

Research Update

A tale of 2 epidemics: link discovered between smallpox and HIV resistance

A London, Ont., virology lab has accidentally uncovered a link between 2 of history's best-known epidemics, AIDS and smallpox (*Science* 1999;286:1968-71). The researchers, who originally worked at the John P. Robarts Research Institute (some have since moved to other centres) found that myxoma virus (a rabbit-specific poxvirus related to human smallpox) uses the same chemokine receptors as HIV to infect immune cells. This is the first time that a virus other than

HIV has been shown to exploit chemokine receptors.

The research team reported that 3 human chemokine receptors, CCR1, CXCR4 and CCR5, all induced infection when mouse cells were exposed to the myxoma virus, which is so lethal to rabbits that it has been used to prevent land from being overrun by them.

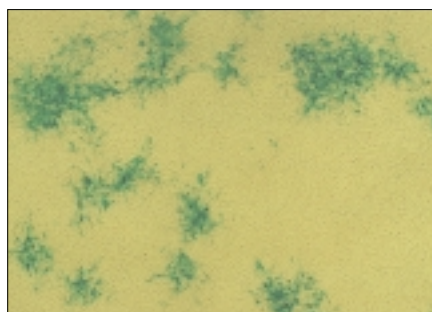
"I think there will be more discoveries of viruses that use these receptors," Robarts virologist Grant McFadden told reporters. "Other viruses and pathogens may offer insights into these receptors."

Because of the involvement of chemokine receptors in inflammation, the discovery will also affect researchers in that field, McFadden added. The Canadian findings may also provide an explanation for the 1% of Caucasians who are immune to HIV infection. It is known that such immunity involves a genetic defect involving chemokine receptors.

"The protective mutation in the CCR5 chemokine receptor gene almost certainly emerged well before HIV be-

gan to infect humans, just about 50 years ago," said Alshad Lalani, lead author of the *Science* article. "Based on genetic analysis, it has been speculated by HIV researchers that the CCR5 mutation probably evolved at least 700 years ago, possibly during the European smallpox plagues." The article reported that myxoma infection of CCR5 mouse cells could be inhibited by RANTES, a protein that normally binds to chemokine receptors, as well as by anti-CCR5 polyclonal antibody or herbimycin A. Pertussis toxin did not prevent infection, and neither did monoclonal antibodies that normally block HIV-1 infection. These findings raise hopes that some form of "blockade" therapy might be possible, McFadden said.

The discovery in McFadden's laboratory was an accidental byproduct of research into chemokine inhibitors. The lab will continue its work on myxoma, but McFadden wants to collaborate with HIV researchers to uncover further implications of the findings. — *David Helwig*, London, Ont.



Microscopic image shows myxoma virus infection of mouse cells expressing human chemokine receptors.

Questioning the association between HRT and prevention of CVD

Postmenopausal women who took hormone replacement therapy (HRT) had fewer cardiovascular risk factors to start with than women who do not, a Swedish longitudinal study has determined (*BMJ* 1999;319:890-3). This means that the lower rates of cardiovascular disease found in women taking HRT could be attributable to better cardiovascular health, not HRT. In a result that is sure to be controversial, the study's authors conclude that it is premature to recommend HRT for the prevention of cardiovascular disease.

The study followed 1201 women for 24 years, of whom 15% eventually used HRT. Those who used it had signifi-

cantly lower blood pressure and were less likely to be obese. HRT users were also more physically active and had higher social status than nonusers.

Dr. Kerstin Rödström of Gothenburg, Sweden, the report's principal author, is critical of previous studies showing a cardioprotective effect of HRT — as much as 50% risk reduction in some studies. "HRT might have a protective effect, but we think this has been exaggerated. In previous observational studies, there might be a selection bias due to higher education, higher economic status and a healthier cohort in HRT users, which are associated with fewer risk factors for CVD."

The cohort of women studied in Sweden has been extensively studied, but Rödström says that there are too few hard end points yet to allow the researchers to find associations between cardiovascular disease in the cohort and risk factors.

What does this mean to physicians counselling patients about HRT? Rödström believes HRT still offers benefits in terms of osteoporosis prevention. "If a woman asks for HRT, look at the benefits and risks. If she doesn't have menopausal symptoms and only wants to have HRT as primary prevention for CVD, I would tell her that it is too early to recommend HRT for this." — *C.J. Brown*, CMAJ