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# Broad-spectrum toxin inhibitors protecting mice against ricin

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## Background

Ricin remains a significant biothreat and biocrime agent for which no treatment exists. Shiga and Shiga-like toxins are involved in a series of potentially fatal infections including the hemolytic uremic syndrome produced by certain strains of *E. coli*. Cholera toxin is responsible for the pathogenicity of *vibrio cholerae*, responsible for water-born, life-threatening, diarrhea.

## Methods

We used a cell-based high-throughput screening to identify chemical inhibitors of cell intoxication by ricin. Sulfation assay and confocal microscopy of cells labeled with intracellular trafficking markers were applied to identify inhibitors action. Nasal instillation of ricin was applied for *in vivo* studies in mice.

## Results

Two molecules, Retro-1 and -2 were found, which protect cells against ricin, Shiga-like toxins and cholera toxin. Another molecule, compound 20, protected cells against ricin and diphtheria toxin. We showed that Retro-1 and Retro-2 selectively block retrograde toxin trafficking at the early endosomes-TGN interface, without affecting compartment morphology or any other trafficking steps. They do not affect retrograde transport of endogenous cargos, demonstrating an unexpected degree of selectivity and lack of toxicity. Retro-2 protects mice from nasal exposure to ricin (1 LD90). In addition, compound 20, which acts at a different level in the cell, also gives some protection against ricin in mice.

## Conclusions

We discovered the first small molecules that show efficacy against ricin in animal experiments, and identified the retrograde route as a potential therapeutic target.

Keywords: toxin, ricin, Shigatoxin, retrograde transport