Cell adhesion to the extracellular matrix (ECM) is integral to the survival and function of most cells.\(^1\) Cells use a wide range of receptors, which function by binding ligands in the substratum and transducing signals through the intracellular domain, to regulate functions as diverse as tissue maintenance, immune response, and development. Studies that address the roles for individual receptors are important for understanding these physiological processes but are often complicated by overlapping ligand specificities between receptors.\(^3\) Here we report a strategy for “rewiring” the interactions between a cell and surface to create unique ligand–receptor bonds at a cell and ECM, but at the same time preserving the biological role of the receptor. We demonstrate this strategy by rewiring a cell-surface integrin receptor for adhesion to a synthetic ligand. The integrins are transmembrane \(\alpha \beta\) heterodimeric receptors that are found on all cell surfaces and that mediate cell adhesion.\(^1\)–\(^6\) Of the 25 known integrins, approximately one-third bind to the integrin, an extracellular stalk domain from fractalkine, and a carbonic anhydrase IV (CAIV) domain at the terminus. The CAIV enzymatic domain of carbonic anhydrase IV (CAIV) (pink). A surface presenting a small-molecule inhibitor of CAIV, benzenesulfonamide, specifically targets the chimeric receptor. (B) A self-assembled monolayer of alkanethiols on gold present benzenesulfonamide at a 1% density with an inert background of tri(ethylene glycol).

Figure 1. Schematic diagram of the complementary engineering of receptor and ligand. (A) The native \(\alpha \beta\) integrin (left) binds a tripeptide ligand, Arg-Gly-Asp. A chimeric receptor (right) was engineered to retain the extracellular domain of \(\beta\) integrin (blue), but on the extracellular side, to comprise a fractalkine stalk domain (yellow) and the enzymatic domain of CAIV (pink). A surface presenting a small-molecule inhibitor of CAIV, benzenesulfonamide, specifically targets the chimeric receptor. (B) A self-assembled monolayer of alkanethiols on gold present benzenesulfonamide at a 1% density with an inert background of tri(ethylene glycol).

![Figure 1](https://example.com/final_image1.png)

Figure 2. Cells expressing the chimeric receptor adhere to a surface presenting benzenesulfonamide. (A) FACS plot of fluorescence vs forward scatter shows a transfected population of 11% (red dots) that express the chimeric receptor and a nontransfected population (black dots). (B) Western blot analysis with an anti-CAIV antibody shows the chimeric receptor to be ~75 kD. (C) Transfected cells attach and spread on a surface presenting benzenesulfonamide. Cells were stained with phalloidin-TexasRed for better visualization of the lamellipodia.

We transfected Chinese hamster ovary (CHO) cells to express the chimeric receptor. Fluorescence activated cell sorting (FACS) analysis using an antibody against CAIV showed that the chimeric receptor was expressed and presented on the membrane surface of CHO cells (Figure 2a). Western blot analysis of cell lysates using the same antibody confirmed that the full-length chimeric receptor was expressed in cells. The apparent molecular weight of the chimeric receptor is slightly higher than the calculated mass of 63 kD based on the amino acid sequence and is due to the posttranslational glycosylation of the mucin-like fractalkine stalk (Figure 2b).

Cells expressing the chimeric receptor adhered to and spread well on SAMs presenting the benzenesulfonamide ligand and were
receptors. 22, 23 A western blot analysis using anti-phosphoFAK subunit of the chimeric receptor is able to activate signaling through cell spreading requires proper signaling from the intracellular was inhibited by soluble benzenesulfonamide (1 mM), and non-characterized by wide lamellipodia (Figure 2c). The adhesion of ligand interactions between a cell and ECM. In this example, we integrated into the circuitry of the cell. 24 indicator that the chimeric receptors have been successfully action of attachment at the leading edge and detachment at the density (Figure 3b, c). Migration, which requires the coordinated of migration distances of transfected cells on SAMs presenting 1% benzenesulfonamide (left) and nontransfected cells on SAMs presenting 1% cyclic Arg-Gly-Asp (right) over 1 h.

Phosphorylation of FAK at Y397 correlates to cell attachment and spreading. This work demonstrates a strategy for rewiring the receptor–ligand interactions between a cell and ECM. In this example, we genetically modified the β1 integrin receptor to promote adhesion to a synthetic surface and found that cell adhesion, signaling, and migration were similar to that observed with wild-type cells on natural ECM proteins. The modularity of this approach allows the β1 domain of the chimeric receptor to be interchanged with either other integrin β subunits or other transmembrane receptors, while retaining the extracellular interaction between CAIV and benzenesulfonamide ligand. We believe that this strategy is applicable to a wide range of cell-surface receptors that participate in adhesion and therefore offers a new opportunity for understanding fundamental biological processes—ranging from mechanotransduction to stem cell differentiation—and for directing the adhesion of many cell types to artificial scaffolds in tissue engineering applications. 25–28 The broad strategy of rewiring cellular pathways to either enhance or redirect a biological function has proven an important tool in biology—including the yeast two-hybrid screens 29 and synthetic receptors for targeted endocytosis 30—and is now available for the study and engineering of cell–ECM interactions.

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Supporting Information Available: Additional figures and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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