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A cell surface clicked navigation system to direct specific bone targeting

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A B S T R A C T

Cell therapies are promising up-and-coming therapeutic strategies for many diseases. For maximal therapeutic benefits, injected cells have to navigate their way to a designated area, including organ and tissue; unfortunately, the majority of therapeutic cells are currently administered without a guide or homing device. To improve this serious shortcoming, a functionalization method was developed to equip cells with a homing signal. Its application was demonstrated by applying an Azadibenzocyclooctyne-bisphosphonate (ADIBO-BP) and azide paired bioorthogonal chemistry on cells for bone specific homing. Jurkat T cells and bone marrow derived stromal cells (BMSCs) were cultured with tetraacetylated *N*-azidoacetyl-D-mannosamine ($Ac_4ManNAz$) to place unnatural azido groups onto the cell's surface; these azido groups were then reacted with ADIBO-BP. The tethered bisphosphonates were able to bring Jurkat cells to hydroxyapatite, the major component of bone, and mineralized SAOS-2 cells. The incorporated BP groups also enhanced the specific affinity of BMSCs to mouse femur bone fragments in vitro. The introduced navigation strategy is expected to have a broad application in cell therapy, because through the biocompatible ADIBO and azide reactive pair, various homing signals could be efficiently anchored onto therapeutic cells.

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1. Introduction

Cell-based therapy, including cell transplantation, has been introduced as a type of advanced therapy.[1] From conventional bone marrow transplantation to selective stem cell therapies, cells have been utilized as treatments for degenerative diseases in the hope that the injected cells could self-regenerate at the affected areas.[2,3] Because of the capability to differentiate into appropriate functional cells, mesenchymal stem cell (MSC) therapy has been considered a magic therapeutic approach in the treatment of many degenerative diseases.[4] For example, MSCs have been proposed as treatment for acute myocardial infarction[1,3,5,6] and degenerative neuronal diseases.[7–9] MSC therapy has also been evaluated for use in bone fracture healing, and bone regeneration of age-related osteoporosis because of the cell's multi-linage potential which enables them to undergo osteogenic differentiation within the bone marrow.[10–13] Though MSC has great therapeutic potential for the hard-to-cure bone defect related diseases, they haven't been proven clinically useful yet. In particular, their poor homing ability has been recognized as a major obstacle in MSC transplantation.[14,15] To improve this issue, genetically engineered MSCs have been introduced to enhance their function[16,17] or homing.[18–20]

Recently, T cell therapy is actively validated in clinical trials.[21–25] Chimeric antigen receptor engineered T (CAR T) cells, armed with artificial surface receptors, are considered one of the most promising cell based therapies in treating malignancies, such as CD19-directed CAR T for relapsed B cell neoplasm and NY-ESO-1 specific TCR engineered T cells for multiple myeloma and synovial sarcoma.[26–28] CAR T cells have been engineered with various targeting receptors to achieve tumor specific efficiency. Examples of the receptors used are: mesothelin specific CAR T for solid tumors, human epidermal growth factor receptor 2 (HER2) CAR T for sarcoma, and CEA CAR T for CEA+ liver metastasis.[29–31]

Instead of genetic engineering methods reported in MSCs or CAR T cells, we introduce a novel and simple chemical strategy for an effective cell surface functionalization to guide targeted delivery. Bioorthogonal click chemistry has been introduced as an effective strategy for cell surface modification, for example, it has been applied to glycan visualization,[32] glycoproteomics,[33] and cell tracking.[34] A copper–free azadibenzocyclooctyne (ADIBO)

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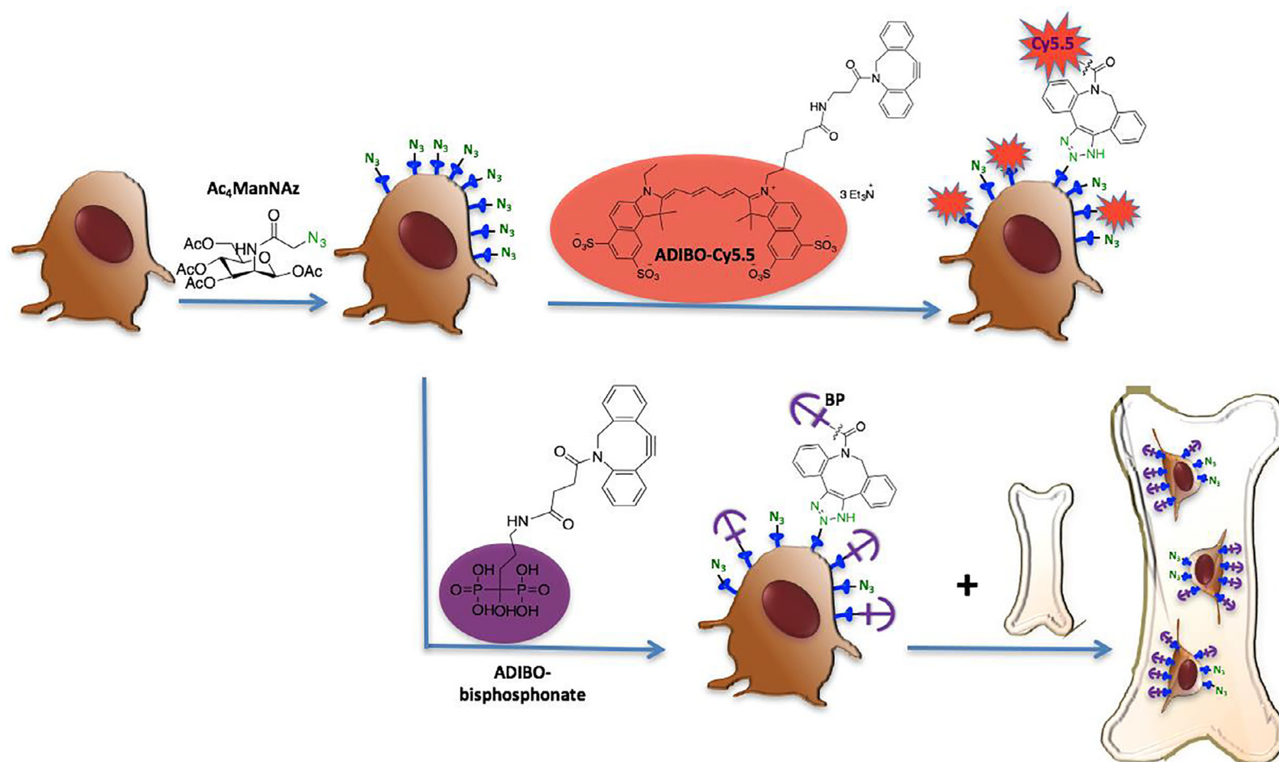


Scheme 1. Schematic diagram of cell functionalization using a bioorthogonal click chemistry. Cells labeled with $Ac_4ManNAz$ spontaneously place the azido groups on their surface to react with ADIBO-Cy5.5 for tracking or ADIBO-BP for bone homing.

and azide (N_3) pair was selected for cell surface bioconjugation because the ADIBO/Azide reaction is biocompatible, effective and especially useful in cell applications.[35,36] To prepare cells with a navigation system, Jurkat cells and bone marrow derived stromal cells (BMSC) were cultured with tetraacetylated *N*-azidoacetyl-D-mannosamine ($Ac_4ManNAz$) to incorporate azido groups onto surface glycoproteins through spontaneous non-selective metabolic glycosylations (Scheme 1). Subsequently, an ADIBO and bisphosphonate (BP) conjugate was attached to the azide-decorated cells. Each step in the cell's self-navigating function towards calcium deposits was validated, and their specific homing to bone was confirmed.

2. Material and methods

2.1. Synthesis of ADIBO-bisphosphonate (ADIBO-BP)

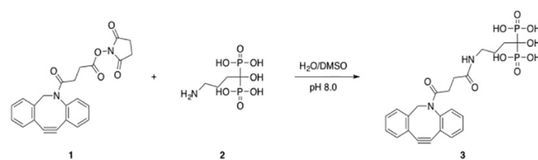
^1H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz with a Bruker (Billerica, MA) 2014 Advance HD III 500 MHz spectrometer at ambient temperature with D_2O as solvent. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The ^1H NMR spectra were referenced to 4.80 in deuterium oxide (D_2O).

High-performance liquid chromatography (HPLC) was performed on an Agilent Technologies (Santa Clara, CA) preparative HPLC system. A Grace Vydac 218TP C18 5 μm column (250 mm * 4.6 mm) was used for analytical HPLC (flow rate, 1.0 mL/min), while a Phenomenex Luna C18 10 μm column (250 mm * 21 mm) was used for preparative HPLC (flow rate, 8.0 mL/min). The mobile phases were 0.1% (v/v) trifluoroacetic acid in water (phase A) and 0.1% v/v trifluoroacetic acid in acetonitrile (phase B).

Liquid chromatography-mass spectroscopy (LC-MS) analyses were performed on Waters (Milford, MA) Acquity UPLC – Waters Zspray™ with a Phenomenex Kinetex C18 1.7 μm column (50 mm * 2.1 mm) operating under electrospray ionization conditions (ESI). The mobile phases used were 0.05% (v/v) trifluoroacetic acid in water (phase A) and 0.05% (v/v) trifluoroacetic acid in acetonitrile (phase B).

High Resolution Mass spectra (HRMS) was collected by the Analytical Core Facility at Memorial Sloan Kettering Cancer Center with Waters Acuity SQD LC-HRMS.

Dimethyl sulfoxide (DMSO) and hydrochloric acid were purchased from VWR. HPLC grade acetonitrile, HPLC grade trifluoroacetic acid, boric acid, and sodium tetraborate decahydrate were purchased from Sigma-Aldrich (St. Louis, MO). Azadibenzocyclooctyne-NHS ester was purchased from Alfa Aesar (Haverhill, MA). Alendronate sodium trihydrate was purchased from TCI (Portland, OR). Ultrapure water was purified with EMD Millipore (Billerica, MA) Milli-Q Advantage A10. All experiments were carried out in a sodium borate buffer (0.5 M, pH = 8.1) at room temperature (r.t., 23 °C), unless otherwise specified. The sodium borate buffer was prepared from boric acid (3.06 g, 48 mmol) and sodium tetraborate decahydrate (Borax, 4.75 g, 12 mmol) in 50 mL H_2O. The pH was then adjusted to 8.1 with hydrochloric acid (0.1 M) and diluted to 100 mL with H_2O.



A solution of Azadibenzocyclooctyne-NHS ester (1) in DMSO (2.5 μmol/1.0 mL) was added into a solution of Alendronate sodium trihydrate (2) in H_2O/sodium borate buffer (0.5 M, pH = 8.1) solution (v/v: 5/1) (2.5 μmol/1.0 mL). A white precipitate appeared and disappeared immediately after shaking. The reaction was monitored by LC-MS. After the complete conversion of (1) (2

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