Article

Design, Synthesis, and Functionalization of Dimeric Peptides Targeting Chemokine Receptor CXCR4

Oliver Demmer†, Ingrid Dijkgraaf‡, Udo Schumacher§, Luciana Marinelli∥, Sandro Cosconati∥, Eleni Gourni‡, Hans-Jürgen Wester‡, and Horst Kessler†⊥*

Institute for Advanced Study and Center of Integrated Protein Science at the Department Chemie, Technische Universität München, Lichtenbergstrasse 4, D-85748 Garching, Germany

Lehrstuhl für Pharmazeutische Radiochemie, Technische Universität München, Walther-Meissner-Strasse 3, 85748 Garching, Germany

Institute for Anatomy II: Experimental Morphology, Universitätsklinikum Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

Dipartimento di Chimica Farmaceutica e Tossicologica, Università di Napoli "Federico II", Via D. Montesano, 49-80131 Napoli, Italy

Chemistry Department, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

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Phone: ++49 + 89/289-13300. Fax: ++49 + 89/289-13210. E-mail: Kessler@tum.de. Address: Institute for Advanced Study, Technische Universität München, Lichtenbergstrasse 2a, D-85748 Garching, Germany.

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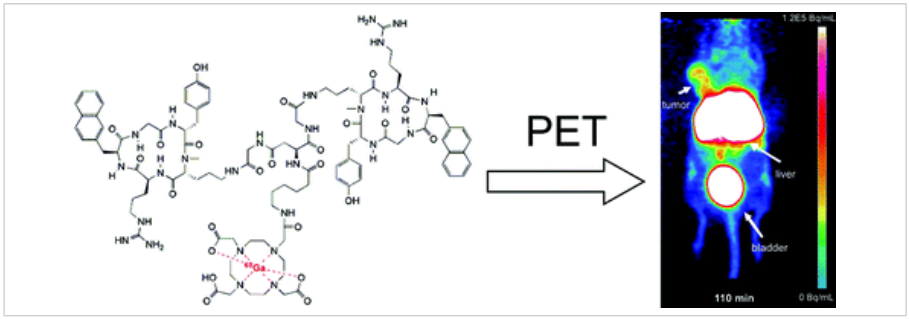

The chemokine receptor CXCR4 is a critical regulator of inflammation and immune surveillance, and it is specifically implicated in cancer metastasis and HIV-1 infection. On the basis of the observation that several of the known antagonists remarkably share a C_2 symmetry element, we constructed symmetric dimers with excellent antagonistic activity using a derivative of a cyclic pentapeptide as monomer. To optimize the binding affinity, we investigated the influence of the distance between the monomers and the pharmacophoric sites in the synthesized constructs. The affinity studies in combination with docking computations support a two-site binding model. In a final step, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) was introduced as chelator for (radio-)metals, thus allowing to exploit these compounds as a new group of CXCR4-binding peptidic probes for molecular imaging and endoradiotherapeutic purposes. Both the DOTA conjugates and some of their corresponding metal complexes retain good CXCR4 affinity, and one ^{68}Ga labeled compound was studied as PET tracer.

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