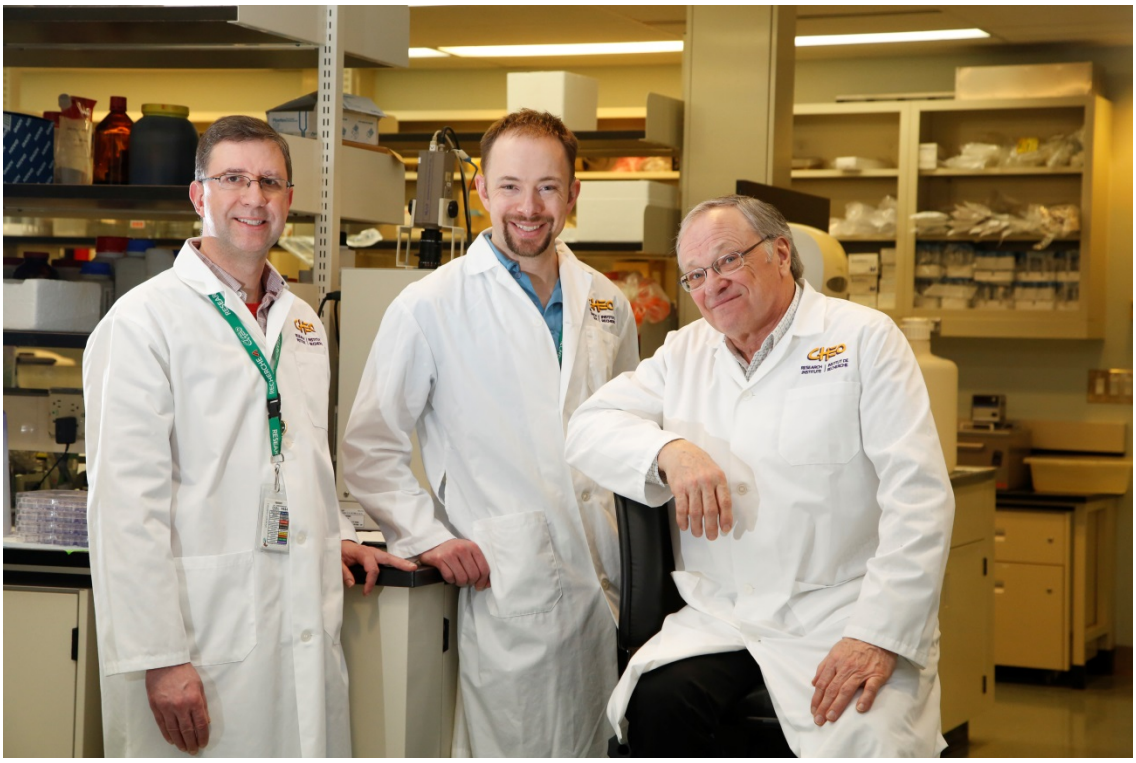
Spy vs Spy: Combination immunotherapy is like high-stakes espionage at the cellular level

by Mike Foster



L-R: Drs. Lacasse, Beug, Korneluk

Halt, who goes there?

Every day our immune system asks that question billions of times, killing off tiny intruders (microbes) and unwanted guests (cancer cells). But cancer cells often have the secret password needed to get past the immune checkpoint guards.

Researchers at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa for decades have been acting like spymasters, collecting, analyzing and creating scientific intelligence on the mechanics at play in this high-stakes espionage and counter-espionage among cells.

A team led by Dr. Robert Korneluk, distinguished professor at the University of Ottawa and a senior scientist at the CHEO Research Institute, recently found that a combination of immunotherapies act like double-agents, delivering a one-two punch to brain cancer tumours in laboratory testing.

"Cancer cells are crafty. They know the secret password and trick or bribe killer T-cells sent by our immune system into leaving them alone," said Dr. Korneluk. "However, a relatively new class of drugs known as immune checkpoint inhibitors blocks that interaction and reminds T-cells to fight the cancer.

Meanwhile, our lab sends in another agent, known as a SMAC Mimetic, which has a double whammy effect: it rallies the T-cells but also makes cancer cells vulnerable to attack."

The revolutionary field of immunotherapy is a relatively new fourth front in the war against cancer alongside chemotherapy, radiation and surgery. Increasingly, researchers across the world are learning how to manipulate the body's immune response to target cancer.

The latest research to emerge from Dr. Korneluk's team, published in Nature Communications, showed for the first time in the world that combining a SMAC Mimetic with two immune checkpoint inhibitors (ICIs) results in almost 100% cure rates for brain cancer tumours in the lab. The combination therapy also proved to be highly effective against breast cancer and multiple myeloma in laboratory testing. The findings add to the team's 2014 research, which found that SMAC Mimetics work well with oncolytic agents that trigger an immune response, amplifying kill rates of cancer cells.

SMAC Mimetics are small-molecule synthetic drugs that mimic key proteins which regulate a cell's survival. In 1995, the Korneluk lab discovered the human Inhibitor of Apoptosis (IAP) proteins, which keep cells healthy and alive. SMAC Mimetics drugs bind to IAPs causing a chain reaction that revs up the immune system, sending killer T-cells to attack cancer cells.

"It's kind of like in Star Wars when they destroy the Death Star by targeting its fatal flaw," said Shawn Beug, lead author of the 2014 and 2017 research. "Tumour cells are normally tough to kill but SMAC Mimetics disable their IAP survival response, triggering a death pathway for agents sent by the immune system."

The CHEO Foundation works tirelessly to raise funds through community support for the hospital's oncology department and supports fundamental research like the work going on at Dr. Korneluk's lab.

Today the research team is eager to learn the outcome of at least two new human clinical trials occurring around the world to examine the impact of this combination of immunotherapies.

Novartis in the U.S. is testing the SMAC Mimetic LCL161 with other agents in a clinical trial involving around 350 patients with colorectal, lung and breast cancer; and Debiopharm in Switzerland has announced a clinical trial for patients with advanced or metastatic lung cancer using their mimetic Debio1143 with an ICI known as avelumab, in collaboration with the Merck-Pfizer Alliance.

"We are at the forefront of this specific field of using SMAC Mimetics in combination with other agents to pack a bigger punch against cancer," Dr. Korneluk said. "We have been working with several drug companies to convince them to try these combinations. We're now very excited to see that our academic research will move out of the laboratory and into the clinic, hopefully taking us one step closer to finding powerful new treatments for cancer patients."

For more information about research at CHEO, please contact Adrienne Vienneau at avienneau@cheo.on.ca, 613-737-7600 x4144