Researchers uncover new drug combination to treat rare pediatric cancer called JMML

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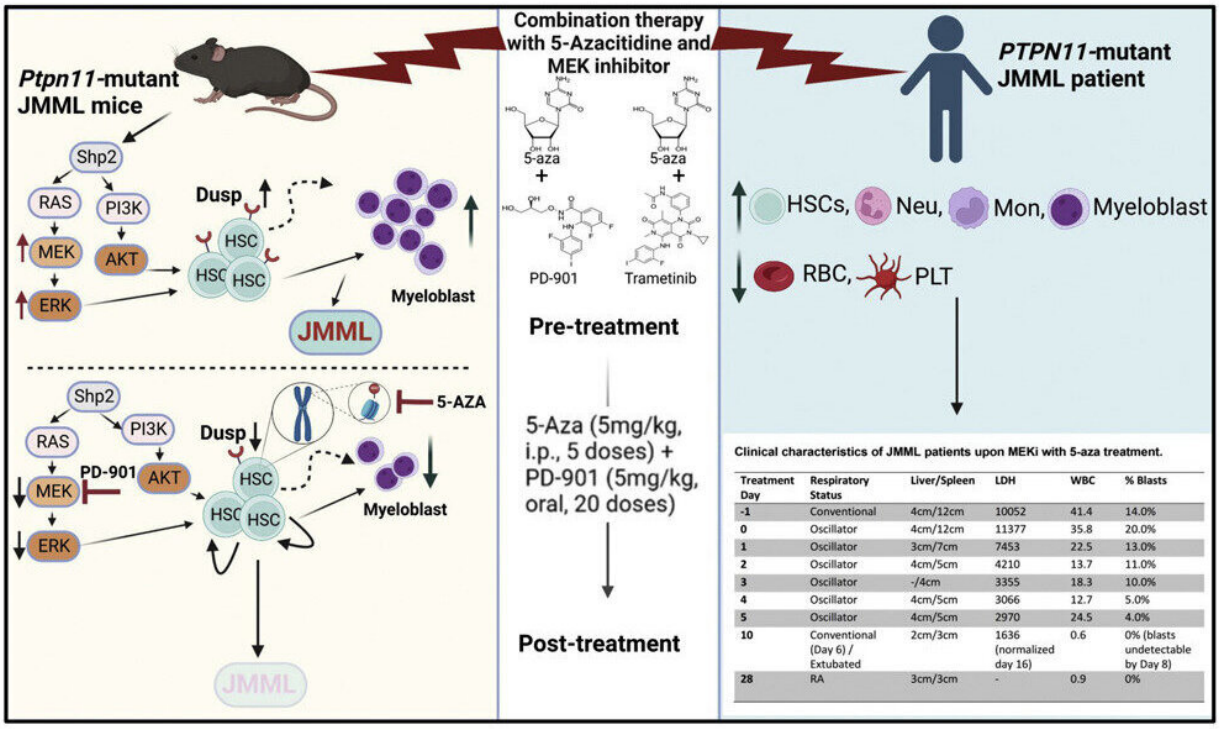

Treatment Day	Respiratory Status	Liver/Spleen	LDH	WBC	% Blasts
-1	Conventional	4cm/12cm	10052	41.4	14.0%
0	Oscillator	4cm/12cm	11377	35.8	20.0%
1	Oscillator	3cm/7cm	7453	22.5	13.0%
2	Oscillator	4cm/5cm	4210	13.7	11.0%
3	Oscillator	-/4cm	3355	18.3	10.0%
4	Oscillator	4cm/5cm	3066	12.7	5.0%
5	Oscillator	4cm/5cm	2970	24.5	4.0%
10	Conventional (Day 6) / Extubated	2cm/3cm	1636 (normalized day 16)	0.6	0% (blasts undetectable by Day 8)
28	RA	3cm/3cm	-	0.9	0%

Credit: *Molecular Therapy* (2023). DOI: 10.1016/j.ymthe.2023.01.030

Indiana University School of Medicine researchers have identified a promising new combination of drugs to treat juvenile myelomonocytic leukemia (JMML), a rare form of blood cancer that affects children. The

group's findings were recently published in *Molecular Therapy*.

JMML is caused by a specific genetic mutation that results in the overactivity of a cellular pathway called Ras/MAPK. There are currently limited therapies available to treat JMML, and other drug treatments have been ineffective.

"Our research findings demonstrated the combination of two drug therapies reduced the number of cancerous stem cells and enlargement of the spleen, and improved blood cell abnormalities often seen in JMML patients," said lead author of the published study Santhosh Pasupuleti, Ph.D., assistant research professor of pediatrics at the Herman B Wells Center for Pediatric Research and a researcher at the IU Melvin and Bren Simon Comprehensive Cancer Center. "These results provide hope for improved therapeutic options for JMML patients and highlight the potential of combination treatments in combating rare childhood disease."

Researchers from IU, Seattle Children's Hospital, University of California, San Francisco and Medical College of Wisconsin used a model of JMML to test a new combination of two drugs, 5-azacitidine and MEK inhibitor PD0325901, and found that it reduced some of the cancerous features of the disease. The combination worked by decreasing the number of cancerous blood stem cells in the model and reducing the activity of the Ras/MAPK pathway.

"The most common treatments for JMML patients today are bone marrow transplants, but unfortunately, nearly 50% of those transplant recipients relapse," said Reuben Kapur, Ph.D., director of the Herman B Wells Center for Pediatric Research, co-program leader of Hematopoiesis and Hematologic Malignancies at the IU Melvin and Bren Simon Comprehensive Cancer Center, and co-author of the study. "Chemotherapy and other medications have also been used but their

responses have not been great. We hypothesized that a combination of targeted medications could be a better option than what's available, and we're thrilled our pre-clinical studies have shown that to be the case."

A clinical trial has been approved to carry out this combination treatment in JMML patients who have failed other therapies. The clinical trial will be led by Elliot Stieglitz, MD, associate professor of pediatrics at University of California, San Francisco. Stieglitz recently conducted a separate clinical trial that found trametinib was effective but not curative on its own in JMML patients who did not respond to regular chemotherapy.

"Based on the information we learned, we will now test the combination of trametinib and azacitidine in patients with newly diagnosed JMML in the hope that the combination will be more effective than either drug alone," said Stieglitz. "Importantly, certain 'lower-risk' JMML patients in the upcoming trial will receive this combination of targeted treatments in place of a more intense treatment called stem cell transplantation. We anticipate this [...] trial of targeted agents will decrease side effects and increase the number of patients who achieve remission compared to conventional treatments."

More information: Santhosh Kumar Pasupuleti et al, Potential clinical use of azacitidine and MEK inhibitor combination therapy in PTPN11-mutated juvenile myelomonocytic leukemia, *Molecular Therapy* (2023). DOI: 10.1016/j.ymthe.2023.01.030

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