ZZ-PE38: a universal technology for immunotherapy (Ramot)

code: 10-2009-83

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The Technology

A novel fusion protein capable of binding to any internalizing IgG, thus forming a specific and potent immunotoxin, has been developed. The antibody-toxin conjugate is formed through an immuno-complex and may be further stabilized by chemical crosslinking. Such immunotoxins undergo efficient internalization, thus delivering the cytotoxic cargo and killing the target cells.

Immunotoxins are potent, targeted, cell-killing agents. They kill target cells via binding to a surface antigen, internalization and delivery of the cytotoxic cargo to the cell cytosol. Internalization is a pre-requisite for immunotoxin drug delivery approaches. To date, immunotoxins have not yet been proven as effective anti cancer agents. A few are undergoing clinical trials.

Potential Applications

- Generating potent, site-specific antibody-toxin conjugates useful as anti cancer therapeutics.
- Determining whether a particular antibody is suitable for anti-cancer therapy that requires internalization of the antibody-toxin conjugate.
- Determining whether a particular cell-surface molecule is a potential immunotherapeutic drug target.

Advantages

- Flexibility with regard to the targeting elements, as any of a variety of antibodies can be selected
- Stable and less toxic
- Simple, homogeneous, easy to construct

Data-to-date

- anti-ErbB2-PE immunoconjugate was cytotoxic for human tumor cell lines expressing varying levels of ErbB2 receptors (breast adenocarcinoma SKBR3 epidermoid carcinoma A431, breast carcinoma T47D and MCF7, mammary carcinoma MDA-MB231).
- IC50 values correlated with the levels of ErbB2 receptor expression.
- SKBR3 and A431 tumor cells were most sensitive to the immunoconjugate with IC50 values of 3.5 ng/ml and 1.8 ng/ml, respectively.
- Nude mice xenografts (s.c. human breast epidermoid carcinoma A431)
- Mice treated at the 0.5 mg/kg dose level were in complete remission of the tumor that lasted for over one month until the animals were sacrificed.
- anti-ErbB2 IgG-PE immunoconjugate had a serum half-life of 240 min.
- Cetuximab ZZ-PE38 forms non-covalently bound complex. IC50 =0.00047 mg/ml
- Treatment in vivo studies resulted in significantly smaller tumor size (SCC-1- H&N) (~70 mm3 to ~40 mm3 and ~20 mm3)
- Cetuximab-ZZ-PE38 complex was more effective than Cetuximab or ZZ-PE38 alone.
- Cytotoxic effect of Cetuximab -ZZ PE38 complex is higher in cells expressing high EGFR
- No cytotoxic effect of Cetuximab-ZZ-PE38 on normal fibroblast cells

Patent status

US 8,043,621 & CIP

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