

Actinium-225 conjugates of MAb CC49 and Humanized $\Delta\text{CH}_2\text{CC49}$

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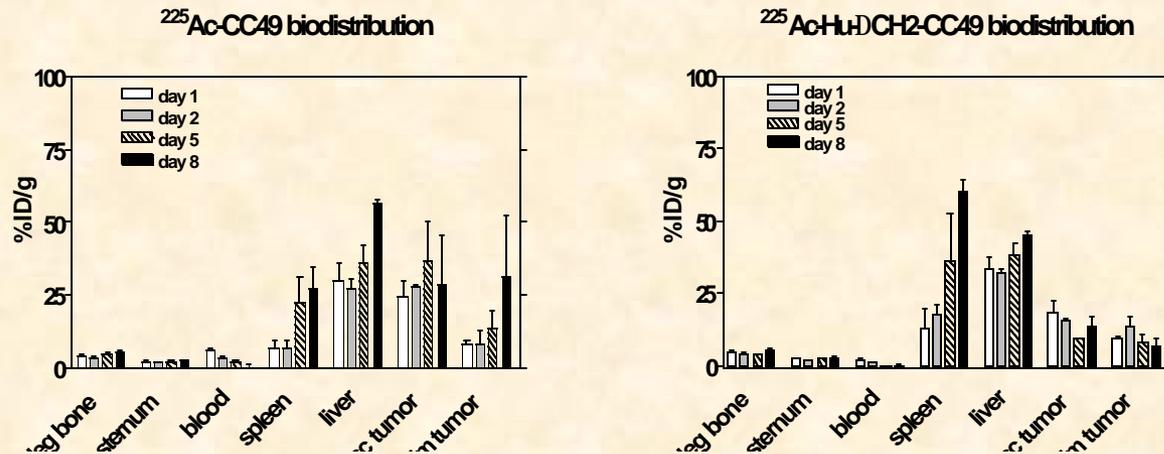
Monoclonal antibodies have been used to deliver radioisotopes to tumors. Radioisotopes that emit alpha particles are particularly attractive since they are extremely toxic at short range, thus limiting damage to the targeted area. Most alpha emitters decay with very short half lives which limits the time for specific accumulation at the tumor site. Actinium-225, with a half-life of 10 days and a yield of 4 alpha particles in its decay chain, may be an ideal choice for tumor-targeted radioimmunotherapy. One of the best monoclonal antibodies to tumor cells, MAb CC49, binds selectively to many human carcinomas with little binding to normal tissue. Furthermore, humanized forms of the parent antibody and smaller molecular forms such as the domain-deleted product Hu- ΔCH_2 CC49, have been prepared and found to be superior delivery systems for radioisotopes.

In this work, we have conjugated a chemical chelator (HEHA) to the antibodies which promotes stable attachment of ²²⁵Ac. Actinium-225 HEHA MAb CC49 conjugates were tested for specific accumulation and cellular distribution in human carcinomas growing in immunocompromised mice. Actinium bound to MAb CC49 and Hu- ΔCH_2 CC49 was delivered efficiently to tumor sites. Using microautoradiography, it was shown that the distribution of the radiolabel within the tumor was non-uniform. This property limits the therapeutic efficiency of alpha emitters. However, at very low injected doses of 0.25 and 0.50 μCi of ²²⁵Ac MAb CC49 retardation of tumor growth was observed. The potential of ²²⁵Ac in radioimmunotherapy has limitations, but recent advances in its delivery and uptake by tumor cells make it a top candidate alpha emitter for endoradioimmunotherapy.

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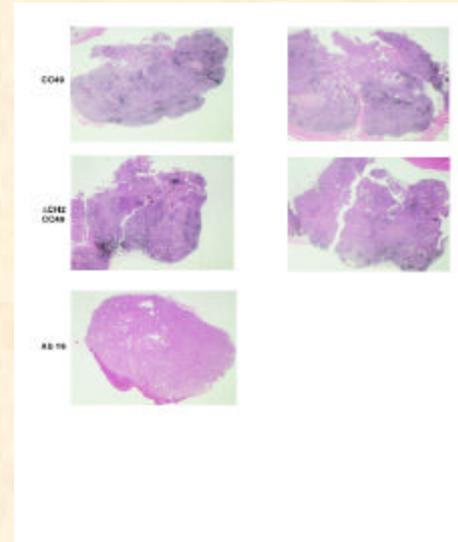
- Monoclonal antibodies have been used to deliver radioisotopes to tumors. Humanized forms of the parent antibody and smaller molecular forms such as the domain-deleted product Hu- $\Delta\text{CH}_2\text{CC49}$, have been prepared and found to be superior delivery systems for radioisotopes.
- A chemical chelator (HEHA) which promotes stable attachment of ^{225}Ac was conjugated to the antibodies. Actinium-225 HEHA MAb CC49 conjugates were tested for specific accumulation and cellular distribution in human carcinomas growing in immunocompromised mice.



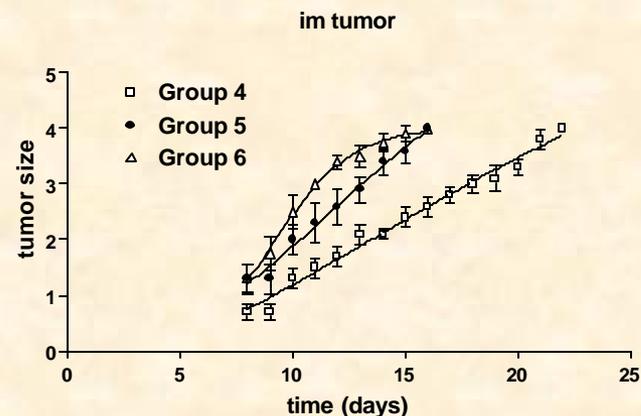
Biodistribution data show that although radioisotope accumulates in the spleen and liver, a relatively large fraction also accumulates in tumors

Actinium-225 conjugates of MAb CC49 and Humanized $\Delta\text{CH}_2\text{CC49}$ (contd.)

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- However, at very low injected doses of 0.25 and 0.50 μCi of ^{225}Ac MAb CC49 retardation of tumor growth was observed. The potential of ^{225}Ac in radioimmunotherapy has limitations, but recent advances in its delivery and uptake by tumor cells make it a top candidate alpha emitter for endoradioimmunotherapy.



Autoradiography shows that radioisotope is distributed non-uniformly in tumors. (^{225}Ac in black). Control MAb 16 (bottom panel does not accumulate in the tumor).



^{225}Ac MAb CC49 (group 4) retards tumor growth relative to ^{225}Ac coupled to non-targeting MAb 16 (group 5) or to untreated controls (group 6).