PA24 Variability in the Structure-Function Characteristics of Polystyrene Sulphonate Macromolecules Impinges on the Efficacy of in-vitro HIV-1 Inhibition

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ABSTRACT TEXT

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Background:
A variety of polyanionic compounds have been shown to be useful in topical microbicide formulations. These compounds are thought to work through similar mechanisms of action (e.g. binding via an electrostatic interaction to positively-charged V3 loop of gp120). However, these compounds vary greatly from each other in many physico-chemical features including structure of the hydrophobe, charge density and, importantly, MWt and MWt distribution. Each of these factors impinge on the efficacy of binding to any sterically-restricted surface including gp120. These compounds all carry a negative-charge at neutral pH, however variation in the magnitude of the surface charge over the pH range encompassing vaginal fluid and semen is not known. As part of a long-term, comprehensive in-depth study of the effect of structure-function characteristics on anti-HIV activity, we have focused on critical evaluation of MWt and the effect on in-vitro HIV-1 inhibition using a candidate polyanion, polystyrene sulphonate (PSSA)

Methods:
Samples of PSSA were obtained from a range of commercial sources, and synthesized in-house using the new technique of controlled radical polymerization (CRP). Molar mass was measured using a state-of-the-art hybrid technique, GPC-LS. Anti HIV-1 activity of solutions of the PSSA was determined by established in-vitro cell-based assays.

Results:
There was a strong correlation between the MWt of PSSA and HIV inhibition; initial data suggests the optimum activity appears to be within the range 5kD to 10kD. All samples of the PSSA were found to have a significant distribution in MWt; even GPC standard material had a pronounced shoulder in the distribution. It is possible that macromolecular polyanions, such as PSSA, may be much more potent than hitherto suspected because most of the activity can accrue from only a small percentage of the total sample. The data suggests that MWt fractionation may increase the activity of polyanionic based microbicides.

Conclusions:
These data suggest that PSSA represent a model compound for structure-function studies of polyanionic microbicides. Further work is ongoing to determine the charge density for optimal performance.

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