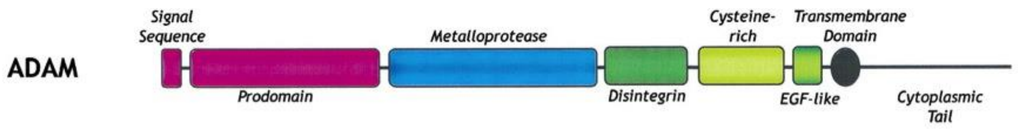
MABs Targeting ADAM12 in Cancer

A novel approach to anti-invasive and anti-metastatic treatment

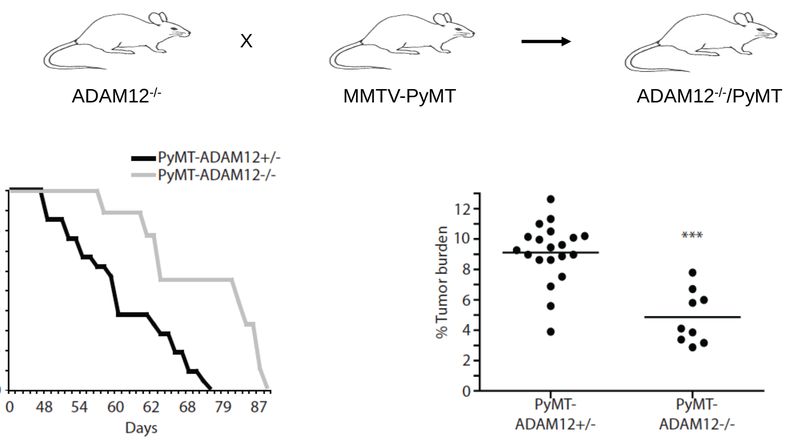
Biotech and Health Care

ADAM12 – A Disintegrin And Metalloprotease



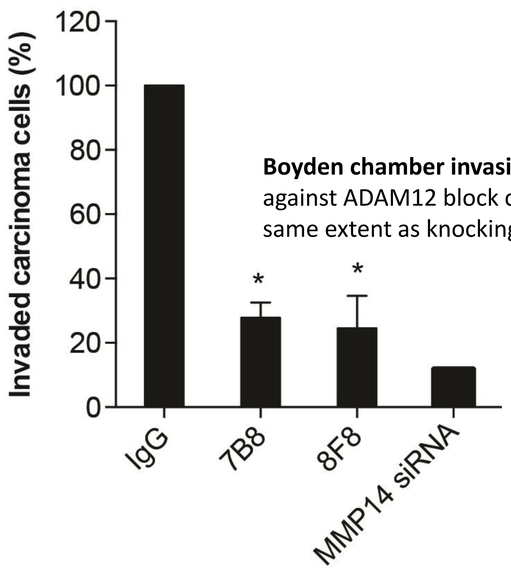
- **is highly expressed in e.g. human breast carcinoma cells and correlates with disease stage**
- **promotes tumor progression in mouse models of cancer**
- **enhance tumor growth independent of its own proteolytic activity**
- **regulates MT1-MMP (MMP14) cell surface levels and activity**

ADAM12-deficiency decreases tumor progression in a mouse model of breast cancer

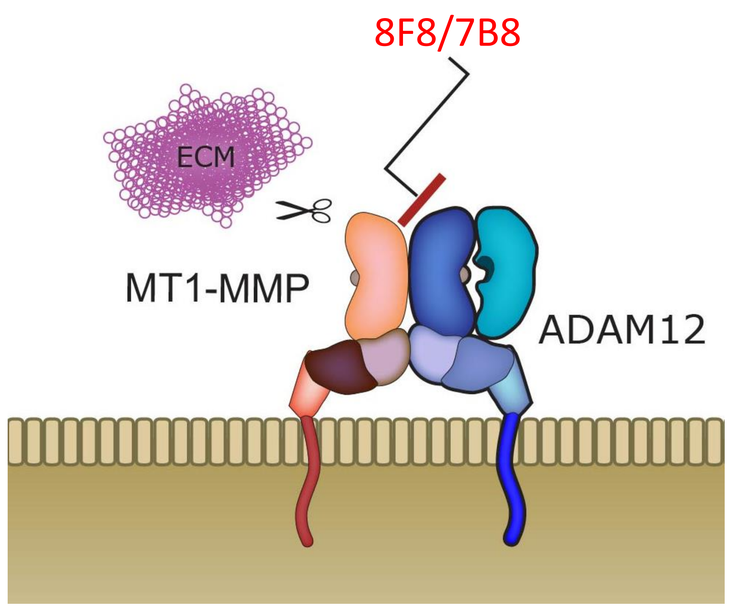


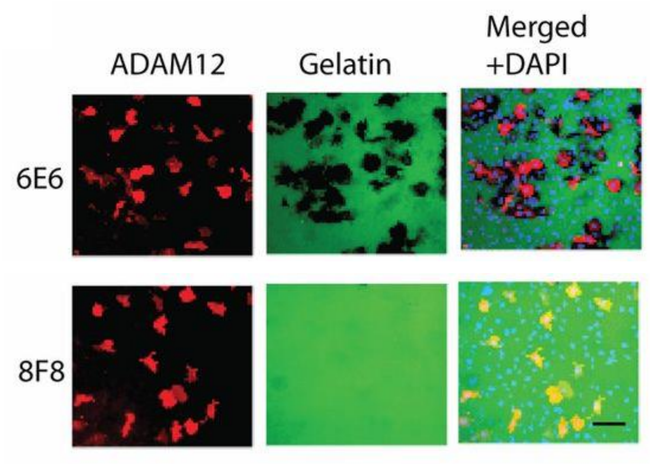
Fröhlich et al. Mol. Cancer Res. 2011

Monoclonal antibodies against ADAM12 block MT1-MMP-mediated extracellular matrix (ECM) degradation and cancer cell invasion in vitro



Boyden chamber invasion assay. Monoclonal antibodies against ADAM12 block carcinoma cell invasion to the same extent as knocking down MT1-MMP expression





Monoclonal antibodies against ADAM12 block the ADAM12-induced MT1-MMP-mediated gelatin degradation

Effect of treating the cells with two different monoclonal antibodies against ADAM12. The 6E6 clone has no effect, whereas 8F8 blocks the ADAM12-mediated MT1-MMP activation.

Value proposition/USP

By using monoclonal antibodies targeting ADAM12 it is possible to prevent metalloprotease MT1-MMP (MMP14)-mediated degradation of the cellular matrix (ECM). Thus, ADAM12 represents a target for anti-invasive and anti-metastatic treatment, which remains an underexplored field in cancer treatment. ADAM12 is expected to be a good cancer drug target because it is expressed at very low levels in normal adult tissues. Yet, it is upregulated upon tissue injury or excessive growth as seen in cancer or re-generation.

Business Opportunity/Objectives

The need for novel anti-cancer treatments remains high and the market opportunities significant. ADAM12 antibodies that can be developed into therapeutic compounds or serve as starting points for antibody drug development are available. An example of an important target indication could be **glioblastoma,** which is extremely invasive. Even as a second or third line treatment, an effective anti-invasive therapy would be of clinical utility. Another early clinical relevant target indication may be **pituitary adenomas.**

Technology description

Two monoclonal antibodies (7B8 and 8F8), developed by immunization of ADAM12-knockout mice both inhibit ADAM12-induced MMP14 activation without affecting ADAM12's own enzymatic activity. Specifically, both antibodies inhibit MMP14-mediated gelatin degradation and in vitro invasion of human breast carcinoma cells.

Development phase

Novo Seed has supported a pre-seed project. While the two antibodies inhibiting the ADAM12-MMP14 cooperation do not affect tumor cell proliferation in vitro or xenograft growth in vivo, they both have a very strong inhibitory effect on in vitro cancer cell invasion through matrigel (Boyden chamber assay). An effect that is similar to the effect of siRNA-mediated knockdown of MMP14. This is shown in the figure above. These findings are well in line with previous reported observations that both mAbs block the ADAM12-induced MMP14 activation and subsequent enhanced ECM degradation. One of the next steps will be to test the efficacy of the 7B8 and 8F8 mAbs in experimental metastasis models in mice.

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