# Cell Surface Engineering for Control of Cell Adhesion

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**Statement of Purpose:** Cell adhesion plays an important role in a number of applications including tissue engineering and cancer therapies. Thus far, research regarding control of cell-substrate interactions has primarily focused on modifications of the substrate.[1,2] Here, we focus on the modification of cell surfaces rather than the substrate. We have developed methods by which polymeric biomaterials can be employed to engineer the surfaces of cells. These techniques demonstrate principles that may be used for various cell-interface applications, such as altering cell adhesion in cancer metastasis,[3] or increasing cell retention after delivery of cellular therapeutics to myocardial infarcts.[4]

**Methods:**

*Cell coating and assessment*. T98 glioma cells were coated with the layer-by-layer (LbL) technique. Poly-L-lysine (PLL), a polycation, and hyaluronic acid (HA), a polyanion, were labeled with fluorescent dyes (Alexa Fluor 594 and 488, respectively; Molecular Probes, Eugene, OR). Cells were incubated first with PLL, then second with HA. Confocal fluorescence microscopy and zeta potential measurements were used to assess the presence of the coating on the cell surface. Cell viability was assessed via the LIVE/DEAD assay (Molecular Probes). The stability of the coatings was evaluated by crosslinking the polyelectrolyte layers with carbodiimide chemistry (EDC/NHS). The coated cells were then treated with hyaluronidase, and zeta potential measurements were obtained to determine the charge of the cell surface.

*Cell adhesion*. HA-based hydrogels were synthesized through a disulfide exchange reaction to fabricate negatively-charged surfaces. Positively-charged surfaces were made by adsorbing PLL onto the surface of HA hydrogels. Coated cells were incubated on the substrates overnight before brightfield microscopy imaging.

**Results and Discussion:**

*Formation of polyelectrolyte coatings on cells*. After incubation with PLL and HA, confocal fluorescent images of cells showed red (corresponding to PLL) and green (corresponding to HA) present at the surfaces of the cells (Fig 1). Zeta potential measurements indicated that surface charge became more positive after incubation with PLL and more negative after treatment with HA. These two results show that cells can be conformally coated with PLL and HA using the LbL technique.

*Effect of coating on cell viability.* Cells remained viable at least 7 days after coating, as shown by green fluorescence after LIVE/DEAD staining.

*Stability of cell coatings.* Sustained negative zeta potential of coated cells after EDC/NHS and hyaluronidase treatments showed that cross-linked cell coatings were more stable than coatings that were not crosslinked.

*Control of cell adhesion*. A greater number of coated cells adhered to surfaces of opposite charge than to those of like charge (Fig. 2). This suggests that cell surfaces can be engineered to control cell attachment.

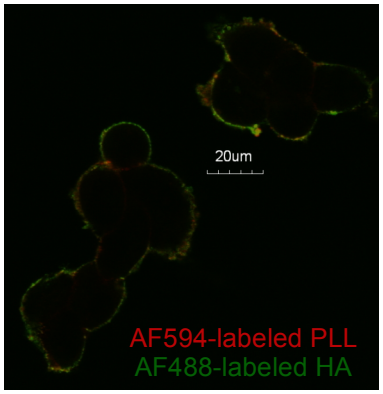


Figure 1. Confocal imaging shows that cells can be coated with polyelectrolyte biomaterials using the LbL method.

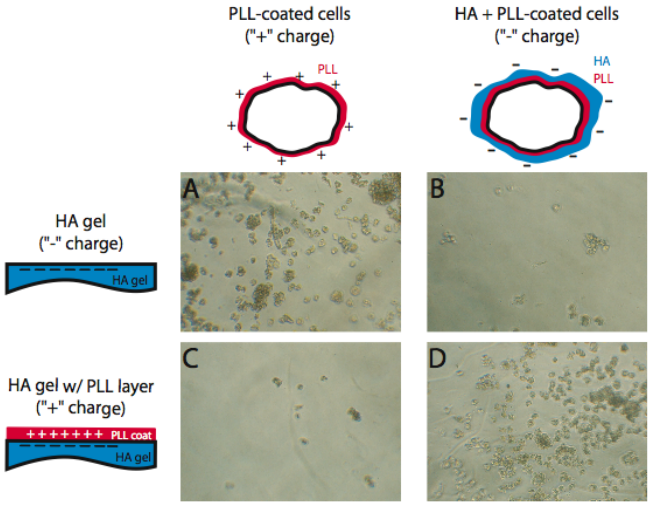


Figure 2. Cells coated with PLL and HA preferentially attach to surfaces of opposite charge (A, D) compared to surfaces of like charge (B, C).

**Conclusions:** Engineering cell surfaces presents a unique approach for control of cell-substrate interactions. Taken together, our results suggest that we can coat cell surfaces with polyelectrolytes, chemically stabilize the coatings, and tailor the surfaces to promote or inhibit cell-substrate adhesion. We consider these proof-of-concept results as promising steps towards future specific physiological applications.

**References:**

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