HuYON007 MultYbody™

A multimeric anti-DR4 IgG1 antibody with potent agonistic activity

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***Summary**: JN Biosciences has developed a proprietary antibody engineering platform that enables conversion of an IgG antibody to a uniform mulitimeric polyvalent form (MultYmab™ technology). Such modified IgG antibody (MultYbody™) works as a potent agonist for death receptor family members of surface proteins. HuYON007 MultYbody™, a humanized multimeric IgG1 antibody against death receptor 4 (DR4) generated by the MultYmab™ technology, potently induced apoptosis of DR4-expressing tumor cells in vitro and significantly prolonged survival of mice inoculated with DR4-positive B lymphoma or myeloma cells in systemic models.*

***The Company:** JN Biosciences is a biotechnology company based in Mountain View CA. It was founded with the dual intent of generating novel therapeutic antibodies against under-appreciated targets that possess potential therapeutic value and developing innovative antibody engineering technologies to improve the efficacy of therapeutic antibodies.*

Introduction: The death receptor family of cell surface proteins require homo-trimerization for induction of intracelluar signal transduction leading to apoptosis of cells. IgG antibodies, which are divalent for antigen binding and therefore homo-dimerize death receptors, cannot induce apoptosis alone. Although Fc receptor-bearing cells can crosslink IgG antibodies bound to death receptors on the surface of other cells, thus inducing apoptosis, the presence of circulating IgG antibodies makes this process inefficient *in vivo*. HuYON007 MultYbody™, a multimeric polyvalent anti-DR4 IgG1 antibody composed of modified heavy chains and intact light chains, has an ability to efficiently crosslink DR4 on the surface without the aid of any other components and potently induce apoptosis of DR4-bearding cells *in vivo*. HuYON007 MultYbody™, which is a potent anti-DR4 agonist, will be an efficacious therapeutics for cancer treatment.

Induction of Apoptosis: An in-house generated anti-DR4 antibody was humanized and converted to the multimeric form (HuYON007 MultYbody™) using the proprietary MultYmab™ technology. HuYON007 MultYbody™ was expressed in a CHO-K1 stable transfectant and purified by protein A chromatography. The activity of HuYON007 MultYbody™ to induce apoptosis was analyzed using the DR4-expressing human myeloma cell line RPMI-8226. As shown in Figure 2, HuYON007 MultYbody™ efficiently induced apoptosis with an EC_{50} value of 2.5 ng/ml. The parental anti-DR4 IgG1 antibody showed no activity to induce apoptosis even at 600 ng/ml.

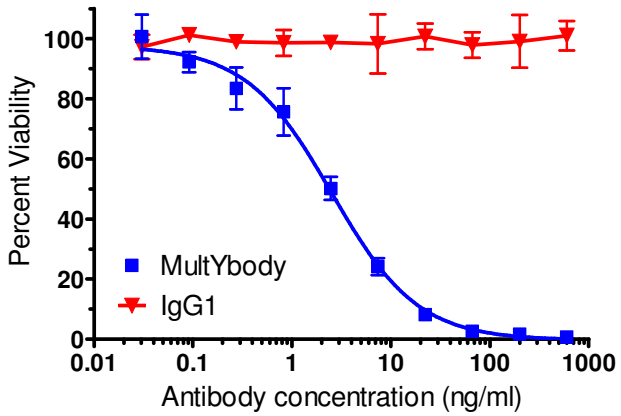

Figure 1. Apoptosis of RPMI-8226 myeloma cells induced by humanized anti-DR4 antibodies

Synergy with Bortezomib: The apoptosis-inducing activity of HuYON007 MultYbody™ was tested in the presence of bortezomib (trade name, Velcade), an FDA-approved small molecule drug for treatment of multiple myeloma. RPMI 8226 myeloma cells were incubated with various concentrations of HuYON007 MultYbody™ and 0, 2.5 or 5 ng/ml of bortezomib (Fig. 2). A combination of HuYON007 MultYbody™ and bortezomib enhanced the level of apoptosis of RPMI 8226 cells when compared to the individual use of each agent. HuYON007 MultYbody™ thus works synergistically with bortezomib for apoptosis of DR4-bearing cells.

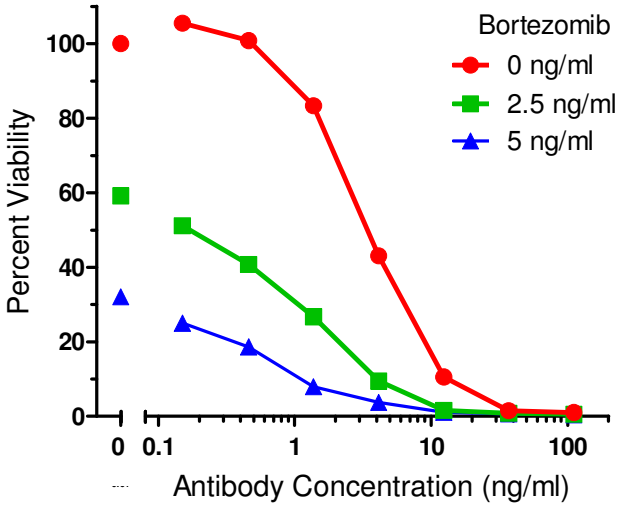

Figure 2. Apoptosis of RPMI-8226 myeloma cells in the presence of bortezomib

Conclusions: HuYON007 MultYbody™, a humanized anti-DR4 multimeric IgG1 antibody generated using the MultYmab™ technology at JN Biosciences, potently induces apoptosis of DR4-expressing cells and significantly prolongs survival of mice administered with RPMI-8226 myeloma cells. The cell-killing activity of HuYON007 MultYbody™ is enhanced in the presence of bortezomib.

Mouse Xenograft Model: The anti-tumor activity of HuYON007 MultYbody™ was examined in a mouse systemic model using RPMI-8226 myeloma cells. The parental humanized anti-DR4 IgG1 antibody was used as a reference. Each test antibody was administered intravenously to ten mice at 0.5 mg/kg on days 4, 7, 11, 14, 18, 21, 25, 28 after inoculation of RPMI-8226 cells. PBS was administered for the no-treatment group. As demonstrated in Fig. 2, HuYON007 MultYbody™ significantly prolonged the survival of tumor-bearing mice when compared to the parental anti-DR4 IgG1 antibody ($P < 0.0001$). The mean survival time was 64 days for the PBS control group, 80 days for the IgG1 group, and longer than 111 days for the MultYbody™ group. No obvious abnormal symptom was found for the surviving eight mice in the MultYbody™-treated group by gross necropsy at study termination (Day 111).

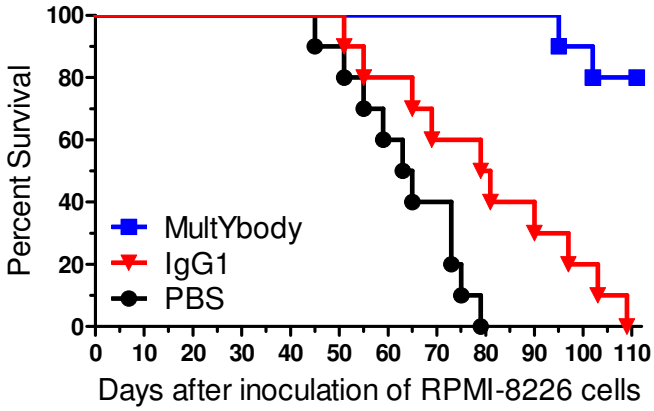

Figure 3. Survival of mice inoculated with RPMI-8226 myeloma cells in a systemic model

***The Opportunity**: JN Biosciences is actively seeking partners for further development and clinical application of HuYON007 MultYbody™. Please send inquiries to: Info@jn-bio.com*