Introduction

CD70 is highly expressed in multiple tumor types including many lymphomas and clear cell renal carcinomas. The expression in lymphomas is not surprising given the role of CD70 in B and T cell activation. However, expression of CD70 at high levels and very high prevalence in renal cancer was initially unexpected. The tightly controlled and limited expression in normal tissues, together with this high level tumor expression makes CD70 an extremely attractive target for antibody-directed therapy. In order to exploit this specificity we have isolated and characterized a human anti-CD70 antibody of high affinity and specificity from transgenic mice. This antibody has been conjugated to highly potent DNA alkylating agents via hydrazine and amino acid based linkers. The resulting CD70 targeted antibody-drug conjugates show potent and curative antitumor activity at low doses; highly specific antigen targeting activity (as shown by comparing CD70 antibody conjugates with isotype control conjugates in vivo), and an extremely wide therapeutic window in both lymphoma and renal cancer models. Furthermore, these CD70 antibody drug conjugates are demonstrating favorable toxicity profiles in larger animals at levels far in excess of the xenograft model determined efficacious doses.

CD70 antibody binding

Expression of CD70 in lymphoma

For such a specific anti-cancer target to function to its maximum with a toxin conjugate system, it is desirable that the targeted antigen is internalized upon antibody binding. The images below show rapid internalization of CD70.1 in lymphoma cell lines from humans and monkeys. Thus CD70 appears to be a suitable target for an antibody drug conjugate and that Rhesus is a suitable tox species for this anti CD70 HuMAb.

Development of toxins

MED2220 is a synthetic analogue of Duocarmycin which is conjugated to CD70.1 via an acid labile hydrazine linker. For internalizing antigens such as CD70, once the hydrazine linker is cleaved in the acid environment of the lysosome or endosome, the active toxin is released by carboxylesterase cleavage. The active toxin is a DNA alkylating agent.

CD70 HuMAb binding to CD70_CD8 fusion protein

Conclusions

CD70 is now recognized as a very specific tumor antigen in lymphomas and renal cancer. The challenge is to develop systems to exploit this specificity leading to an efficacious and safe anti cancer therapeutic. We have developed a high affinity fully human anti CD70 antibody as a mechanism to target CD70 positive tumors. With the toxin and linker systems described here we show complete cures in CD70 positive lymphomas and renal cancer models with single, low dose treatments. Cures have been achieved at even lower doses such that the efficacy/toxicity window in mice can be as large as 200 fold. These CD70 antibody drug conjugates have also been tested in larger animals at doses above the curative doses described here with no evidence of adverse toxicity.