

# Researchers overcome chemotherapy resistance in the lab

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Researchers from McGill University's Faculty of Medicine have discovered a compound that reduces resistance to chemotherapy agents used to treat cancer. Their results were published in the June issue of *The Journal of Clinical Investigation* (JCI).

Dr. Jerry Pelletier, PhD candidate Marie-Eve Bordeleau, and post-doctoral fellow Francis Robert, of the Department of Biochemistry and the McGill Cancer Centre – along with colleagues from Boston University, the Sloan-Kettering Cancer Center, the University of Vienna and the Howard Hughes Medical Institute – conducted an extensive study on a class of natural products known as cyclopenta benzofuran flavaglines (CBF).

Working with mice genetically modified to mimic human leukemias, they discovered that one particular CBF compound, silvestrol, can effectively re-sensitize tumors to chemotherapy, making them susceptible to the killing effects of anticancer drugs.

"One of the major problems with cancer therapy is that the tumours either fail to respond or stop responding over time to various chemotherapy drugs," Pelletier said. "One reasonable explanation for why this happens is the normal process of protein synthesis in the cell is usurped, principally because cancer cells grow faster and have higher metabolic needs. The normal checks and balances are no longer present."

Pelletier's lab at the Department of Biochemistry and McGill Cancer

Centre focuses on high-throughput assays of various compounds to determine their anti-cancer effectiveness. One that showed promise was silvestrol, a natural compound derived from *Aglaia silvestris*, a large genus of trees and shrubs found in Malaysia, South China and some Pacific islands. It has been used in Malaysian folk medicine for generations, but never as a cancer therapy.

"We made a conscious decision early on in our research to also screen for natural products," Pelletier says. "Silvestrol is not a synthetic compound you can buy from commercial suppliers."

In the lab, Pelletier explained, silvestrol therapy re-sensitized leukemia cells which had already demonstrated resistance to the chemotherapy agent doxorubicin.

"Essentially, we have turned off the cancer cell's survival signals, which is associated with resistance," he said.

However, he cautioned, though synthetic silvestrol is now starting to become available, trials in humans and possible treatments are still many years away.

Source: McGill University

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