Sanquin Blood Supply

Licensing Opportunity

LIFE SCIENCES CENTER AMSTERDAM

Breaking the boundaries for antibody therapy against cancer

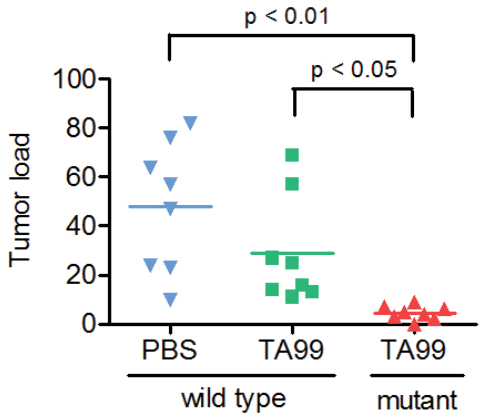
- **This technology may reduce the frequency and/or dosing of** therapeutic antibody therapies significantly reducing there costs.
- **This technology could significantly increase the overall effectiveness of antibody therapy thus increasing the cure- and survival- rates of patients.**
- **This technology could dramatically increase the range of antibody therapeutics that would be suitable for clinical application by significantly increasing ADCC.**

Biological Therapeutics| Monoclonal Antibodies 2011

Background

Therapeutic antibodies, such as Rituxan® or Herceptin®, have provided a major breakthrough in the treatment of cancers, particularly non-Hodgkin lymphoma and breast cancer. The major advantage of therapeutic antibodies, as opposed to e.g. chemotherapy, is the high degree of specificity for cancer cells and their application to patients therefore results in much less side-effects.

Therapeutic antibodies act by binding to cancer cells turning them into targets for killing by the immune system. Unfortunately, one common and major clinical problem of antibody therapy against cancer is the lack of potency to eradicate all cancer cells. This has not only limited the efficacy of antibody therapy, but also the development of novel antibody therapeutics.



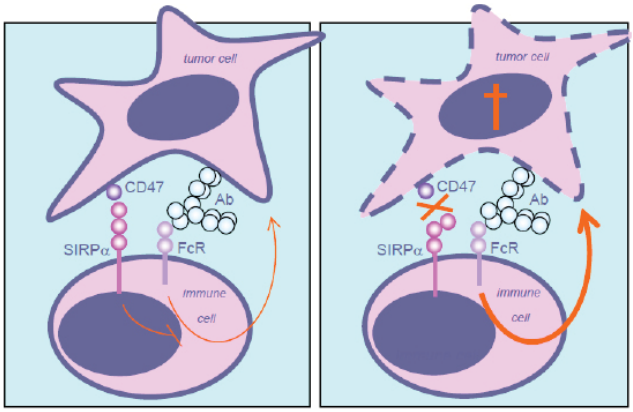
A role for CD47-SIRPα interactions in restricting the destruction of cancer cells by immune cells. The antibody-dependent destruction of melanoma cancer cells is enhanced in mice expressing a mutated SIRPα protein, which lacks the cytoplasmic tail and is therefore unable to provide intracellular inhibitory signals. Normal 'wild-type' mice or SIRPα-'mutant' animals were injected with B16F10 melanoma cells and (suboptimal concentrations of) the therapeutic antibody TA99. Tumor development in the lungs was determined after 3 weeks. While under these conditions the therapeutic antibody TA99 has little effect on tumor development in normal mice it essentially destroys the tumors in SIRPα-mutant animals.

The Technology

Researchers at Sanquin have discovered that the efficacy of the antibody-mediated destruction of cancer cells, also termed antibody dependent cellular cytotoxicity (ADCC), is limited by an intrinsic mechanism that relies on the molecular interaction between two proteins CD47 and SIRPα that are present on cancer and immune cells, respectively (figure 1).

By interfering with the CD47-SIRPα interaction we may enhance the killing of cancer cells by therapeutic antibodies thus improving current and future therapeutic antibody based therapies.

Enhancing the clinical effect of therapeutic antibodies against cancer by interference with CD47-SIRPα interactions.



Left panel: Therapeutic antibodies (Ab) bind to both cancer cells and Fc-receptors (FcR) on immune cells triggering cancer cell destruction by antibody-dependent cellular cytotoxicity (ADCC). However, this process is limited by interactions between CD47 expressed on cancer cells and the inhibitory receptor SIRPα on immune cells.
Right panel: By interference with the interaction between CD47 and SIRPα the antibody-induced destruction of tumor cells is enhanced because it is relieved from its intrinsic limitation.

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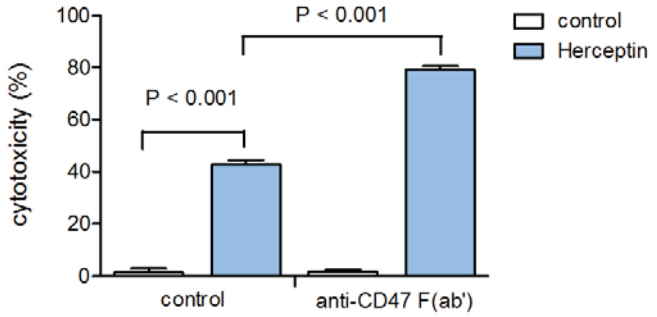

Enhancement of human therapeutic antibody-mediated tumor cell destruction by interfering with CD47-SIRP¤ interactions. Inhibition of CD47-SIRP¤ interactions by anti-CD47 F(ab')2 antibody fragments in a human ADCC assay involving SKBR-3 breast cancer cells, Herceptin© (Trastuzumab) therapeutic monoclonal antibody, and human neutrophils. Cytotoxicity was determined using 51Cr-realease assay. Note that targeting CD47-SIRP¤ interactions synergistically enhances Herceptin©-mediated breast cancer cell killing. Also note that anti-CD47 F(ab')2 antibody alone is not affecting tumor cell killing.

Key publications

1. Mark P. Chao, Ash A. Alizadeh, Chad Tang, June H. Myklebust, Bindu Varghese, Saar Gill, Max Jan, Adriel C. Cha, Charles K. Chan, Brent T. Tan, Christopher Y. Park, Feifei Zhao, Holbrook E. Kohrt, Raquel Malumbres, Javier Briones, Randy D. Gascoyne, Izidore S. Lossos, Ronald Levy, Irving L. Weissman, and Ravindra Majeti (2010) Anti-CD47 Antibody Synergizes with Rituximab to Promote Phagocytosis and Eradicate Non-Hodgkin Lymphoma. Cell. 2010 Sep 3;142(5):699-713.

2. Glennie, M. J. and J. G. J. van de Winkel (2003) Renaissance of cancer therapeutic antibodies. Drug Discovery Today 8:503-510.

Intellectual Property

Patent application EP2111869A1, filed: 23.04.2008
Direct link.

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