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## GIVING MULTIPLE DISEASES A KNOCKOUT PUNCH

**FOCUS:** Identification of new therapeutics for blood cancers.

Myeloproliferative neoplasms (MPNs) are a group of diseases (polycythemia vera, essential thrombocythemia, primary myelofibrosis) in which excessive production of blood cells increases the risk of blood clotting, often leading to strokes and heart attacks. Most commonly diagnosed after age 50, there are no curative therapies for MPNs, with many patients experiencing drug resistance and significant side effects. In some cases, patients' conditions can turn into acute leukemia.

For years Dr. Ji had been studying a relatively unknown protein called PLEK2, which is important for red blood cell development. Through this work he discovered that PLEK2 is regulated by JAK2 protein, which is often mutated in MPN patients. This mutation makes blood cells hyper-proliferate, causing disease.

"We had been working on the pathogenesis of MPN, focused on JAK2, and we discovered that JAK2 controls the expression of PLEK2," Dr. Ji says. "When we knocked out PLEK2 in mouse models, we were thrilled to find that the result was a dramatically lower blood cell count and less blood clotting. We then performed high throughput screening and identified small molecule compounds that bind to PLEK2 and make it non-functional."

With help from the Harrington Discovery Institute, Dr. Ji's lab is working on optimizing the compounds—making them more potent, and testing pharmacokinetic data to see how the compounds are processed in the body. The goal is to use these compounds to treat MPN patients who have increased risks of blood clotting.

*"The Harrington consultants have been a tremendous help—their consultation is making a significant difference in the development of these compounds."*

### Harrington Discovery Institute

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