Thus, it is known in the field that external beam high doserate irradiation can cause increased antigen expression and that radioimmunotherapy and monoclonal antibody therapy can cause reduced antigen expression in cancer cells.

The present standard of administration radioimmunotherapy as a reduction treatment, e.g., rituximab (the antibody) is given as a conditioning treatment before Zevalin (the radioimmunoconjugate).

A problem with this approach is that experimental work and clinical data have indicated that antibody therapy can cause antigen drift that is a selection pressure towards cells with low antigen expression, which become treatment resistant (Musto and D'Auria, 2011). This has also been indicated in experimental RIT (Elgström et al, 2012).

Therefore would a targeted therapeutic option that could cause the opposite, i.e., an increase of antigens on treated cells be a very valuable therapeutic tool.

**Summary** ~~**of the invention**~~

The present ~~invention~~ disclosure relates to radioimmunoconjugates that are capable of upregulating expression of one or more antigens. The upregulated antigens can be the antigens that are targeted by the radioimmunoconjugates, different antigens expressed on the same cells or a combination.
This expression allows targeting and specific inhibition of cancer cells and cells of the immune system.

In one aspect, the present invention refers to a radioimmunoconjugate comprising a monoclonal antibody targeting CD37, an optional linker, a radionuclide, in upregulating antigen expression of an antigen on the surface of B-cell cancer cells, wherein; the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy in a single administration or in a repeated administration pattern, and the administration of anti-CD20 antibody is 0-15 days after administration of radioimmunoconjugate. In another aspect, the present invention refers to a) a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, a radionuclide, and b) an anti-CD20 antibody, for use in the treatment of a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, wherein the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy in a single administration or in a repeated administration pattern, and the administration of anti-CD20 antibody is 0-15 days

after administration of radioimmunoconjugate. In yet another aspect, the present invention refers to use of a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, and a radionuclide, in the manufacture of a medicament for treating a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, the use comprising a radioimmunoconjugate, to be administered, comprising, a monoclonal antibody targeting CD37, an optional linker, a radionuclide, and an anti-CD20 antibody to be administered, wherein the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy to be administered in a single administration or in a repeated administration pattern, and wherein anti-CD20 antibody is to be administered 0-15 days after administration of radioimmunoconjugate.

Thus, one ~~aspect~~ example of the present ~~invention relates~~ disclosure describes ~~to~~ a radioimmunoconjugate comprising a monoclonal antibody, an optional linker, and a radionuclide, for use in upregulating antigen expression of one or more antigens.

In one ~~embodiment~~ example of the present ~~invention~~ disclosure are the one or more upregulated antigens expressed on the surface of B-cell cancer cells.

In another example ~~embodiment~~ of the present disclosure ~~invention~~ is the upregulation done prior to immunotherapy or immunoconjugate therapy in a patient suffering from cancer.

In a further example ~~embodiment~~ of the present disclosure ~~invention~~ is the patient suffering from a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma and chronic lymphocytic leukemia.

In yet another example ~~embodiment~~ of the present disclosure ~~invention~~ is the radiolabeled monoclonal antibody HH1.

In one example ~~embodiment~~ of the present disclosure ~~invention~~ is the linker a chelating linker selected from the group consisting of p-SCN-bn-DOTA, DOTA-NHS-ester, p-SCN-Bn-DTPA and CHX-A''-DTPA.

In another example ~~embodiment~~ of the present disclosure ~~invention~~ is the radionuclide selected from the group consisting of $^{47}Sc$, $^{67}Cu$, $^{90}Y$, $^{105}Rh$, $^{117}mSn$, $^{131}I$, $^{149}Tb$, $^{153}Sm$, $^{161}Tb$, $^{165}Dy$, $^{177}Lu$, $^{186}Re$, $^{188}Re$, $^{211}At$, $^{212}Pb$, $^{212}Bi$, $^{213}Bi$, $^{223}Ra$, $^{224}Ra$, $^{225}Ac$, and $^{227}Th$.

In a further example ~~embodiment~~ of the present disclosure ~~invention~~ is the upregulated antigen selected from the group consisting of CD37, CD19, CD20, CD21, CD22, HLA-DR, CD23, CD39, CD52, CDw75, and CD80.

In yet another example ~~embodiment~~ of the present disclosure ~~invention~~ is the radioimmunoconjugate formulated as a pharmaceutical composition.

In another example ~~embodiment~~ of the present disclosure ~~invention~~ comprises the pharmaceutical composition one or more pharmaceutically acceptable carriers or adjuvants.

In a further example ~~embodiment~~ of the present disclosure ~~invention~~ is the use for a combinational therapy where the radioimmunoconjugate is followed by simultaneous or post-treatment with antibody therapy, immunoconjugate therapy or a combination thereof.

In another example ~~embodiment~~ of the present disclosure ~~invention~~ is the upregulated antigen CD20, and the upregulation is followed by anti-CD20 antibody therapy with rituximab in a single administration or in a repeated administration pattern.

In yet another example ~~embodiment~~ of the present disclosure ~~invention~~ is the simultaneous or post-treatment targeting a different antigen than the radioimmunoconjugate.

Another example ~~aspect~~ of the present disclosure discloses ~~invention relates to~~ a method of upregulating antigen expression comprising administration of a radioimmunoconjugate to a person in which an upregulated antigen expression would be advantageous.

In one example ~~embodiment~~ of the present disclosure ~~invention~~ is the person suffering from a B-cell malignancy.

In another example ~~embodiment~~ of the present disclosure ~~invention~~ is the use a combinational therapy where the radioimmunoconjugate is followed by simultaneous or post-treatment with antibody therapy, immunoconjugate therapy or a combination thereof.

In another example ~~embodiment~~ the radioimmunotherapy and immunotherapy or immunoconjugate therapy is repeated in several cycles.

In another example ~~embodiment~~ the radioimmunotherapy is given as a low dose which by itself has a low cell kill effect in tumors, but has a significant antigen upregulation.

**Brief description of the figures**

Figure 1 shows increase in CD20 and CD37 expression for Daudi cells after 24 h incubation with Betalutin (t = 0 after removal of Betalutin in addition of fresh medium) as measured by flow cytometry.

Figure 2 shows upregulation of CD37 and CD20 for Daudi cells incubated during 1 h and 24 h with $^{177}$Lu-tetulomab (Betalutin) as measured by flow cytometry.

11. The radioimmunoconjugate for the use according to anyone of claims 1-10, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable carriers or adjuvants.

12. Use of a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, and a radionuclide, in the manufacture of a medicament for treating~~A method of treatment of a of~~ a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, the use comprising:

- ~~administration of~~a radioimmunoconjugate, to be administered, comprising,

- a monoclonal antibody targeting CD37,

- an optional linker,

- a radionuclide, and

~~- administration of:~~

- an anti-CD20 antibody to be administered, wherein

the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy to be administered in a single administration or in a repeated administration pattern, and ~~the administration of~~ wherein anti-CD20 antibody is to be administered 0-15 days after administration of radioimmunoconjugate.