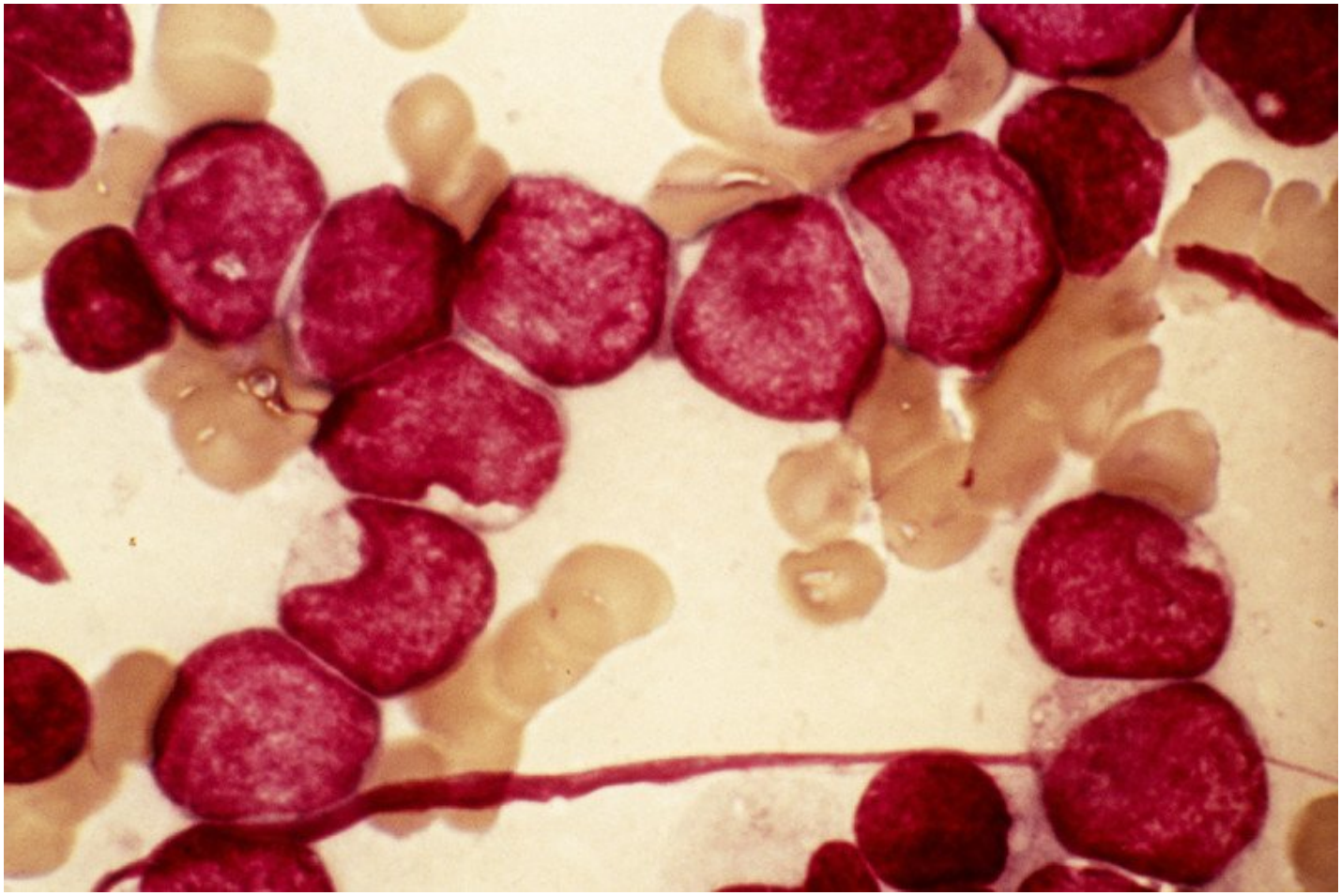
Findings from Two Patients Shed New Light on Drug Resistance in AML

By Julie Grisham, **Wednesday, June 27, 2018**



Acute myeloid leukemia starts in the blood-forming cells of the bone marrow. Source: Pr. J. Bernard/CNRI/Science Source.

Summary

Drug resistance is when a tumor stops responding to a targeted therapy. It is a serious problem in cancer treatment. Now, a multidisciplinary team has discovered a previously unknown mechanism of resistance to a new leukemia drug.

Last summer, the US Food and Drug Administration **approved enasidenib** (Idhifa®) for the treatment of **acute myeloid leukemia** (AML). Enasidenib works differently than most cancer drugs. Rather than killing leukemia cells, it turns them into normal blood cells. Memorial Sloan Kettering hematologist-oncologist **Eytan Stein** led the pivotal clinical trial that resulted in the drug's approval.

Now, a collaborative team of researchers is reporting that people who take enasidenib can develop resistance to it — and in a way never seen before. The findings are being **reported in *Nature***.

"Everyone who studies precision medicine spends a lot of time thinking about why some people respond to certain drugs and why some stop responding or never respond at all," says physician-scientist **Ross Levine**, who was one of the paper's senior authors, along with Dr. Stein. "MSK has been one of the leaders in figuring this out."

The discovery was made by a team of doctors, laboratory researchers, and pharmaceutical company scientists. They used cells from people who were being treated with enasidenib to uncover why the drug sometimes stops working.

Targeting a Mutation Found in Several Different Cancer Types

Enasidenib is approved for people with AML that is driven by a mutation in a gene called *IDH2*. About 15% of people with AML have this mutation. *IDH2* mutations and mutations in the related gene *IDH1* are found in other types of leukemia as well as **myelodysplastic syndromes**, glioblastoma, and **bile-duct cancer**.

The proteins made from mutated IDH genes can drive cells to become cancerous. MSK President and CEO **Craig Thompson** conducted much of the fundamental research on IDH mutations and their relationship to cancer. He is one of the co-authors of the *Nature* paper.

> "The finding about IDH2 suggests that genetic resistance is more complicated than we thought."

Ross L. Levine
physician-scientist

Researchers had previously shown that only one of the two copies of the *IDH2* gene needs to be mutated to drive cancer. The other one is usually normal. In the new paper, the investigators report that when cells developed resistance to enasidenib, the additional mutations that allowed the cells to resist the drug occurred on the normal copy of *IDH2*.

This stands in contrast to how resistance develops against most targeted cancer therapies. In those cases, an already mutated gene develops an additional mutation that allows the cancer cell to fend off the drug's effects. "The finding about *IDH2* suggests that genetic resistance is more complicated than we thought," says Dr. Levine, who is a member of MSK's **Human Oncology and Pathogenesis Program (HOPP).**

Just two patients were in the study, but the investigators learned a great deal. Experiments with laboratory models allowed them to study how the mutations work. The findings suggest that some people may develop resistance to IDH inhibitors due to a mutation on the same copy of the gene that carries the cancer-causing mutation.

Dr. Levine says that this prediction was confirmed when the researchers identified a third patient being treated with a similar drug that targets a mutation in *IDH1*. The IDH inhibitor stopped working in this person when a resistance mutation appeared on the copy of the *IDH1* gene with the cancer-causing mutation. This suggests that the process may be universal to all IDH-blocking drugs. "It's a small number of people, but we're quite confident that we'll see this same mechanism in others moving forward," he adds.

Targeting IDH mutations is a growing area of cancer drug development. Earlier this month, Dr. Stein was a co-first author of a paper **published in the *New England Journal of Medicine*** that looked at another drug that targets the *IDH1* mutation in people with AML. The multicenter phase I trial reported data on 125 people whose cancer had stopped responding to other treatments. The researchers found that of those treated with the drug, ivosidenib, almost 42% responded. Nearly 22% had a complete remission, meaning that their cancer was no longer detectable. The overall survival was longer than what would be expected in people with this stage of AML and severe side effects were rare. The researchers plan to continue studying the drug in larger, placebo-controlled trials.

A New Biomarker for Drug Resistance

After the people in the study developed resistance, their tumors started growing again. Doctors were able to switch them to other drugs that worked in a different way, however, so they were not affected by the additional mutation. There are a number of other **treatment options for people with AML**. These include both FDA-approved therapies and experimental drugs being tested in **clinical trials**. Many people with AML ultimately receive **stem cell or bone marrow transplants**, which offer the opportunity for a cure. However, many people are not able to undergo transplants, which makes developing new drugs an important focus.

> "Now that we know resistance to enasidenib can develop, we can start to monitor people for it."

Andrew M. Intlekofer
physician-scientist

"Now that we know resistance to enasidenib can develop, we can start to monitor people for it by conducting blood tests," says first author **Andrew Intlekofer**, who is also a physician-scientist in HOPP. "Over the course of therapy, we can use the protein as a biomarker for the formation of resistance. Then we'll know we need to offer a different treatment."

Far-Reaching Implications for Other Cancers

Understanding how resistance to enasidenib develops could lead to the development of additional drugs. Although, Dr. Intlekofer adds, more research is needed before new drugs can be identified. He also notes that the new discoveries about enasidenib could apply to other drugs that work in a similar way. Treatment of other cancers that are characterized by *IDH1* and *IDH2* mutations could be affected as well.

Dr. Levine highlights the importance of collaboration when conducting this kind of research. Working closely with scientists from Agios, the company that makes enasidenib, was of particular importance, he says. "To do this kind of work, it

requires a great team. Everyone who worked on this study made important contributions. This work was one of the most satisfying research experiences I've ever had."

The Nature study was funded by the National Cancer Institute grants K08 CA201483, K08 CA181507, R01 CA168802-02, R35 CA197594-01A1, U54 OD020355, and P30 CA008748; the Leukemia and Lymphoma Society; the Burroughs Wellcome Fund; the Susan and Peter Solomon Divisional Genomics Program; the Steven A. Greenberg Fund; the Translational and Integrative Medicine Research Fund; the American Association for Cancer Research; the American Society of Hematology/Robert Wood Johnson Foundation; Cycle for Survival; and the **Marie-Josée and Henry R. Kravis Center for Molecular Oncology**. The NEJM study was funded by Agios, which also makes ivosidenib.

PREVIOUS

In the News

NEXT

FDA Approves Enasidenib (Idhifa), a First-of-Its-Kind Drug, for Advanced Blood Cancer