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Alefacept is a novel dimeric fusion protein produced by recombinant DNA technology in a Chinese hamster ovary. It comprises the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc portion of human-IgG1, and selectively targets memory T cells. It is approved for the treatment of psoriasis,[9] and has been studied in patients with steroid resistant/dependent GVHD after HSCT (hematopoietic stem cell transplantation) with some success.[10] Given the dismal responses seen with conventional immunosuppressive treatments for GVHD after transfusion or solid organ transplantation,[1,3] alefacept may offer a reasonable treatment alternative in a setting cwhere outcomes have generally been fatal. Its use may also provide a clinical model for bone marrow failure states.

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To the editor:

NGR and isoDGR are separate moieties binding to different receptors

Bieker et al interestingly reported that NGR peptide–directed targeting of a truncated form of the human coagulation-inducing protein tissue factor (tTF-NGR) is able to induce thrombosis in the tumor vasculature of preclinical models and to inhibit tumor perfusion in humans.[1] This work represents a further piece of evidence indicating that peptides containing the NGR (asparagine-glycine-arginine) motif can selectively bind to tumor vessels and can therefore be exploited for ligand-directed targeted delivery of various drugs and particles to tumors.[2] In addition, it provides support for developing peptide-based targeting approaches for the treatment of cancer.

However, the authors claim that tTF is delivered to blood vessels through the binding mediated by the GNGRAHA linear peptide to both aminopeptidase N (CD13) and αvβ3 integrin expressed onto the tumor endothelium. In our opinion, this conclusion may be questioned because the authors neither formally prove that GNGRAHA is able to bind to αvβ3 integrin, nor provide indirect evidence of it through the quantitation of Asn deamidation (ie, Asn → isoAsp/Asp generating new αvβ3-binding ligands[3]) of the NGR motif in the tTF-NGR product, a nonenzymatic conversion that can occur at variable extent during manufacturing due to the exposure of the product to varying conditions of pH, temperature, and buffering. In addition, published data demonstrate that NGR-containing peptides other than GNGRAHA bind to CD13[4] and lack the necessary pharmacophoric requirements to bind to αvβ3,[5] providing support for the concept that NGR and isoDGR motifs as 2 separate moieties binding to different receptors. Although different NGR-containing peptides do not necessarily display the same features, including binding properties and affinities along with the extent of in vitro and in vivo stability, Curnis et al[3] showed that in defined experimental conditions (incubation in 0.1 M ammonium bicarbonate buffer, pH 8.5, for 16 h at 37°C), the Asn of the NGR site of both fibronectin fragments and synthetic CNGRCGVRY cyclic peptide (called NGR-2C) is not stable and can undergo deamidation, thus inducing the formation of isoAsp-containing ligands able to bind to αvβ3, unlike NGR-2C.[5] However, these experimental conditions are nonphysiologic and induce Asn deamidation with surprisingly rapid kinetics (half-life of 3-4 hours[3]), whereas these kinetics might differ significantly in vivo. Consistently, we hypothesise that a NGR-containing intravenous product in vivo undergoes deamidation with a much longer half-life, thus accompanied by a negligible generation of αvβ3 ligands. Therefore, to draw reliable binding predictions, it is critical to quantify the amount of isoAsp content in any NGR-containing drug preparation and to test deamidation kinetics in appropriate in vivo experimental models.

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