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PNP inhibitor LR 09 (Ulodesine) is a potential game-changer in leukemia treatment for Laevoroc Immunology

LR 09, a metabolic immune-checkpoint inhibitor that can initiate graft-versus-leukemia effect in relapsed allogeneic stem-cell transplant (SCT) patients, could become the new standard of care for leukemia.

Originally developed for psoriasis and gout but later discontinued, the purine nucleoside phosphorylase (PNP) inhibitor Ulodesine now shows promise as an immune checkpoint inhibitor to treat leukemia.

"This oral immuno-oncology agent is expected to initiate graft-versus-leukemia effect in patients relapsing after allogeneic SCT, effectively activating the transplanted immune system to recognize and fight the leukemia," said Thomas Mehrling, hematologist–oncologist, co-founder and CEO of Laevoroc Oncology, a Swiss immuno-oncology company.

Anecdotal but durable responses including complete remissions were noted in leukemia patients with the PNP inhibitor forodesine hydrochloride, two of whom received treatment post-SCT relapse. "Relapse carries a very poor prognosis for patients and places a heavy burden on health systems; our vision is to cure this disease with our game-changing innovation," Mehrling said.

Laevoroc Immunology acquired commercial rights to LR 09 in 2021, has an agreement with the University of California, Los Angeles (UCLA) to support the drug's development, and received an orphan drug designation from the US Food and Drug Administration (FDA) in December 2022.

PNP inhibitor led to complete remission

Lia Gore, head of pediatric hematology/oncology/bone marrow transplant (BMT) at the University of Colorado Cancer Center, treated a three-year-old girl who achieved complete remission with the PNP inhibitor forodesine in 2005. From a pharmacological viewpoint, forodesine is analogous to LR 09 but its development in the United States was discontinued. It is approved for treating peripheral T cell lymphoma in Japan.

Gore's patient relapsed four months after a BMT for refractory T cell acute lymphoblastic leukemia (ALL), then received six months of forodesine therapy. "It was a very aggressive leukemia," Gore said. "She was definitely cured, and is about to graduate from university." Gore treated five patients in a clinical trial with forodesine, two of whom had received SCT beforehand, but the patient described was the only one to achieve complete remission and survive. "It is difficult to predict who will respond. All five patients had aggressive refractory leukemias with multiple relapses, which are much more difficult to treat."

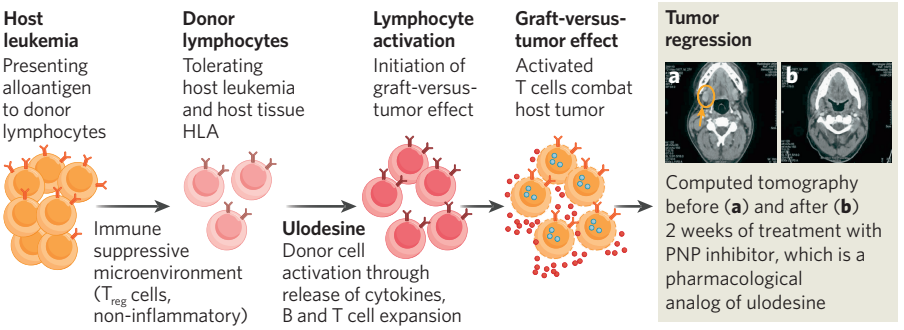

Fig. 1 | Displaying potential to treat leukemia. Inhibition of PNP reverses immunologic failure through release of cytokines and activation of T and B cells initiating graft vs tumor effect leading to durable responses in post stem cell transplant relapse leukemia patients. HLA, human leukocyte antigen; PNP, purine nucleoside phosphorylase; T_{reg}, regulatory T cell.

Gore noted. About 35–45% of patients with T cell ALL relapse following a BMT; typically, around 15–20% can be cured with subsequent therapy.

Acknowledging that LR 09 is at the preclinical stage and that more information is needed, Gore said she is hopeful of success based on the mechanism of action. "We still need dramatically better therapies for refractory disease, and we need more specific therapies for T cell leukemia and lymphoma."

Research data support LR 09 for leukemia treatment

Published in the *Journal of Clinical Investigation*, UCLA's key preclinical data provide mechanistic insight into the immunoregulatory functions of PNP[1].

PNP is a novel metabolic immune checkpoint. The data show that LR 09 is a metabolic immune checkpoint inhibitor activating the immune system through the release of cytokines, expansion of germinal center B cells and follicular helper T cells (Fig. 1). The data support LR 09's development to treat patients relapsing after SCT, as the drug can initiate graft-versus-leukemia effects and provide durable responses.

PNP regulates Toll-like receptor 7 (TLR7) signaling by restricting the availability of (deoxy) guanosine ligands necessary for TLR7 activation. Overriding this checkpoint promotes TLR7 activation, triggers spontaneous germinal center responses in the absence of exogenous antigen, and accelerates the onset of autoimmunity-linked phenotypes in MRL-LPR mice.

Caius Radu, UCLA research team lead, said the mechanism of action of LR 09 shows there is a 'good chance of recovery in patients' who relapse after allogeneic SCT. "But in my opinion, Laevoroc has something that has potential way beyond the setting of relapsed patients. The research gives a much better understanding of TLR7 activation and how LR 09 actually works, opening up the possibility for its use in settings that have not previously been considered. The established safety of Ulodesine is extremely important, because a lot of promising clinical candidates ultimately show an unanticipated level of toxicity," Radu said.

"I don't see any red flags. It's effective in terms of inhibiting PNP, it's very effective in mice and patients, and given its mechanism of action could be used across a variety of malignancies including converting a cold tumor into one that could better respond to immunotherapy. Importantly, the people who drive the science at Laevoroc are dedicated in their research and have been very passionate about Ulodesine for a long time."

1. Abt, E. R. et al. *J. Clin. Invest.* **132**, e1608 (2022).

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