KIR3DL2 belongs to the killer immunoglobulin-like (Ig)-like receptors (KIR) family and bears 3 extracellular Ig-like domains. KIR3DL2 is naturally expressed on some NK cells and minor sub-populations of CD8+ and CD4+ T cells. Physiologically, KIR3DL2 is an inhibitory receptor for human leukemia antigen (HLA) class I regulating NK cell activation. Remarkably, KIR3DL2 is also aberrantly overexpressed on subtypes of T lymphoma leukemias, such as Sezary Syndromes, transformed Mycosis Fungoides and HTLV-I+ Adult T Cell Leukemia (Obemba, B.; H. Hemmati, 2007), making it a unique therapeutic target in cancer.

We have generated a series of anti-KIR3DL2 monoclonal antibodies (mAbs) binding selectively to KIR3DL2. Their efficacy was evaluated in vitro and in vivo against KIR3DL2-expressing tumors and Sezary cell lines to disease model. Various modes of action, such as complement-dependent cytotoxicity (CDC) and antibody-dependent cell cytotoxicity (ADCC) were found involved in their antitumor activity. In parallel, other anti-KIR3DL2 mAbs were also developed as sensitive tools for the detection by immunohistochemistry (IHC) of KIR3DL2 on tumor biopsies.

Owing to the highly restricted expression pattern of the target on some T-leukemia/lymphoma cells and to the promising efficacy profile of our anti-KIR3DL2 mAb candidates, an antibody-based therapy targeting KIR3DL2 stands as a potentially unequalled strategy in several orphan diseases with critical unmet medical need.

The KIR molecules and their ligands

**Efficacy in vivo in mouse xenograft models**

Human tumor cells HUT78 were engrafted in NOD-SCID mice. Tumor growth (glycemic control: 5.41 ± 0.13 mmol/L; control: 10.98 ± 1.16 mmol/L) was measured with 3-10× higher tumor volumes in the control group compared to the mAb #1 group. Tumor volumes in the mAb #1 group were reduced to 30% of the control values. These results demonstrate the potential of KIR3DL2 as a novel therapeutic target in cancer.

**Ado-ADCC in vitro against HUT78 Sezary cell line**

Close-ranging ADCC activity of mAbs H7 and H8 against HUT78, with also NK cells purified from healthy volunteers’ blood as effector target (E/T ratio 1/10). The activity of anti-CD3 antibodies is evaluated as positive control.

**Autologous ex vivo NK killing of primary Sezary leukemic cells**

Sezary patient PBMC were prepared immediately after blood sampling and analyzed by flow cytometry: representative images of double staining for CD4 and CD8 cells are displayed. The co-expression of CD4 and CD8 cells are displayed in red (CD4), and in green (CD8). The activity of anti-CD3 antibodies is evaluated as positive control. The activity of anti-CD3 antibodies is evaluated as positive control.

**Biomarker and diagnostic tools**

We have generated a series of novel anti-KIR3DL2 mAbs. Based on in vitro and in vivo results, we have humanized 2 mAbs (H7 & H8) for further development. The first anti-KIR3DL2 mAb lead candidate will be chosen by mid-2013 and IND-enabling regulatory studies will be initiated.

We have successfully completed most steps in the selection of our mAb candidates that will be developed for the treatment of KIR3DL2-positive cancer cell lines. Since these cancer cell lines have been found to express KIR3DL2, the development of novel KIR3DL2-directed therapies holds promising therapeutic promise.