ABSTRACT

Therapy using antibody-drug conjugates (ADCs) is a promising approach in better targeting cancer cells. Many pharmaceutical and biotechnology companies have initiated programs for ADC discovery. Moradec LLC has developed state-of-the-art secondary antibody-drug conjugates (2°ADCs) as tools for effective, economic, and relevant ADC discovery. These 2°ADCs are conjugated with cleavable or non-cleavable linkers to different cytotoxic small molecules, such as MMAE, MMAF, Dolastatin 10, DM-1, DM-4, Duocarmycin, and Calicheamicin. Instead of individually conjugating your target mAbs, using the 2°ADCs in a cell-based cytotoxic assay is a quick and economical alternative to pre-screening the mAbs as ADC candidates against cancer cells. In addition, the 2°ADCs are great tools for identifying relevant receptors on cancer cells for ADC targeting.

INTRODUCTION

Therapy using antibody-drug conjugates (ADCs), which consist of an antibody linked to a cytotoxic drug, have become a new targeted therapy against cancer. The idea is based on the premise of selective binding of the ADCs to target cancer cells via the monoclonal antibody (mAb) portion and specific release of the drugs to do their damage upon internalization of the ADCs. This achieves target-specific killing of tumor cells while minimizing systemic toxicity of the cytotoxic drug.

Prior to the use of ADCs in cell-based assays, each mAb is typically conjugated with a cytotoxic drug directly. This step is time consuming and expensive, requiring milligram quantities of purified antibodies, separate conjugation of each antibody, and further isolation of the ADC from the unconjugated drug. Using secondary antibody-drug conjugates (2°ADC) in a cell-based cytotoxic assay is a quick and economical alternative to pre-screening mAbs as ADC candidates against tumor cells. Instead of conjugating the mAbs individually with a cytotoxic drug, the naked antibody is added directly to the cells in the presence of a 2°ADC. Internalization of the mAb/2°ADC complex can achieve a similar effect of dose-dependent drug release within the cells as that of the direct antibody-drug conjugate, while cells expressing low density of the targeted receptor are not affected.

RESULTS

Moradec has developed multiple panels of 2°ADCs linked to many highly sought-after cytotoxic small molecules. These ADCs are designed with the following concepts in mind: 1) The secondary antibodies recognize either the Fc or Fab portion of human or mouse IgGs typically found in the format of many therapeutic antibody discovery programs. 2) The small molecule toxins include the well-known tubulin inhibitors such as Monomethyl Auristatin A (MMAE), Monomethyl Auristatin F (MMF), Monomethyl Dolastatin 10 (DM10), Dolastatin 3 (DUAA3), and Maytansinoids 1 (DM1) and 4 (DM4), plus potent DNA damaging reagents such as Duocarmycins SA (DMAF) and Calicheamicin (CALC). 3) The linkers connecting the secondary antibodies to the small molecule drugs are either cleavable or cleavable by endosome cathepsins or free thiols reducing molecules. Moradec’s 2°ADCs are better suited for targeting tumor cells via either tubulin polymerization inhibition or DNA strand-breaking mechanisms, which are the cornerstone of action for tumor killing. They are also suitable as surrogates for cell-based screening because of the relevant drugs and linkers compared to the same panel-based secondary conjugates, which kill cells via a ribosome inactivation mechanism.

Moradec provides state-of-the-art secondary antibody-drug conjugates linked to potent cytotoxic small molecules such as MMAE, MMAF, DM1, or Duocarmycin, etc. These 2°ADCs alone have minimal toxicity while showing specific and potent killing of tumor cells in the presence of appropriate primary antibodies recognizing overexpressed tumor markers. Instead of laborious and expensive conjugation of individual monoclonal antibodies, using the 2°ADCs in cell-based assays is a faster and cheaper approach for prescreening target antibodies against cancer cells. More importantly, since the 2°ADCs are conjugated with well-sought-after cytotoxic drugs such as potent tubulin inhibitors or DNA damaging molecules, testing relevant MOA and efficacy of different drug-linker combinations has become much easier without spending lots of money and time on individual conjugation. Our approach allows you to make better decisions on the final format of your antibody-drug conjugates and be more confident of the MOA tested in the initial proof-of-concept studies. Hence Moradec’s 2°ADCs are great tools for your ADC discovery.