

Siemens Competition

Math : Science : Technology

Regional Finalist

Names: Jason Lee, David Lu and Allen Lee

High School: Millburn High School, Mills E. Godwin High School

Mentor: Dave Durrant

Project Title: *Identification of compounds to overcome carbapenemase-related multidrug resistance in Enterobacteriaceae* (Microbiology)

The expression of the carbapenemase gene in *Enterobacteriaceae* is a key mechanism for multidrug resistance and a major healthcare problem. Virtual screening can facilitate identification of candidate compounds that can inhibit carbapenemase to reverse the resistance against carbapenems. Several publically available software programs, including AutoDock, DOCK Blaster, iStar iDock and others, were used for virtual screening of two carbapenemases, KPC-2 and NDM-1. Promising compounds were tested biologically by their ability to enhance bactericidal activity of imipenem against *Klebsiella* strains known to express KPC-2 or NDM-1. Synergisms with imipenem were investigated by calculation of the combination index. From virtual screening, approximately 50 compounds were identified for biological testing against *Klebsiella* expressing KPC-2 or NDM-1. Five compounds had activity with an inhibitory concentration IC_{50} less than 2 mM. The most potent one had an IC_{50} at 0.5 mM against NDM-1-positive *Klebsiella*. Two compounds showed a strong synergism with imipenem with combination index less than 0.1 at ED_{75} (75% effective dose). Active KPC-2 and NDM-1 inhibitors were identified using virtual screening and demonstrated to be synergistic with imipenem. These compounds can facilitate further structure-activity analysis to design more potent inhibitors.