# Methodology to identify drug candidates for multidrug resistant cancers

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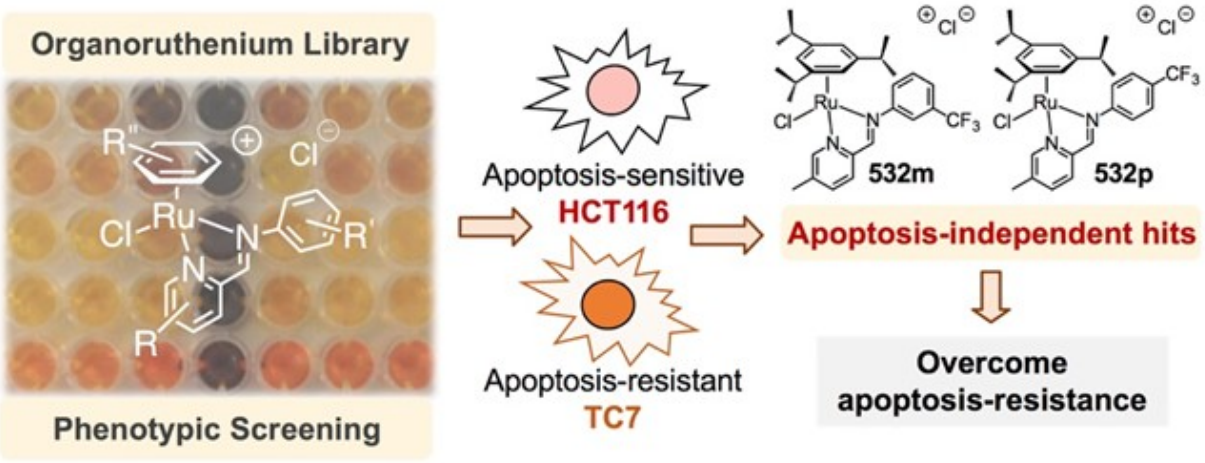


Figure shows a phenotypic screening approach to identify apoptosis-independent Ru-arene Schiff-base complexes. Credit: CHOW Mun Juinn

NUS chemists have developed a simple and robust bio-screening method to identify anticancer drug candidates to overcome multidrug resistance (MDR).

Certain types of cancer can adapt and become insensitive to a form of programmed cell death called apoptosis. This phenomenon is known as MDR, in which the cancer cells no longer respond to medications. MDR is becoming more prevalent and affects patients suffering from a variety of cancer types. It is a major factor in the failure of a number of cancer

treatments. Most anticancer drugs work by the apoptosis mechanism and finding new drug candidates that can induce alternative forms of cell death may be a way to circumvent MDR. This will potentially improve the clinical outcome for the patient.

In 2014, Prof ANG Wee Han and his team from the Department of Chemistry, NUS discovered that organoruthenium compounds are capable of killing cancer cells via an apoptosis-independent pathway that is distinct from many clinical drugs (Ang et al, Chemical Science, 2016). These ruthenium-based compounds were discovered through a tedious workflow process. This workflow required multiple phases of screening, validation, and detailed biological activity studies. The whole process took a long time and involved a large amount of research work.

"Even then, it lacked the specificity that we wanted and still required a small element of luck to identify such compounds from a library of 500 compounds," said Prof Ang. He added, "We wanted a methodology that could more quickly identify these apoptosis independent-compounds with a high degree of accuracy, eliminating 'luck' from the equation."

In their recent work, Prof Ang and his team, which included a research student from Nanyang Polytechnic, developed an improved strategy to effectively identify drug candidates which do not use the apoptosis mechanism. The strategy is based on the concept of "Phenotypic Screening". Using this, they have identified two novel organoruthenium compounds with apoptosis-independent pathways. The method involves screening libraries of compounds in both apoptosis-sensitive and apoptosis-resistant cancer cell phenotypes. By comparing the activity of the compounds in both phenotypes, the team could accurately identify compounds that induced apoptosis-independent cell death. Thereafter, they further validated
their modes of action.

Although such phenotypic screening strategies are not new, this is the first time that they have been specifically adapted for the identification of metal-based apoptosis-independent compounds. This may potentially lead to the discovery of better drugs for effective treatment of MDR cancers.

**More information:** Mun Juinn Chow et al. Apoptosis-independent organoruthenium anticancer complexes that overcome multidrug resistance: self-assembly and phenotypic screening strategies, *Chem. Sci.* (2017). DOI: 10.1039/C7SC00497D

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