

PA41 CCR5 sequestration by RANTES analogues: a rational and plausible strategy for topical prevention of HIV infection.

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ABSTRACT TEXT

Recent years have witnessed a welcome explosion in the development of topical strategies to prevent HIV infection. We present here the rationale for inducing sequestration of the HIV coreceptor using modified RANTES analogues as a microbicide strategy to prevent HIV infection. First, CCR5 expression is not necessary as congenital absence of its surface expression has no deleterious phenotype. Our lead microbicide compound, PSC-RANTES mimics this by promoting durable CCR5 sequestration in human blood cells and blocks HIV infection in these cells, in human epidermal Langerhans cells and in human ectocervical explants. This is an important strategy since sequestration of a host-encoded coreceptor is far less likely to promote viral escape mutation than targeting a viral element or use of a small molecule to block virus-coreceptor binding. This prediction is likely accurate since our sustained efforts to select for PSC-RANTES-resistant mutants in vitro have failed (Mosier, Microbicides '06). What is more, PSC RANTES is not absorbed systemically after topical administration thus selection for resistant viruses is not anticipated even if administered to persons who are HIV infected but not aware of it. In contrast to other foreign proteins, since PSC RANTES differs in structure from the native host RANTES molecule in only a few places, it is less likely to be immunogenic (but this must be proven).

While no untoward inflammatory effects have been seen to date, the agonist activity of this agent must be explored in more detail. In terms of activity, PSC-RANTES is the only single agent topical strategy that has to date provided "complete" (10/10 animals) protection against SHIV 162P3 transmission in the rhesus vaginal challenge model. Finally, we now have access to a fully recombinant RANTES analogue that sequesters CCR5 and has in vitro antiviral activity comparable to that of PSC-RANTES (Hartley, Microbicides '06). Detailed estimates of the cost of production by microbial fermentation suggest that the cost of production would be a few cents per dose (Offord, Microbicides '06). Thus topical sequestration of CCR5 using a RANTES analogue deserves further evaluation as a promising strategy to prevent HIV infection in the developing world.

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