Cell

# Body Art Gets Smart

Whether we are simply too busy to make it a priority or lack affordable access, there are a multitude of reasons why preventative healthcare too often takes a back seat. In the absence of preventative care, underlying illnesses can fester, and windows of opportunity for disease screening and early diagnosis lapse. What if, however, predictive disease indicators could be reliably monitored without visiting a physician? Inroads toward this end are under active investigation and could even change the way we think about body art.

Interest has been growing among pockets of biomedical engineers in the development of so-called biomedical tattoos. Such tattoos utilize various strategies to report in real-time health metrics with disease value. While some strategies are somewhat more invasive and involve injected biosensors, others involve thinly printed devices that adhere to the skin, resembling temporary tattoos.

Synthetic biology applications using engineered cells represent an exciting avenue of exploration taking advantage of the diversity of signals to which cells have evolved to sense and respond. A recent study from Martin Fussenegger and colleagues reports the development of designer cells that can be implanted subcutaneously to monitor blood calcium levels and respond by producing melanin at the onset of mild hypercalcemia (Tastanova et al., 2018). Because increased blood calcium commonly occurs in a number of cancers and other pathological conditions, detection of hypercalcemia could be a useful readout for dangers lurking on the horizon. In order to detect and report on calcium levels, HEK293 cells were designed to ectopically express CaSR, a calcium-sensing G protein-coupled receptor, as well as tyrosinase under the control of operator modules that are induced by the signaling cascade initiated by CaSR. Cleverly, tyrosinase is the rate-limiting enzyme for melanin synthesis, and therefore, its activity results in production of a dark pigment. These engineered biosensor cells were tested in *ex vivo* pig skin as well as mice bearing hypercalcemic breast and colon adenocarcinoma cells, where the melanin pigment that accumulated was visible even to the naked eye.


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Genetically programmed cells can also be integrated into tattoo-like wearable devices, using an optimized 3D-printing strategy in which bacterial cells in hydrogel inks are fabricated into arrays that consist of cells programmed to respond to stimuli (Liu et al., 2017). While the cells used in the proof-of-concept study produced GFP in response to chemical inducers such as AHL, rhamnose, or IPTG, such cells could be rewired to sense and respond to a variety of medically relevant readouts.

With incidence rates of diabetes on the rise, millions of people could benefit from continuous glucose-monitoring systems, and a strategy to do that with a wearable device would be transformative. Making headway in this direction, Joseph Wang and colleagues report on a proof-of-concept tattoo-based epidermal device that extracts glucose from interstitial fluid and uses an enzyme-based biosensor to report on glucose levels (Bandodkar et al., 2015). The printed tattoo-like glucose sensor was tested on human subjects and was responsive to post-meal glycemic spikes.

Perhaps the closest technology of this kind to traditional tattoos comes out of the DermalAbyss project, a collaborative effort between MIT and Harvard Medical School researchers. As a proof-of-concept, DermalAbyss has created biosensor inks that change color in response to cues from the interstitial fluid (Vega et al., 2017). While still in the research phase with further optimization required to improve biosensor attributes including selectivity, color, and detection ranges as well as important safety profile characterizations, the biosensors have been tested in an *ex vivo* pig skin model.

It will be interesting to see how these technologies develop and what incarnations of them make it to the market. With wearable UV detectors that track sun exposure already commercially available in the temporary tattoo market, it is surely only a matter of time.

## REFERENCES

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