The uptake in the cell line Raji was compared for bismuth conjugated to HH1 or streptavidin. In the latter case cells had been presaturated with biotinylated-HH1.

It was found that the number of chelators required to ensure functional RIC when labeled with ^{212}Bi or ^{213}Bi was a limiting factor. It was therefore suggested to use biotinylated HH1 instead of a HH1 based RIC. Once bound to the cells, the biotinylated HH1 could then be targeted with radiolabeled streptavidin.

Thus, the work suggests that HH1 labeled with an alpha-particle-emitting radionuclide was less useful due to insufficient specific activity at the chelator concentrations deemed tolerable for the HH1 to retain sufficient binding ability.

It was also indicated in the paper that a beta-emitter would be even less suitable for constructing a functional RIC compared with an alpha-emitter (Henriksen et al, 1997) as the authors stated that targeted radiotherapy with beta-emitter should be inferior in disseminated disease because cross-fire is essential for obtaining sufficient effect.

Thus, the above cited work teaches away from using a directly chelated HH1 in radioimmunotherapy and also away from using HH1 in a beta-emitter based RIC.

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

The present ~~invention~~disclosure relates to a radioimmunoconjugate that binds human CD37 comprising murine monoclonal antibody HH1, a linker, and a radionuclide selected from the group consisting of ^{211}At, ^{213}Bi, ^{212}Bi, ^{212}Pb, ^{225}Ac, ^{227}Th, ^{90}Y, ^{186}Re, ^{188}Re, ^{199}Au, ^{194}Ir, ^{166}Ho, ^{159}Gd, ^{153}Sm, ^{149}Pm, ^{142}Pr, ^{111}Ag, ^{109}Pd, ^{77}As, ^{67}Cu, ^{47}Sc, and ^{177}Lu.

In one aspect, there is disclosed herein a radioimmunoconjugate that binds human CD37 comprising:

a) murine monoclonal antibody HH1,

b) a chelating linker, and

c) a radionuclide selected from the group consisting of ^{177}Lu, ^{212}Pb, ^{225}Ac, ^{227}Th and ^{90}Y.

In an ~~embodiment~~example of the present ~~invention~~disclosure the linker is a chelating linker and the radionuclide is ^{177}Lu.

An ~~aspect~~example of the present ~~invention~~disclosure relates to a pharmaceutical composition comprising a radioimmunoconjugate of the present ~~invention~~disclosure, and a pharmaceutically acceptable carrier.

In another aspect, there is disclosed herein a pharmaceutical composition comprising a radioimmunoconjugate as defined above, and a pharmaceutically acceptable carrier.

In an ~~embodiment~~example of the present ~~invention~~disclosure the pharmaceutical composition of the present ~~invention~~disclosure comprises one or more additional antibodies or radioimmunoconjugates.

In another ~~embodiment~~example of the present ~~invention~~disclosure one or more additional antibodies or radioimmunoconjugates target CD20.

In another aspect, there is disclosed herein a radioimmunoconjugate that binds human CD37 comprising:

a) murine monoclonal antibody HH1,

b) a chelating linker, and

c) a radionuclide selected from the group consisting of ^{177}Lu, ^{225}Ac, ^{212}Pb, ^{227}Th and ^{90}Y,

for use in the treatment of a B-cell malignancies selected from non-Hodgkin lymphoma and chronic lymphocytic leukemia.

In a further aspect, there is disclosed herein a radioimmunoconjugate that binds human CD37 comprising:

a) murine monoclonal antibody HH1,

b) a chelating linker, and

c) a radionuclide selected from the group consisting of ^{177}Lu, ^{212}Pb, ^{225}Ac, ^{227}Th and ^{90}Y,

for use in therapy.

A further ~~embodiment~~example of the present ~~invention~~disclosure relates to a pharmaceutical composition of the present ~~invention~~disclosure for treating B-cell malignant cells expressing the CD37 antigen.

In a further aspect, there is disclosed herein the use of a pharmaceutical composition as defined above in the manufacture of a medicament for treatment of a B-cell malignancy selected from non-Hodgkin lymphoma and chronic lymphocytic leukemia.

In an ~~embodiment~~example of the present ~~invention~~disclosure the pharmaceutical composition is for treatment of non-Hodgkin lymphoma and chronic lymphocytic leukemia.

In a further aspect, there is disclosed herein the use of the radioimmunoconjugate as defined above, in the manufacture of a medicament for the treatment of B-cell malignancies.

An ~~aspect~~example of the present ~~invention~~disclosure relates to the use of the radioimmunoconjugate of the present ~~invention~~disclosure for the treatment of B-cell malignancies.

An ~~embodiment~~example of the present ~~invention~~disclosure relates to the use of the radioimmunoconjugate of the present ~~invention~~disclosure administered in combination with or in addition to other therapy.

In an ~~embodiment~~example of the present ~~invention~~disclosure the therapy is selected from pretreatment, chemotherapy, monoclonal antibody therapy, surgery, radiotherapy, and/or photodynamic therapy.

In another ~~embodiment~~example of the present ~~invention~~disclosure the therapy comprises pre-treatment using anti-CD20 and/or anti-CD37 monoclonal antibody prior to the treatment with the radioimmunoconjugate of the present ~~invention~~disclosure.

An ~~aspect~~example of the present ~~invention~~disclosure relates to a method for treatment of a B-cell malignancy selected from non-Hodgkin lymphoma and chronic lymphocytic leukemia, comprising administration of an effective amount of a pharmaceutical composition of the present ~~invention~~disclosure.

In one aspect, there is disclosed herein a kit for the production of the radioimmunoconjugate as defined above comprising two or more vials, wherein one vial contains a conjugate comprising a chelator linked to a murine monoclonal antibody HH1; and a second vial contains a radionuclide.

Another ~~aspect~~example of the present ~~invention~~disclosure relates to a kit for the production of the radioimmunoconjugate of the present ~~invention~~disclosure comprising two or more vials, wherein one vial contains a conjugate comprising a chelator linked to a murine monoclonal antibody HH1; and a second vial contains a radionuclide.

An ~~embodiment~~example of the present ~~invention~~disclosure relates to a kit of the present ~~invention~~disclosure, wherein the content of one or several of the vials are either lyophilized or in a solution.

In another ~~embodiment~~example of the present ~~invention~~disclosure the radioimmunoconjugate is generated by mixing the content of the two vials.

Brief description of the figures

Figure 1
Cell-bound antibody immediately (A) and 96 hours (B) after washing for incubation of Raji, Rael and Daudi cells with ^{111}In-HH1, ^{111}In-rituximab, ^{125}I-HH1 and ^{125}I-rituximab.

Figure 2
Activity bound to Daudi cells after incubation with ^{177}Lu-HH1 or ^{177}Lu-rituximab for 2 h (A) and 18 h (B). Blocked cells were blocked with 100 µg/ml unlabeled antibody.

Figure 3
Growth of Daudi cells incubated with ^{177}Lu-HH1 (A) or ^{177}Lu-rituximab (B) for 2 h before washing.

Figure 4
Growth of Daudi cells incubated with ^{177}Lu-HH1 (A) or ^{177}Lu-rituximab (B) for 18 h before washing.

Figure 5
Biodistribution of ^{111}In-labeled via chelator to HH1 in mice with Daudi xenografts.

17. A radioimmunoconjugate that binds human CD37 comprising:

a) murine monoclonal antibody HH1,

b) a chelating linker, and

c) a radionuclide selected from the group consisting of ^{177}Lu, ^{212}Pb, ^{225}Ac, ^{227}Th and ^{90}Y,

for use in therapy.