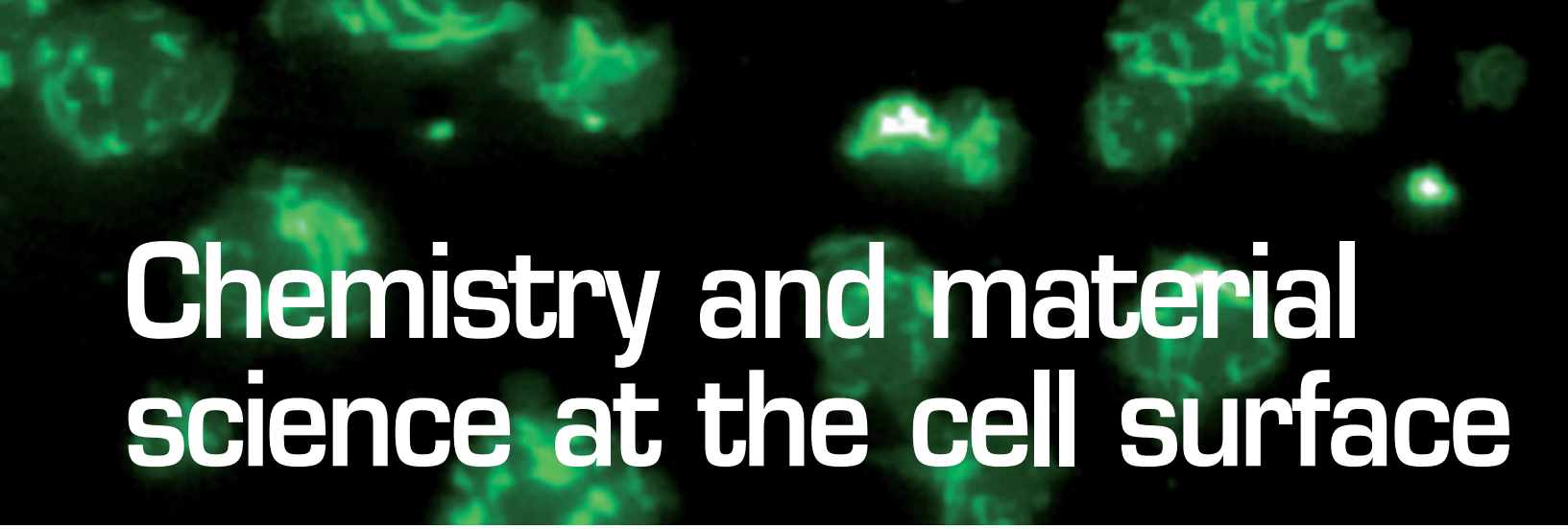

Chemistry and material science at the cell surface

Cell surfaces are fertile ground for chemists and material scientists to manipulate or augment cell functions and phenotypes. This not only helps to answer basic biology questions but also has diagnostic and therapeutic applications. In this review, we summarize the most recent advances in the engineering of the cell surface. In particular, we focus on the potential applications of surface engineered cells for 1) targeting cells to desirable sites in cell therapy, 2) programming assembly of cells for tissue engineering, 3) bioimaging and sensing, and ultimately 4) manipulating cell biology.

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The interface of chemistry, material science and biology presents many opportunities for developing innovative tools to answer fundamental biology questions and diagnose/treat various diseases. The past decade has witnessed an explosion in the development of novel materials and methods, including some on a nano-scale, which can be applied to fields including tissue engineering, diagnostics, drug delivery, and medical devices. A particularly exciting subject in the field is the direct engineering and manipulation of living cells, the basic structural and functional unit of living organisms. Excellent examples include controlling cell fate by biomaterial scaffolds[1,2], labeling cells with molecular and nanoparticle probes for imaging and visualization of cellular processes and molecular pathways[3-5], delivery of diverse species into cells[6,7], and patterning cells for drug discovery[8-10]. This review focuses on the engineering of the cell surface, a fertile ground for chemists and material scientists to manipulate cell phenotypes and biological fates. This will open up new avenues for biologists to interrogate basic cellular functions, or advance cell-based therapies and diagnostics. The cell membrane is a highly heterogeneous and dynamic environment comprising mainly proteins, lipids, and carbohydrates, which mediate cell-cell and cell-niche communication and intracellular signaling, ultimately governing cell fate[11,12]. To date, cell surface engineering has primarily been a subject of molecular biology. However, tools developed by chemists and material scientists provide simple alternatives to the genetic and biosynthetic approaches. Specifically, targeting molecules, molecular and nanoparticle probes, polymer patches, and nanostructures can be introduced onto the cell surface by conjugation (covalently and non-covalently), or by utilizing biomolecular recognition such as antibody/antigen and biotin/streptavidin interactions. These tools greatly enhance our ability to use and manipulate cells, and answer biological questions. This review highlights the most recent developments in this field with particular focuses on the use of cell surface engineering strategies for

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1) **targeting cells to desirable sites in cell therapy,**
2) **programming assembly of cells with substrates or cells in tissue engineering,**
3) **bioimaging and sensing, and**
4) **manipulating cell biology.**

Cell encapsulation, cell-matrix interactions, and the detailed mechanisms of chemical reactions involved in cell surface modification, which are subjects of several recent excellent reviews[11,13-19], will not be discussed here.

Cell targeting

Delivery of systemically infused cells, particularly stem/progenitor cells, into damaged or diseased tissue holds enormous promise for the treatment of a variety of diseases worldwide[20]. For instance, hematopoietic stem cell (HSC) transplantation (i.e. bone marrow transplantation), which has been used in the clinic for several decades to treat blood diseases and cancer, requires systemically infused HSCs to home to the bone marrow from the blood. Mesenchymal stem cells (MSCs) are similarly believed to home to various sites of inflammation and injury in the body after being systemically infused. MSCs which are capable of differentiating into connective tissue cells types that can produce bone, cartilage and fat, and produce immunomodulatory cytokines, are currently being tested in clinical trials for treatment of numerous diseases including graft versus host disease, myocardial infarction, multiple sclerosis, and skeletal tissue repair, among others[20]. Unfortunately, systemically administered therapeutic cells home to the target sites at low efficiencies (typically < 1%), which is due to, at least in part, the lack of expression (or loss during culture expansion) of key homing receptors[21]. Therefore, efforts have been made to introduce cell homing ligands onto cell membranes. Cell homing ligands (on the homing cell) and receptors (on the endothelium) allow homing cells to tether, roll, adhere and then transmigrate on endothelium as part of the cell homing cascade. Methods include genetic[22-24] and enzymatic engineering[25], treatment with cytokines[26] and, as will be discussed here in detail, chemical approaches[27,28] (Fig. 1a). For instance, we have recently developed a simple platform technology to chemically attach cell adhesion molecules to MSC surface to improve homing efficiency to inflamed tissues[27]. Specifically, this chemical approach (Fig. 1b) involves a stepwise process including:

1) treatment of cell amine groups with sulfonated biotinyl-N-hydroxy-succinimide (NHS) to introduce biotin groups on the cell surface,
2) addition of streptavidin that binds to the biotin on the cell surface and presents unoccupied binding sites, and
3) attachment of biotinylated homing ligands. In our model system, a biotinylated sialyl Lewis X (SLeX), a ligand that binds to P and E selectins expressed on the inflamed endothelium and allows cells to roll on the endothelial layer, was conjugated on the MSC surface.

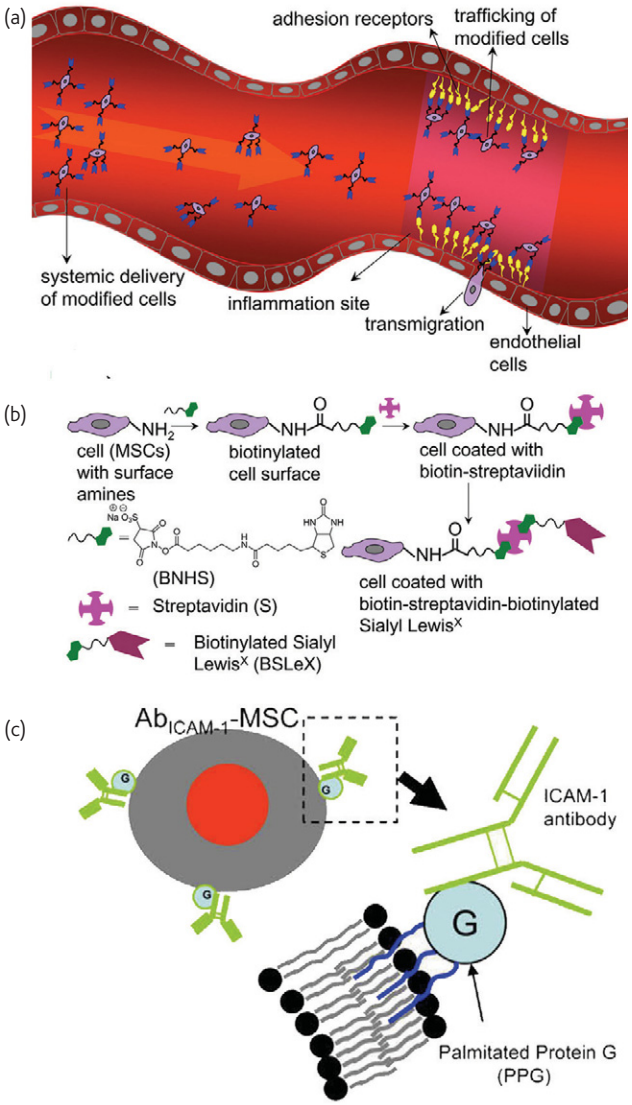

Fig. 1 a) Schematic showing targeting of cells from blood to inflamed endothelium expressing receptors that bind to ligands engineered on the cell surface. Two methods of engineering the homing ligand onto the cell surfaces, using covalent and noncovalent chemistry, are shown in b) and c), respectively. b) Stepwise process of attaching SLeX to MSCs using biotin-streptavidin linkers, and c) incorporation of palmitated protein G into the cell membrane and subsequent conjugation with an ICAM-1 antibody. (a) and b) reprinted with permission from[27]. ©ACS 2008. c) adapted with permission from[28]. ©Elsevier 2009).

The SLeX modified MSCs demonstrated a robust rolling response on a P-selectin coated substrate under shear stress conditions *in vitro*[27] and on inflamed endothelium *in vivo* (Sarkar *et al.* unpublished). In addition, homing ligands can be introduced onto the cell membrane using non-covalent chemical modification[28,29]. In a recent work from Dennis and co-workers[28], MSCs were treated with palmitated protein G where the palmitate chain was incorporated into lipid bilayer via hydrophobic interactions and protein G provides generic binding sites for antibodies (Fig. 1c). In their proof-of-concept work, intercellular cell adhesion molecule-1 (ICAM-1) antibodies were conjugated onto MSCs