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Electronic Control of Cell Detachment Using a Self-doped Conducting Polymer

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Controlled release is important in numerous areas, such as cell biology and regenerative medicine,^[1] self-cleaning surfaces,^[2] micro-manufacturing,^[3] and drug release.^[4] In cell biology, there is a need for active control of parameters related to cell cultivation such as adhesion, spreading and detachment. Two fundamentally different strategies are commonly applied to detach cells; targeting either cell adhesion proteins or the substrate supporting the cells. The latter is believed to be less harmful, as the native structures of cell adhesion and surface-bound extracellular matrix proteins are maintained, whereas enzyme treatments may cause severe damage to membrane and extracellular matrix proteins.^[5] Maintaining the surface proteins is of special importance in tissue engineering where cell layers must remain intact when detached and transferred for further construction^[6] or transplantation.^[1] Less harmful techniques that rely on external stimuli have been explored. These include temperature responsive hydrogels,^[1] electroactive self-assembled monolayers,^[7-9] heparin hydrogels covalently bound to indium tin oxide (ITO) electrodes,^[10] polyelectrolyte coatings,^[11] liposome-coated magnetite nanoparticles^[12] and ultrasound.^[13] In contrast to

enzymatic treatments, these techniques provide temporal or spatial control for cell detachment^[7,10] in cell sheet engineering^[1,8,11,12] and cell co-culturing.^[9,14] In addition to provide spatiotemporal control and to be less harmful to cells, an alternative detachment method should combine control over the detachment rate, cells fully released from the carrier substrate, no harsh conditions during actual detachment, and simple low-cost manufacturing.

Here we show an electronic detachment technology based on thin films of a water-soluble derivative of the conducting polymer poly(3,4-ethylenedioxythiophene) called PEDOT-S:H. Applying a potential to PEDOT-S:H films immersed in electrolyte results in detachment and disintegration of the polymer from the underlying electrode (**Figure 1a**). We demonstrated the use of this technology for electronic control of cell detachment by releasing adherent human epithelial cells in the absence of any enzymatic treatment. In comparison to enzyme treated cells, the preservation of membrane proteins was greatly improved.

Conducting polymers is an emerging technology platform possible to utilise in electronic devices and systems. Polymers such as polypyrrole^[15] and PEDOT^[16] have been explored in organic bioelectronics to record and regulate functions in biological systems. One of the most stable conjugated polymers is PEDOT, which has been used in various applications.^[17]

The synthesis of conjugated polymers that enable easy processing in aqueous media has been one of the major challenges in this field.^[18,19] Recently we reported a successful synthetic route to a fully water-soluble form of PEDOT-S.^[20] This polymer showed a substantial degree of self-doping and conductivity above 12 S cm^{-1} . Dynamic light scattering analysis of PEDOT-S in water showed an average particle size of 2 nm, suggesting that PEDOT-S exists as single chains or aggregates of only a few polymer chains in water solution. However, it was not possible to process this material as thin films that were stable in aqueous electrolytes as interactions between the polymer and substrate were too weak. Therefore we synthesized a modified version of this polymer, PEDOT-S:H (**Figure 1b**), with enhanced adhesive properties. Key structural properties include very high degree of intermolecular self-

doping, giving good adhesive properties to different substrates as well as high conductivity (30 S cm^{-1}). Complete synthetic and characterization details are given in the Supporting Information. Upon electrochemical oxidation the self-doping process is accompanied by an expulsion of charge balancing protons to the surrounding electrolyte, and charge neutralization leads to the inclusion of cations.^[17] When oxidizing the polymer beyond its pristine state (20-30% doping level),^[18] more anions are needed to compensate for the additional positive charges on the polymer backbone. These anions can be supplied from either the covalently attached sulfonate groups on PEDOT-S:H (more self-doping), or from inclusion of the surrounding electrolyte. We anticipate that the reorientation of the polymer chains due to a higher degree of doping and swelling caused by anion and solvent inclusion, can be used to tune the adhesive properties of the polymer thus enabling electronic control of detachment.

To evaluate detachment, thin films of PEDOT-S:H were successfully coated on top of various conductive substrates, such as gold, ITO and PEDOT, which resulted in thin films that were stable as they were immersed in electrolyte solutions (0.1 M NaCl, aq). Ions were required to ensure stability by neutralizing the repulsive forces between PEDOT-S:H molecules. However, if the PEDOT-S:H films had not been sufficiently dried after casting (80°C for 30 minutes) they were swiftly dissolved into the electrolyte medium for all tested substrate electrodes. This highlights the importance of removing deionized water from the polymer system to ensure stability of coated films. Adhesion, which was evaluated using a standard tape test, of PEDOT-S:H films was found to be optimal on the PEDOT:PSS coatings (OrgaconTM foil), which is tentatively explained by the amphiphilic character of PEDOT-S:H and an overall similar character of the two polymers. An additional advantage of using PEDOT:PSS as the substrate electrode is the possibility to utilize bar coating for manufacturing of PEDOT-S:H layers, thus enabling easy manufacturing on large area electrode surfaces. To maintain the optimal adhesive properties obtained on PEDOT:PSS

surfaces for other substrates as well, a layer of PEDOT:PSS can of course be included as a conductive adhesion promoter. Atomic force microscopy showed that the surfaces were uniform with a low degree of roughness (Supporting Information, Figure S4). When a potential difference was applied between PEDOT-S:H bar coated on PEDOT:PSS and a counter electrode, PEDOT-S:H detached. The detachment progressed through swelling and cracking (**Figure 2a**) into small pieces, which were subsequently split into smaller flakes. The detachment time depended mainly on the magnitude of the applied potential (Figure 2c). A minimum potential (>0.7 V) was required in order for the detachment to occur, in accordance with the oxidation peak of PEDOT-S:H (Figure 2b). At lower potentials no detachment was observed, not even after applying the potential (0.6 V) for 24 hours. In most cases moderate mechanical stimulation such as repetitive pipetting of the electrolyte or gentle shaking of the container was needed to fully detach PEDOT-S:H films from the substrate.

Using standard photolithography in combination with reactive ion etching PEDOT-S:H was patterned to enable spatial control of detachment (Supporting Information, Figure S5). Matrices of PEDOT-S:H containing individually addressable squares ranging from 5000 μm down to 100 μm , separated by 100 μm or 50 μm lines, were realised on PEDOT:PSS (**Figure 3**). Individual detachment of these squares was enabled by applying 1 V for less than one minute (Figure 3c-d).

A possible complication due to the water solubility of PEDOT-S:H is spontaneous detachment in aqueous electrolytes. Bar coated PEDOT-S:H films immersed in electrolyte (0.1 M NaCl) for one week (longer times were not tested) with no potential applied showed that this was not the case. To test whether extended soaking affects the detachment dynamics when a potential is applied, films were soaked for up to seven days before applying the potential. This had no significant effect on detachment time (Figure 2d). Cell culture medium is far more complex than NaCl. Films soaked in RPMI-1640 medium for 24 h prior to addressing showed detachment as expected when medium was supplemented with 1% serum,

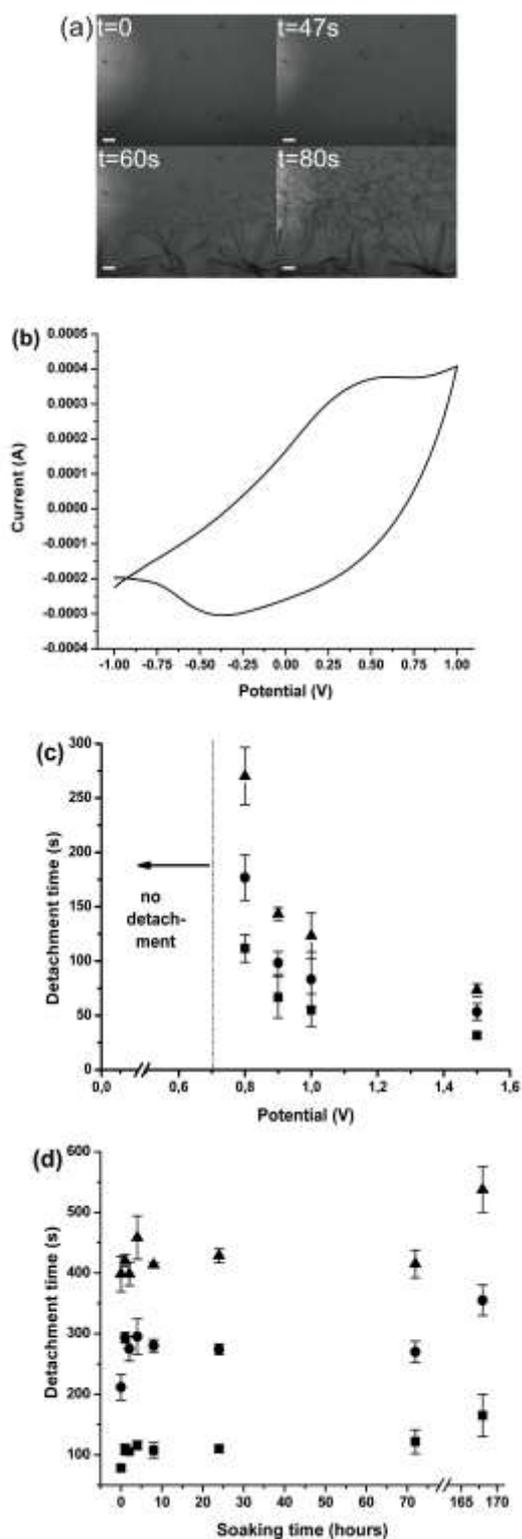


Figure 2. a) Sequential images of PEDOT-S:H detachment from a PEDOT:PSS electrode using a potential of 1 V. The initial stages of detachment; the propagating swelling and cracking are shown. Scale bar = 200 μm . b) Cyclic voltammogram of PEDOT-S:H. c) Detachment time of PEDOT-S:H films at different applied potentials. d) The influence of soaking times on detachment time of PEDOT-S:H, using a potential of 1 V. In (b), (c) and (d), bar coated PEDOT-S:H on PEDOT:PSS was used. In c and d, squares, circles and triangles represent initial, partial (half film detached) and complete detachment, respectively. Error bars = mean \pm SEM, n=3.

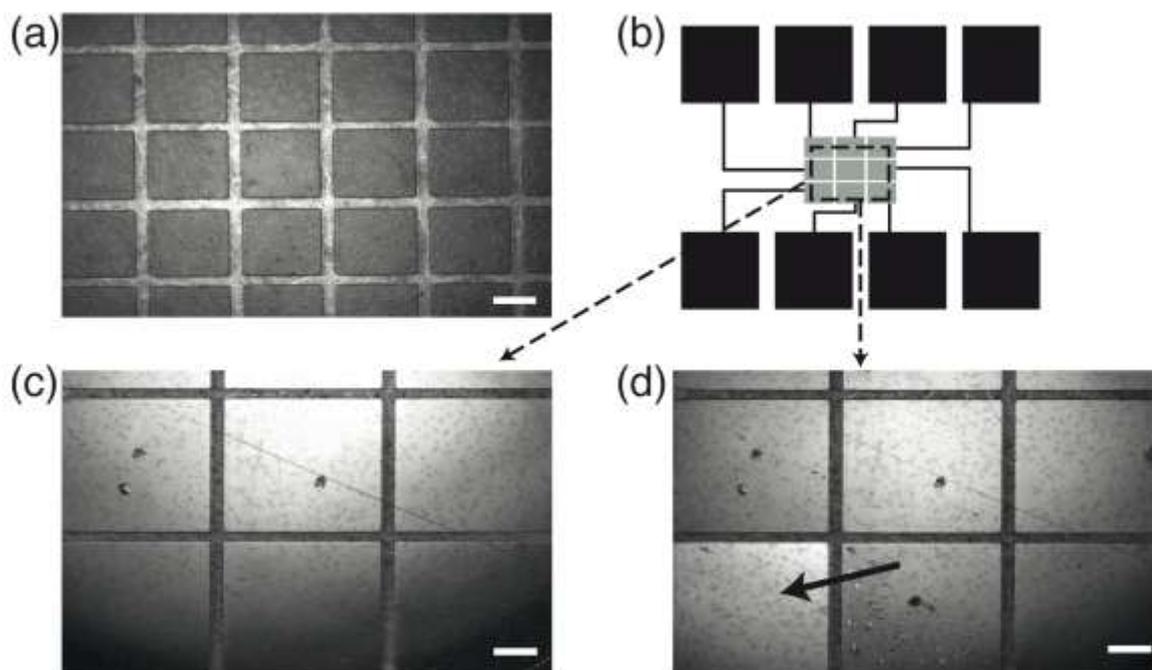


Figure 3. a) Patterned surface of PEDOT-S:H, with squares 500 μm in size separated by 100 μm lines. b) Illustration of individual addressing of PEDOT-S:H squares (grey) within a matrix, including contact pads and addressing lines (black). c) and d), Photographs of a patterned matrix before (c) and after (d) applying 1 V to the lower left square within the matrix, leading to detachment of this square. Detachment reveals the underlying PEDOT:PSS substrate which is lighter in color compared to the other squares where PEDOT-S:H remains (d). Separating lines are 100 μm wide, and the squares are 1000 μm . All scale bars=300 μm .

whereas detachment was abrogated in presence of 10% serum. The latter may be because the applied potential generates an electric field that might promote protein interactions to the PEDOT-S:H surface. To overcome this, cell culture medium was replaced by NaCl or phosphate buffered saline (PBS) just prior to applying the potential. By doing so, detachment occurred as normal.

To evaluate PEDOT-S:H as a cell hosting material, human epithelial T24 cells were used. Following 24 h incubation of cells seeded into custom-designed polymer-coated cell culture dishes (Supporting Information, Figure S6) or conventional glass-bottomed dishes, characteristics of cell adhesion were analyzed by fluorescence microscopy. On PEDOT-S:H, immuno-staining of the focal adhesion-associated protein vinculin and actin showed cells forming small, point-like focal adhesion complexes, no apparent stress fibers, and a relatively

smaller covering of the surface area as compared to cells on glass, where in addition, formation of large focal adhesion complexes and stress fibers were observed (**Figure 4a,b**). In accordance with previous reports describing the effect of soft versus rigid surfaces on focal adhesion complexes and actin stress fibers,^[21] our data illustrate the soft nature of PEDOT-S:H. Cells seemed however to adhere equally well to both substrates. Gentle pipetting of cells cultivated on glass or the PEDOT-S:H substrate (no bias application) caused similar numbers of cells to detach (Figure 4c).

Viability of cells cultivated on the polymer was measured in a standard cellular lactate dehydrogenase (LDH) colorimetric assay. After 24 h, cells cultivated on PEDOT-S:H showed similarly low LDH release as cells grown in the control dish (Figure 4d). The intact membrane integrity of cells on both surfaces is apparent when comparing to total LDH released from lysed cells. To analyze cell functionality, we took advantage of the documented role of T24 cells in innate immunity.^[22] Via TLR4-mediated signaling, T24 cells efficiently respond to immunogenic substances, i.e. bacterial lipopolysaccharide (LPS), by production of pro-inflammatory cytokines. Cells were washed, then stimulated with RPMI-1640 containing LPS for 6 h, when IL-8 production was measured. Figure 4e shows the ratio of stimulated IL-8 production in cells grown on PEDOT-S:H versus cells grown in control wells. A ratio of 1 indicates that both surfaces promote cellular responses to the same degree.

In our attempt to generate a device for electronic control of cell detachment, we next analyzed which parameters to use for detaching PEDOT-S:H, now with cells cultivated on top. After substituting the RPMI-1640 medium for PBS, a potential of 1.0 V had to be applied for 900 s to obtain detachment. This prolonged time, as compared to time required in the absence of cells, is likely due to increased resistance, seen by the lower current density (Supporting Information, Figure S7), and slower swelling process due to decreased water flow. Any effects of applied potential on cell viability, measured by maintained membrane integrity, were analyzed by the LDH cytotoxicity assay. Supernatants withdrawn from the PEDOT-S:H

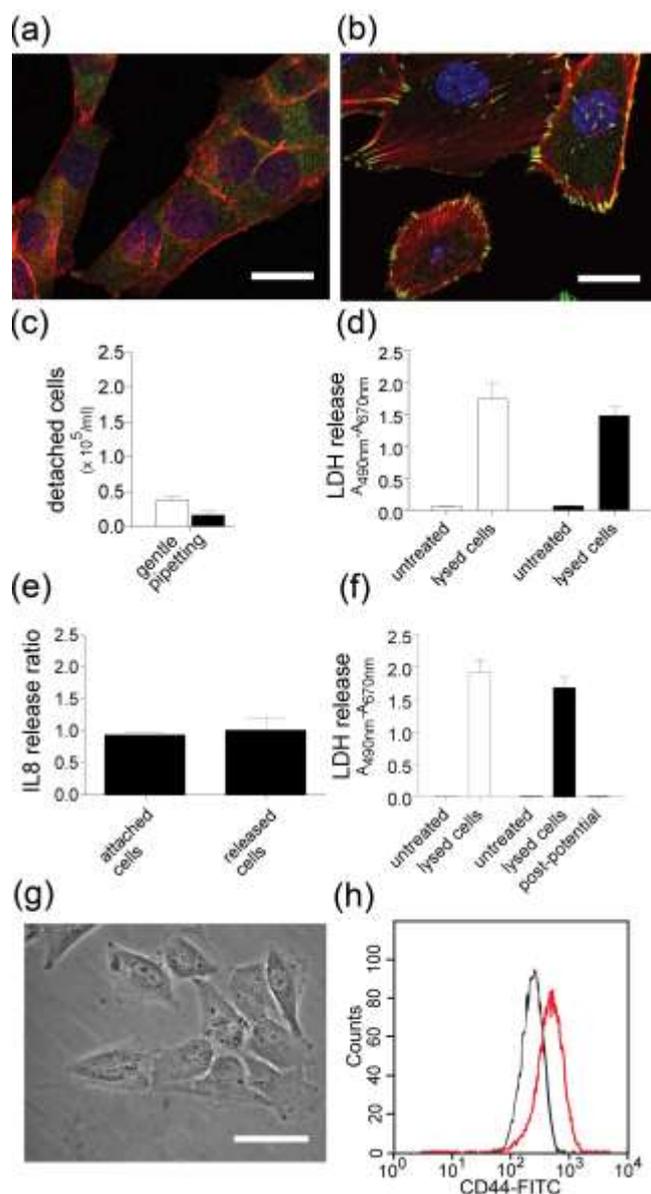


Figure 4. Evaluation of PEDOT-S:H as a cell hosting material. a) and b) Focal adhesion-associated protein vinculin (green), actin cytoskeleton (red) and nuclei (blue) of cells growing on PEDOT-S:H (a) and glass (b). Scale bars = 50 μm . c) Number of detached cells after gentle pipetting on cells cultured on a control surface (white bar) and unbiased PEDOT-S:H (black bar) presented as mean \pm SD, $n = 4$. d) Viability, measured as LDH release, of untreated cells hosted on a control surface (white bars) and PEDOT-S:H (black bars). Maximal LDH release is obtained after cell lysis. Data represent mean \pm SEM, $n = 5$. e) IL8 production in response to LPS. Ratio of IL8 response from cells growing on PEDOT-S:H versus control surface was determined. The left column represents cells attached to the surfaces (no bias application), whereas the right column shows the response from suspension cells after release by electronic detachment (PEDOT-S:H) and trypsinization (control surface). Data represent mean \pm SEM, $n = 4$. f) Viability of cells on a control surface (white bars) and PEDOT-S:H (black bars) before (untreated) and after (post-potential) bias application. Maximal LDH release (lysed cells) is shown from cells on both substrates. Data represent mean \pm SEM, $n = 5$. g) Cells reseeded on cell culture plastic after electronic detachment of PEDOT-S:H. Scale bar = 25 μm . h) Flow cytometry histogram showing counts and intensity of cells released by trypsinization (black) or detachment of the PEDOT-S:H surface (red). Data represent one of two experiments.

dish before and after applying the potential contain barely detectable levels of LDH, similar to the non-treated control dish (Figure 4f). Disruption of the membrane integrity using lysis buffer shows the same maximum level of LDH whether cells are cultivated in traditional dishes or the PEDOT-S:H dish.

After application of the electric potential and gentle pipetting, PEDOT-S:H and cells were released from the PEDOT:PSS surface. Detached cells were separated from remaining PEDOT-S:H fragments by passing the sample through a 70 μm pore filter. While we cannot fully exclude that polymer remnants may still attach to the cells, no adverse effects are observed on cell viability and function. By seeding the cells in fresh medium in conventional cell culture dishes that are incubated over night, we show that released cells are suitable as inoculum for a fresh cell culture, and that cells assume their natural morphology (Figure 4g). Neither did the detachment procedure, and possible polymer contamination, affect cellular function as determined by LPS-stimulated IL-8 release. Following electronic detachment from the PEDOT-S:H dish, or trypsinization of cells on the control surface, cells were harvested by centrifugation, washed, and stimulated in suspension with LPS for 6 h. Analysis of IL-8 production showed similar LPS responsiveness in both cases (Figure 4e). Though we cannot explicitly rule out cell-associated polymer contamination, our functional assay indicates it ought to be minor.

Quantification of cell numbers revealed that the efficiency of release using PEDOT-S:H was about 50% compared to trypsin treatment. Yet, the PEDOT-S:H technique may be advantageous, since trypsinization un-specifically digests numerous membrane-associated proteins. To analyze the integrity of membrane proteins after releasing cells by trypsinization or by detachment of PEDOT-S:H, fluorescence activated cell sorting (FACS) was performed. Following detachment, cells were mixed with a FITC-conjugated antibody against the trypsin sensitive surface antigen CD44 that is expressed by cells used in this study. FACS analysis

showed increased fluorescence intensity from cells detached using PEDOT-S:H compared to cells released by trypsin (Figure 4h). This substantial improvement in preservation of the CD44 surface antigen demonstrates the gentle character of the PEDOT-S:H technique.

In conclusion, thin films of a substituted poly(3,4-ethylenedioxythiophene) derivative have been evaluated for active control of cell detachment. PEDOT-S:H possesses high degree of intermolecular self-doping, providing a homogenous electronic material that changes its cross-linking properties when oxidized. Processing the polymer from water enables cheap, easy and green manufacturing of devices using printing or standard photolithographic technologies on a variety of surfaces. By incorporating PEDOT-S:H thin film electrodes into customized, optically transparent cell culture devices, we have developed a new method for electronic control of cell detachment. Whereas cell detachment works well with cells cultivated and used within 24 h, it is currently unknown whether protein deposition on the surface will hamper the use of this technique for cells requiring longer incubation times. Cell detachment studies showed the PEDOT-S:H system to clearly improve preservation of cell surface antigens as compared to traditional trypsinization. Our technology combines high spatial resolution of detachment (comparable to other non-enzymatic methods^[9,10]) with easy processing and short detachment time. These are all sought-after features in the expanding field of regenerative medicine as well as general cell biology. We foresee that automated local detachment will become a valuable tool when integrated with existing imaging techniques and pattern recognition software.

Experimental

PEDOT-S:H coating: PEDOT-S:H (20 mg ml⁻¹, aq) was spin- or bar coated (using a BYK Gardner bar coater at speed 100 mm s⁻¹) on PEDOT:PSS foil (Agfa-Gevaert Orgacon™ F-350) washed in acetone and deionized water or ITO on glass. Both substrates were treated with a reactive ion etch of oxygen plasma. The coated films were dried in an oven at 80°C for

30 minutes. The PEDOT:PSS dispersion (Baytron P, H.C. Starck) was spin coated on ITO on glass.

Set up for detachment characterisation and cyclic voltammetry: Bar coated PEDOT-S:H on PEDOT:PSS was used to characterise the detachment. The PEDOT-S:H/PEDOT:PSS substrate (3 cm²) was placed in a plastic container filled with NaCl (0.1 M, aq), a platinum counter electrode was placed opposite and a Ag/AgCl reference electrode in between. An electrical potential was applied between the PEDOT-S:H/PEDOT:PSS substrate and the counter electrode using a potentiostat (μ Autolab, EcoChemie). In cyclic voltammetry, the scan rate was 50 mV s⁻¹. When photographing the detachment a Nikon SMZ1500 microscope was used. A gold wire was used as counter electrode and NaCl (0.1 M, aq) as electrolyte.

Potential titration: Using the set up described above with PEDOT-S:H bar coated on PEDOT:PSS, and applying potentials between 0.2 and 1.5 V, the detachment time was estimated. As a control, 0.6 V was applied to one substrate for 24 hours. The container was shaken gently at regular intervals.

Effect of soaking on detachment time: Bar coated PEDOT-S:H on PEDOT:PSS was used. Substrates were placed in NaCl (0.1 M, aq) for up to one week, before a potential of 1 V was applied.

Patterning: Poly(methyl methacrylate), PMMA, (50 mg ml⁻¹ in diethyl carbonate), was spin coated on top of bar coated PEDOT-S:H on PEDOT:PSS. Photoresist (Shipley-1818) was spin coated on top of PMMA. After exposure, the substrates were developed in Microposit MF-319, followed by washing in NaCl (0.1 M, aq). Reactive ion etching with O₂ and CF₄ was used for patterning. Photoresist and PMMA were removed using acetone. When detaching the patterned matrix, a drop of electrolyte (0.1 M NaCl, aq) was placed on top and a potential of 1 V was applied between one of the squares and a gold wire placed in the electrolyte.

Cell culture: T24 human bladder carcinoma cells (ATCC nr: HTB-4) were propagated according to supplier's recommendations in RPMI-1640 (Sigma) supplemented with fetal

bovine serum (10%), L-glutamine (0.3 g l⁻¹) and penicillin; streptomycin (100 U ml⁻¹; 100 µg ml⁻¹). PEDOT-S:H surfaces were prepared for cell culture by attaching a Plexiglas ring using Sylgard 184™ silicon rubber (diameter: 30 mm). 3 ml of a suspension containing ~ 4x10⁴ cells ml⁻¹ cell culture media was added to the wells and incubated over night in 37°C, 5% CO₂, humidified incubator.

Detachment assay: Cells growing on glass and PEDOT-S:H substrate without bias application were washed twice in PBS. Gentle pipetting was applied three times by soaking up and pushing out the PBS in the well, while moving the pipette tip closely over the cell layer. Detached cells in the supernatant were counted in a Buerker haemocytometer. n = 4, mean value ± SD is displayed.

Electronic detachment and reseeding of cell: Cell media was replaced with PBS (3 ml, pH 7.4) and cells were gently washed twice. Detachment of cells was achieved by applying 1.0 V for 900 s using a Gamry potentiostat and a Ag/AgCl reference electrode, combined with repeated pipetting. To remove PEDOT-S:H fragments, cells were passed through a 70 µm cell strainer (BD Biosciences) and centrifuged (500 rcf). The cell pellet was reconstituted in supplemented RPMI-1640 and reseeded in a 30 mm cell culture dish.

LDH assay: LDH Cytotoxicity Detection Kit^{PLUS} (Roche) was used to assess possible cytotoxic effects due to electronic detachment. Before and after bias application, supernatants were withdrawn for LDH measurement according to supplier's protocol, in parallel to supernatants from cells growing on control surfaces. Lysing the cells with supplier's lysis buffer was used to obtain maximal LDH release. Reactions were performed as triplicates in 96 well plates and analysed at 490 nm and 650 nm in a Spectra Max 190 plate reader (Molecular Devices).

IL8 assay: T24 cells cultivated overnight on PEDOT-S:H or glass were washed with PBS, and incubated at 37°C, in fresh, supplemented RPMI-1640 medium with or without addition of 50 ng/ml lipopolysaccharide (LPS, O55:B5, Sigma). The same procedure was performed on cells

that had been electronically detached from PEDOT-S:H, or detached by trypsinization from the control surface after centrifugation (500 rcf) and resuspension in medium with and without LPS. After 6 h, supernatants were withdrawn, and analysed for IL8 according to supplier's protocol of the IL8 Detection Kit (KPE-56791, BioSite). Absorption of the reactions, performed as triplicates in 96 well plates, was measured at 405 nm and 650 nm in a Spectra Max 190 plate reader (Molecular Devices). The IL8 release ratio $[\text{IL8}_{+\text{LPS}}/\text{IL8}_{-\text{LPS}}]_{\text{PEDOT-S:H}} / [\text{IL8}_{+\text{LPS}}/\text{IL8}_{-\text{LPS}}]_{\text{control surface}}$ was calculated for attached or released cells and displayed as mean value \pm SEM (n = 4).

Immuno-cytochemistry: Cells grown on PEDOT-S:H surfaces and Adcell slides (Thermo Scientific) were fixed in 3.7% formaldehyde diluted in PBS, pH 7.4, for 15 min at room temperature. Actin filaments were stained with TRITC-phalloidin ($1 \mu\text{g ml}^{-1}$). Nuclei were stained with Hoechst 33258 ($1 \mu\text{g ml}^{-1}$). The primary antibody to stain focal adhesion complexes was monoclonal Anti-Vinculin Clone hVIN-1 Mouse Ascites Fluid (Sigma). Specimens were analyzed in an Olympus FV1000 Confocal microscope.

Flow cytometry: Mouse anti-human CD44 FITC-conjugated monoclonal antibody (clone F10-44-2) from Millipore was used. Cells were fixed in 3.7% formalin in PBS, washed and stained with $10 \mu\text{l}$ antibody diluted in $50 \mu\text{l}$ PBS with 1% BSA for 30 min on ice in the dark. A Becton Dickinson FACScan, with a 488 nm laser and three colors was used. Cell Quest-Pro was used for analysis.

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Supporting Information is available online from Wiley InterScience or from the author.

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An electronic detachment technology based on thin films of a poly(3,4-ethylenedioxythiophene) derivative is evaluated for controlled release of human epithelial cells. When applying a potential of 1 V, the redox-responsive polymer films detach and disintegrate and at the same time release cells cultured on top in the absence of any enzymatic treatment with excellent preservation of membrane proteins and cell viability.

Keyword: bioelectronics, cell detachment, conducting polymers, electrochemistry, polymerization

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Electronic Control of Cell Detachment Using a Self-Doped Conducting Polymer

