrate stiffness<sup>1,8</sup>. Similarly, a confining edge could impose a ‘jammed’ state, in which cells undergo regulation of cell shape and reinforce cell–cell junctions towards

one side, but lack the junction near the free edge<sup>9</sup>. In addition, extracellular topologies may directly translate into membrane curvature and altered tension, which induce signalling to the actin cytoskeleton via F-BAR domain proteins<sup>10</sup>. Thus, substrate geometry potentially controls cancer stem cell induction via an integrated programme comprising cell–matrix and cell–cell adhesions, as well as membrane curvature regulation and trafficking proteins. However, the specific mechanosensory mechanisms by which cells translate substrate curvature into differential signalling remain to be resolved. Such understanding is essential, since cells exposed to complex conditions *in vivo* are often mobile and encounter multiple topologies sequentially, thereby being likely to face tissue geometries that consolidate a malignant phenotype. Knowledge of how mechanosensory adhesion mechanisms and autocrine growth factor signalling cooperate may thus open new avenues for cancer therapy, such as targeting the curvature-sensing function therapeutically in order to revert stemness and to sensitize cancer cells to complementary treatments.

Beyond cancer biology, deciphering how cells interpret the micro- and nanotopology of tissues is crucial for the rational design of advanced cell culture and medical implants. Complex cell–carrier devices will benefit from the inclusion of multicomponent interfaces in two and three dimensions, with shapes and ligand combinations suited to recapitulating niche properties typical of resident or moving cells. Innovative material

design could then increase the precision of steering cell stemness or differentiation (for the preconditioning of cells *in vitro*) and could support, for example, stem-cell-like (rather than differentiation) states after adoptive cell transfer *in vivo*<sup>11</sup>. Creating tissue-like patterns that are able to programme cells thus shows strong prospects for biomedical applications. □

Bettina Weigelin and Peter Friedl are at the David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA and in the Department of Cell Biology, Radboud University Medical Centre, 6525GA Nijmegen, Netherlands. Peter Friedl is also a member of the Cancer Genomics Center, 3584 CG Utrecht, Netherlands.  
e-mail: PFriedl@mdanderson.org;  
Peter.Friedl@radboudumc.nl

#### References

- Ozdemir, T., Xu, L.-C., Siedlecki, C. & Brown, J. L. *Integr. Biol.* **5**, 1407–1416 (2013).
- Kilian, K. A., Bugarija, B., Lahn, B. T. & Mrksich, M. *Proc. Natl Acad. Sci. USA* **107**, 4872–4877 (2010).
- Lee, J., Abdeen, A. A., Wycislo, K. L., Fan, T. M. & Kilian, K. A. *Nature Mater.* **15**, 856–862 (2016).
- Weigelin, B., Bakker, G.-J. & Friedl, P. *J. Cell Sci.* **129**, 245–255 (2016).
- Pegoraro, A. F., Fredberg, J. J. & Park, J.-A. *Exp. Cell Res.* **343**, 54–59 (2016).
- Nelson, C. M., VanDuijn, M. M., Inman, J. L., Fletcher, D. A. & Bissell, M. J. *Science* **314**, 298–300 (2006).
- Wu, S. K. *et al. Nature Cell Biol.* **16**, 167–178 (2014).
- Wang, Y. *et al. Biomaterials* **32**, 6737–6744 (2011).
- Haeger, A., Krause, M., Wolf, K. & Friedl, P. *Biochim. Biophys. Acta* **1840**, 2386–2395 (2014).
- Tsujita, K., Takenawa, T. & Itoh, T. *Nature Cell Biol.* **17**, 749–758 (2015).
- Adutler-Lieber, S. *et al. J. Autoimmun.* **54**, 100–111 (2014).

## BIOMEDICAL MATERIALS

# A restorative synthetic skin

Synthetic elastomers designed to mimic the functional properties of human skin show potential applications in cosmetics, topical drug delivery and wound dressings.

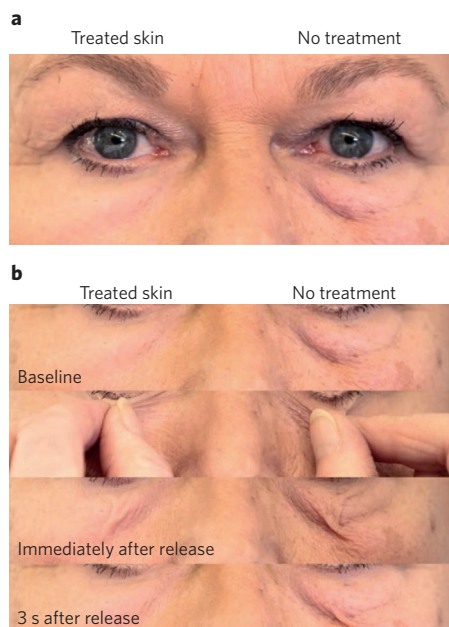
John A. Rogers and Guive Balooch

Skin is the largest and most visible organ of the human body. Its essential functions include physical protection, temperature regulation, water retention and vitamin production. Skin also provides a sensory interface with our surroundings, and in a social and psychological context, skin plays a role in establishing interpersonal bonds and in defining a sense of self. From the perspective of materials science, skin is an exceptionally complex,

time-evolving and self-healing multilayered system, with a hierarchical construction that incorporates critical features with length scales from nanometres to millimetres. The broad functionality of the skin is critical to health and wellbeing, although both can be detrimentally impacted by certain disease states, exposure to harmful environmental factors and, over time, by natural ageing. As a restorative strategy to address such problems, Robert Langer and colleagues<sup>1</sup>

now describe in *Nature Materials* a crosslinked polymer coating with a tailored composition to reproduce the functional properties of skin when applied topically. This thin, soft and transparent ‘second skin’ is able to restore the functional and aesthetic properties of aged skin to a state that more closely resembles its original, youthful form.

The material itself is formed *in situ* following the topical application of a mixture of polysiloxane and fumed silica.



**Figure 1** | Human trials of 'second skin' functional performance. **a**, Images of the restorative effects of the topical application of a synthetic 'second skin' material on the herniated fat pads of the lower lids. **b**, Time-lapse images from video footage of skin retraction following a dermatological tenting test. Decreases in distensibility, increases in elastic recoil and reductions in the protrusion of the pads lead to significantly improved appearance. Figure adapted from ref. 1, Nature Publishing Group.

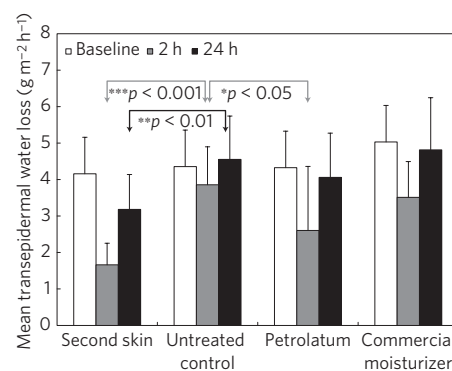
A second application containing platinum to promote catalytic hydrosilylation yields a three-dimensionally crosslinked silicone elastomer, with crosslinking occurring within minutes at room temperature. Light-scattering nylon particles are also embedded near the material surface to eliminate strong specular reflections and provide a natural appearance. The result is a soft, conformal and invisible 'second skin' layer with a thickness similar to that of the uppermost part of natural skin, the stratum corneum. Through systematic studies of more than one hundred formulations using different polysiloxane chain lengths, crosslink densities and amounts of silica, the authors were able to identify materials with elastic moduli and fracture strains that suitably replicated those of human skin. The established biocompatibility of silicones, their intrinsically adhesive surfaces, and their excellent breathability represent additional attractive features of this system.

The restorative effects of this 'second skin' layer on the mechanical properties of the underlying skin follow from its excellent elastic characteristics. As a means of quantitation, the authors examined, in extensive human studies, the elastic

properties of bare and coated skin to measure distensibility and elasticity. For aged skin, the soft mechanical reinforcement associated with the 'second skin' film increases these two properties to values that approximate those of the original, youthful state. As expected, removal of the coating eliminates these enhancements. An additional and less intuitive effect is the ability to mechanically reshape the skin. For example, the visual observation of flattened herniated fat pads of the lower lids after topical application suggests that shrinking of the 'second skin' as it cures induces forces that reduce the protrusion of these pads. The result is an improvement in appearance that previously was only possible through plastic surgery. Figure 1 presents images that illustrate these dramatic effects. Additional studies will help to reveal the combined mechanical, optical and morphological phenomena that most likely underpin these remarkable observations.

In addition to enhanced mechanics, this layer reduces the rate of natural processes of transepidermal water loss. Comparative studies quantitatively demonstrate that the presence of a 'second skin' slows water loss from clinically dry skin, with effective and time-invariant operation for more than 24 hours after application (Fig. 2 summarizes these results). This performance exceeds that of petrolatum, the most effective skin occlusive reported in the literature. Commercial moisturizing creams offer some benefit immediately after application, but cease to function after just a few hours. The versatility in the chemistry of the 'second skin' material suggests that tailored formulations will allow for water barrier properties that are personalized to a user's skin condition.

Beyond their immediate possibilities in cosmetics, these same materials have potential utility in advanced wound dressings, vehicles for pharmaceutical delivery and barriers to environmental exposure. This research also complements separate efforts in the development of skin-like semiconductor devices, sometimes referred to as epidermal electronics, as a basis for next-generation wearable technologies such as physiological health monitors, clinical diagnostics and brain/machine interfaces<sup>2</sup>. These devices often make use of thin silicone materials as supports for electronics configured in filamentary fractal mesh networks<sup>3,4</sup>, and the synthetic materials reported by Langer *et al.* clearly have additional utility in this broader context. Such collective and complementary advances in chemistry, materials science, mechanics, electrical



**Figure 2** | Enhanced skin barrier function and sustained skin hydration for subjects with dry skin. These results summarize comparative performance information on the 'second skin' material in this context. At two hours, the sites treated with petrolatum and the 'second skin' demonstrated significantly reduced transepidermal water loss compared with the untreated control values ( $*p < 0.05$  and  $***p < 0.001$ ). A reduction in the transepidermal water loss was sustained with the 'second skin' over the course of 24 hours ( $**p < 0.01$ ). At 24 hours, the differences measured for petrolatum and for the commercial moisturizer were not statistically significant when compared to the untreated control. The error bars represent one standard deviation from the mean. The  $p$  values were calculated based on one-way ANOVA analyses. Figure adapted from ref. 1, Nature Publishing Group.

engineering and biosensing suggest a promising future for synthetic skins, where passive and active multifunctional operation combined with skin-like physical properties can offer important new capabilities in bio-integrated functional materials and devices. □

John A. Rogers is at the College of Engineering, University of Illinois, Urbana, Illinois 61801, USA. Guive Balooch is the Global Vice President of the Technology Incubator for L'Oreal Research and Innovation, New York, New York 10014, USA. e-mail: jrogers@illinois.edu

#### References

1. Yu, B. *et al.* *Nature Mater.* **15**, 911–918 (2016).
2. Kim, D.-H. *et al.* *Science* **333**, 838–843 (2011).
3. Jang, K.-I. *et al.* *Nature Commun.* **6**, 6566 (2015).
4. Fan, J. A. *et al.* *Nature Commun.* **5**, 3266 (2014).