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Treatment and cure strategies for WHIM syndrome immunodeficiency

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Gain-of-function mutations in chemokine receptor CXCR4 cause the autosomal dominant immunodeficiency disorder WHIM syndrome. We have conducted a Phase 1 clinical trial of plerixafor, a specific CXCR4 antagonist, in patients with WHIM syndrome. Treatment was well-tolerated over 6 months and was associated with reduced infection frequency and wart burden. Interestingly, patient WHIM-09 was spontaneously cured in adulthood by chromothripsis (chromosome shattering) of one copy of chromosome 2, which fortuitously deleted the WHIM allele of CXCR4 and 163 other genes. In mice Cxcr4 haploinsufficiency was sufficient to phenocopy the apparent engraftment advantage of the chromothriptic HSC in WHIM-09. This suggests a mechanism for the patient's cure and a general cure strategy for WHIM syndrome by CXCR4 editing.