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Sialic Acid Engineered Prodrug Nanoparticles for Codelivery of Bortezomib and Selenium in Tumor Bearing Mice

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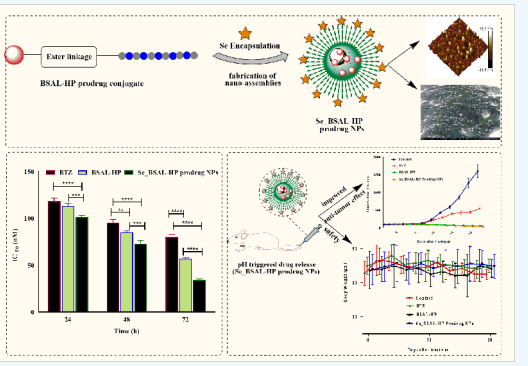
ABSTRACT: Most cancer patients rarely benefit from monodrug therapy because of both cancer complexity and tumor environment. One of the main reasons for this failure is insufficient accumulation of the optimal dose at the tumorous site. Our investigation implies a promising strategy to engineer prodrug nanoparticles (NPs) of bortezomib (BTZ) and selenium (Se) using sialic acid (SAL) as a ligand to improve breast cancer therapy. BTZ was conjugated with SAL and HPMA (*N*-2-hydroxypropyl methacrylamide) to prepare a prodrug conjugate; BTZ-SAL-HPMA (BSAL-HP) and then fabricated into prodrug NPs with Se (Se_BSAL-HP prodrug NPs). The self-assembly of prodrug NPs functionalized with Se showed size (204.13 ± 0.02 nm) and zeta potential (−31.0 ± 0.11 mV) in dynamic light scattering (DLS) experiments and spherical shape in TEM and SEM analysis. Good stability and low pH drug release profile were characterized by Se_BSAL-HP prodrug NPs. The tumor-selective boronate-ester-based prodrug NPs of BTZ in combination with Se endowed a synergistic effect against cancer cells. Compared to prodrug conjugate, Se_BSAL-HP prodrug NPs exhibited higher cell cytotoxicity and enhanced cellular internalization with significant changes in mitochondria membrane potential (MMP). Elevated apoptosis was observed in the (G2/M) phase of the cell cycle for Se_BSAL-HP prodrug NPs (2.7-fold) higher than BTZ. *In vivo* studies were performed on Sprague−Dawley rats and resulted in positive trends. The increased therapeutic activity of Se_BSAL-HP prodrug NPs inhibited primary tumor growth and showed 43.05 ± 0.2-fold decrease in tumor volume than the control in 4T1 tumor bearing mice. The surprising and remarkable outcomes for Se_BSAL-HP prodrug NPs were probably due to the ROS triggering effect of boronate ester and selenium given together.



1. INTRODUCTION

Breast cancer is a global health concern among women accounting for almost one-third of three major types of cancers (lung, breast, and colorectal).[1] It is a highly complex type of cancer with five major subtypes; out of those estrogen receptor (ER) type is a highly aggressive subtype accounting for more than 80% of breast cancer cases. The standard drugs used for breast cancer treatment are anthracycline-, taxane-, and platinum-based derivatives as a single agent or in combination. Unfortunately, metastasis, drug resistance, and chronic toxicity of existing medications have become new paradigms and hurdles. Therefore, the search for novel drug candidates as single or combination is a need for urgent attention.

Targeted nanotherapeutics showed a steep increase in cancer therapeutics with the ability to improve solubility, pharmacokinetics, and release of drug selectively at the target site. Enormous progress in nanomedicine is still addressing certain challenges which point out the need to amalgamate the prodrug approach with NPs.[2] Prodrug NPs leveraged the strength of the drug delivery platform by releasing active molecules on demand, avoiding premature loss of drug, improving drug circulation time, and reducing toxicity.[3] Esterification is the most common approach used for the synthesis of prodrugs as esterase enzymes are ubiquitously present in the major organs of the body.[4] Here, we explored an approach composed of synthesis and fabrication of prodrug NPs using HPMA (copolymer) for combinatorial delivery of bortezomib (BTZ) and selenium (Se).

BTZ is a proteasome inhibitor that offers significant merits and desired therapeutic activity against solid tumors as a single agent or in combination. BTZ is available in the market (Velcade) as a lyophilized product with D-mannitol. The boronic acid of BTZ forms a complex with dihydroxy groups of D-mannitol solution via an ester bond.[5] This bond breaks in acidic pH, releasing boronic acid. Mannitol receptors, which are widely distributed on the surface of dendritic cells and macrophages,

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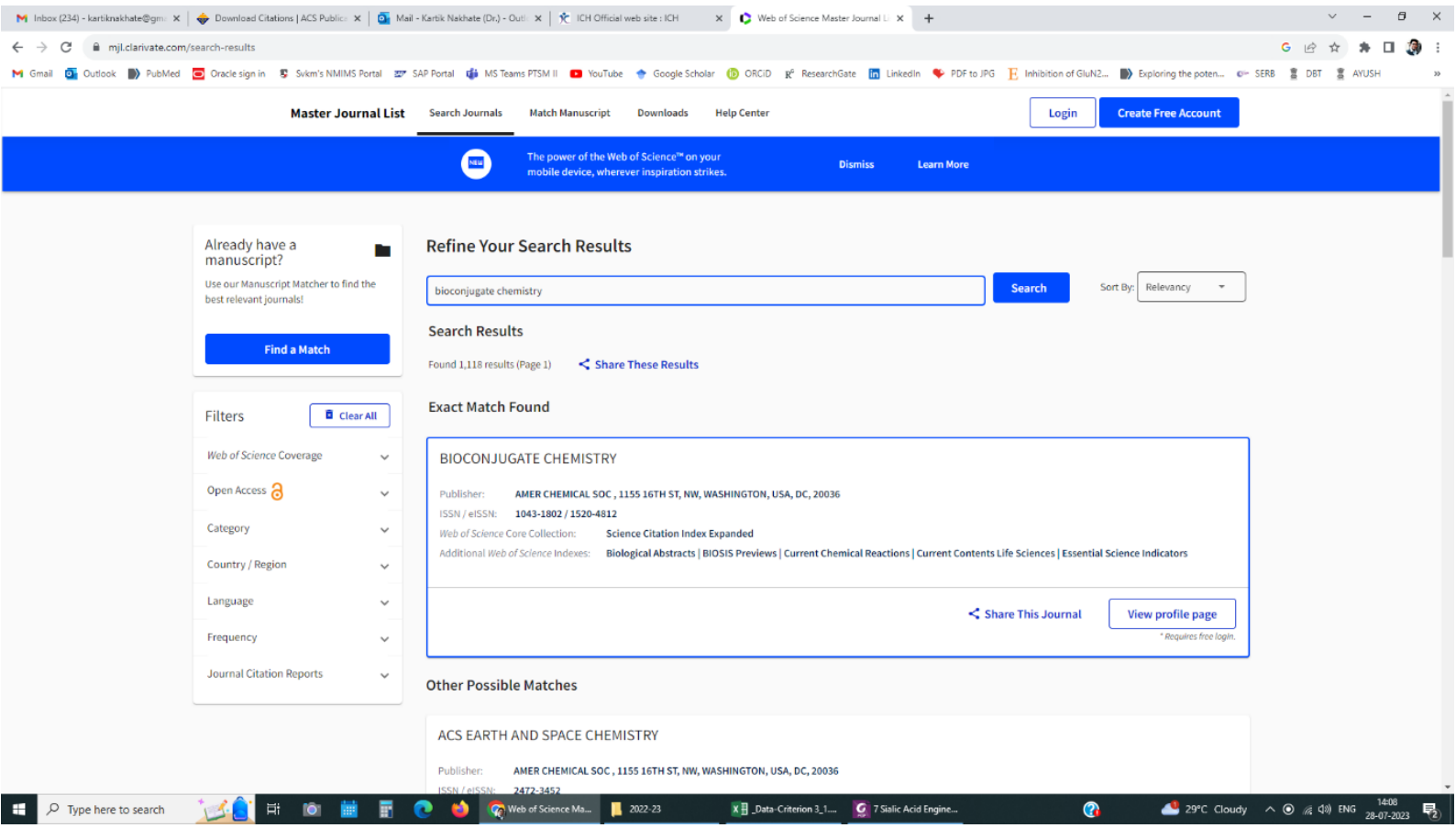
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