1152 IN VITRO ANTICANCER AND IMMUNOMODULATORY ACTIVITIES OF A NOVEL MOLECULAR GLUE COMPOUND NBT-018

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Background Targeted protein degradation is a rapidly exploding drug discovery strategy which uses small molecules to recruit disease-causing proteins for rapid destruction via the ubiquitin-proteasome pathway. It shows great potential for treating diseases such as cancer, autoimmune, infectious, inflammatory, and other diseases, especially for those with "undruggable" pathogenic protein targets. Here we report one 'molecular glue' type of protein degrader NBT-018, which binds cereblon (CBRN) and has selective anti-cancer and immunomodulatory activities.

Methods NBT-018 was screened out from our chemical library. Its biological activity was examined using cancer cell survival assays and immunological assays with various types of human cells including various cancer cell lines, PBMCs and enriched immune cells including NK, CD4+ T cells and CD14+ derived macrophages, as well as dg T cells. Luminex-based immunoassay was used to measure cytokine release from immune cells. Automatic western blot was used to quantify degradation of targeted proteins in sensitive cells.

Results NBT-018 selectively Inhibited proliferation of leukemia and myeloma cells such as H292, HL-60, Jurkat cells in *in vitro* experiments (IC50 7.3, 0.12, 1.2 μM respectively); while it had little inhibitory effects on other cancer cells tested including lymphoma, breast cancer, colorectal carcinoma and glioblastoma cells (RIVA, Granta-529, RL, Farage, HCT116, U87, T98G, A172, MCF-7, IC50 > 100 μM). NBT-018 also enhanced production of T cell cytokines (such as IL-2, IFN-g, etc) from anti-CD3/CD28 stimulated normal human PBMC or from mixed culture of allotypic PBMCs. At 100 nM NBT-018 significantly enhanced SLP76 (Ser376) phosphorylation in Jurkat cells stimulated with anti-CD3/CD28 for 15 min; or in the coculture of Jurkat and HCT116 cells in the presence or absence of a bispeci?c T-cell engager. In addition, NBT-018 modulated production of inflammatory cytokines from PBMC stimulated with toll-like receptor agonists including LPS (TLR4), resiquimod (TLR7 and TLR8) and Poly (I:C) (TLR3). Furthermore, NBT-018 enhanced killing activities of human NK and dg T cells against K562 cells. However, NBT-018 had no appreciable effect on phagocytosis of CD14-derived macrophages, THP-1 monocytic cells and immortalized microglial cells (IMG). Finally, NBT-018 was found to bind CRBN and cause the degradation of IKZF1/2/3 in several lines of leukemia cells.

Conclusions Our data showed that NBT-018, a novel 'molecular glue', had anticancer and immunomodulatory activities such as modulation of expression of cytokines in immune cells and induction of cancer cell-killing activities of NK and dg T cells. NBT-018 could be a promising cancer immunotherapeutic agent targeting both cancer cells and immune cells.

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