

Mutations in JAK3 gene identified in subtype of lymphoma provide potential drug target

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A substantial proportion of NK/T-cell lymphomas harbor Janus Kinase 3 gene mutations. Patients with these lymphomas might benefit from treatment with a Janus Kinase inhibitor according to a study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Very little was known about the genetic and molecular defects causing NK/T-cell lymphoma before we started this work," said Bin Tean Teh, M.D., Ph.D., director of the National Cancer Center Singapore-Van Andel Research Institute Translational Research Laboratory at the NCCS, and professor at the Duke-NUS Graduate Medical School in Singapore. "There is no effective treatment and this type of cancer carries an extremely [poor prognosis](#).

"It is tremendously rewarding to have identified genetic mutations that appear to have an important role in driving the cancer in a considerable fraction of cases. Moreover, we are excited that there is a drug already in phase III trials for the treatment of rheumatoid arthritis that targets the [mutant protein](#). We are in the process of planning a clinical trial to study whether this drug benefits NK/T-cell [lymphoma patients](#)," said Teh.

NK/T-cell lymphoma is a very aggressive form of lymphoma. It is particularly prevalent in Asia.

"Many years ago, I and a colleague came to the Van Andel Research Institute in Grand Rapids, Mich.," said Teh. "My colleague unfortunately

developed NK/T-cell lymphoma and passed away. It was the only case of this cancer ever diagnosed in Grand Rapids. As this illustrates, it is a relatively rare subtype of lymphoma in the United States, but it is responsible for the deaths of a large number of people in Asia, in particular in China and Korea. It accounts for almost half of all T-cell lymphomas in some parts of Asia.

"The passing of my colleague, whom I was very close to, was the reason that I started studying NK/T-cell lymphoma. It has been a complicated puzzle, but I feel that we have pieced together enough that we will have an impact on a large number of patients with this disease."

To identify [genetic mutations](#) that might have a functional consequence, Teh and his colleagues sequenced all the genes in NK/T-cell lymphoma cells from four patients. In addition to mutations in genes known to be associated with cancer, they detected mutations in the Janus Kinase 3 (JAK3) gene in the cancer cells from half of the patients. The researchers conducted follow-up sequencing of NK/T-cell lymphoma cells from an additional 65 patients and identified JAK3 mutations in 23 of those patients.

The mutations enabled NK/T-cell lymphoma cell lines to grow in culture in the absence of the normally essential growth factor IL-2. This meant that the mutations caused dysregulated activation of JAK3, and suggested that JAK3 might be a good drug target.

Consistent with this idea, a JAK inhibitor that is currently being assessed in phase III clinical trials as a treatment for [rheumatoid arthritis](#) killed cultured NK/T-cell lymphoma cell lines by a process known as apoptosis.

"We are currently putting together a proposal to test JAK inhibitors as a treatment for NK/T-cell [lymphoma](#) with JAK3 [mutations](#)," said Teh. "I

am hopeful that we might have found a molecular target for the treatment of a least some patients with this otherwise fatal disease."

Provided by American Association for Cancer Research

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