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Title: An antedrug of the CXCL12 neutraligand blocks experimental allergic asthma without systemic effect in the mouse

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Body: The chemokine receptor CXCR4 and its chemokine CXCL12 are involved in normal tissue patterning, and also in the recruitment of immune and inflammatory cells as successfully demonstrated in the airways using agents that block either CXCL12 or CXCR4. In order to achieve selectivity in drug action on the CXCR4/CXCL12 pair in the airways, drugs should be delivered as selectively as possible in the treated tissue, and should not diffuse in the systemic circulation where it may reach undesired organs. To this end, we created a short-lived drug - or soft drug - based on the CXCL12-neutralizing small molecule, chalcone 4, which blocks binding of CXCL12 to CXCR4. We show that the compound, carbonitrile-chalcone 4, blocks the recruitment of eosinophils to the airways in ovalbumin-sensitized and challenged mice in vivo when administered directly to the airways by intranasal route (300 nmol/kg; 45% reduction), but remains inactive when administered systemically by intraperitoneal route (350 µmol/kg). We show that the lack of effect at a distant site is due to the rapid degradation of the molecule to inactive fragments. This approach allows selective action of the CXCL12 neutraligands in the airways, even though the target protein is widely distributed in the organism.