Cancer researchers ID potential treatment for deadly lymphoma

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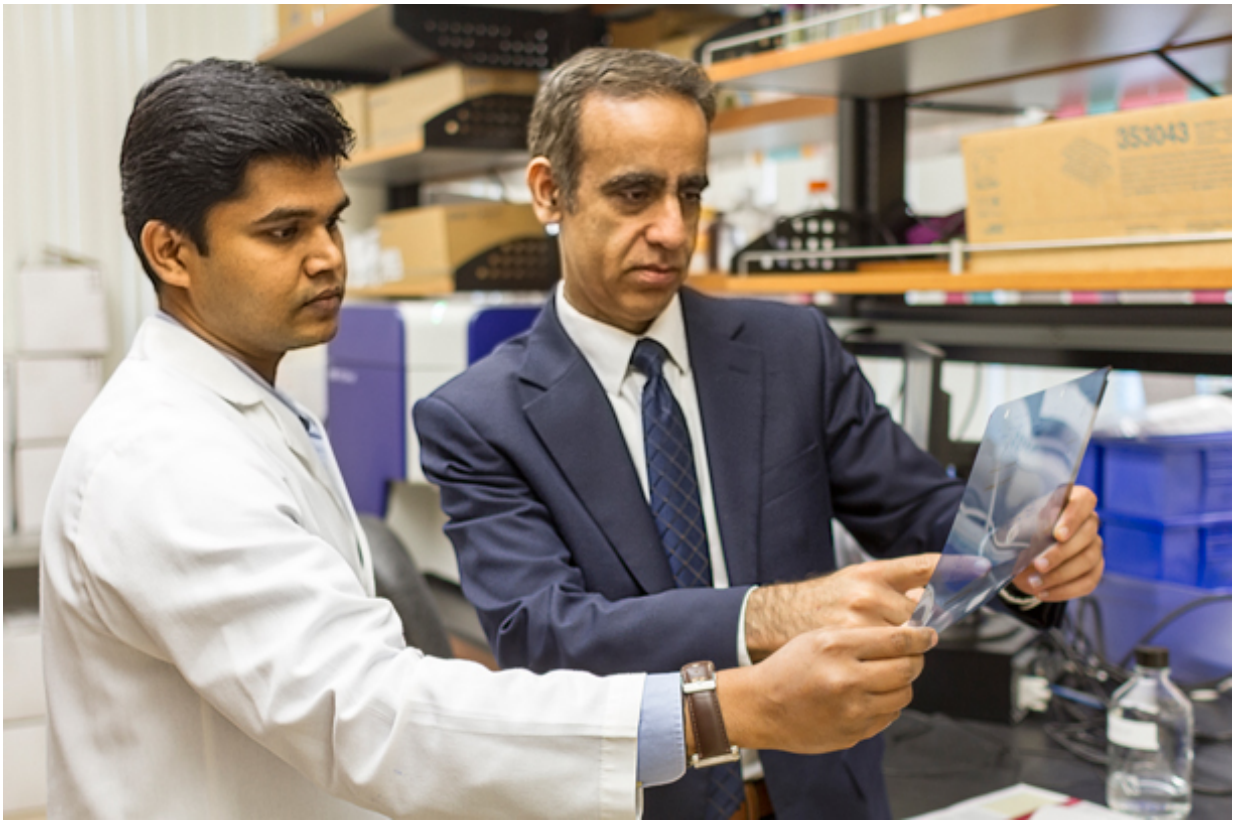

Ramakrishnan “Ram” Gopalakrishnan and Preet Chaudhary review images related to their study of primary effusion lymphoma (PEL).

New research from the University of Southern California (USC) Norris Comprehensive Cancer Center has identified a potential treatment for a

rare but previously incurable form of lymphoma that is observed primarily in patients with HIV/AIDS infection.

The study's lead author is Ramakrishnan "Ram" Gopalakrishnan, PhD, a research associate in the lab of Preet Chaudhary, MD, PhD, chief of the Jane Anne Nohl Division of Hematology and Center for the Study of Blood Diseases at the Keck School of Medicine of USC. In Gopalakrishnan's laboratory tests involving animal models, he found that the disease known as primary effusion lymphoma (PEL) can be treated effectively by a class of drugs already approved by the FDA.

These immunomodulatory drugs, or IMiDs, were actually more effective on PEL than they have been on the cancer for which they were approved, multiple myeloma.

"That was the 'ah ha' moment," Chaudhary said recently about the research published June 29 in the peer-reviewed scientific journal *Oncogene* from the Nature Publishing Group. "We have this disease for which there is no cure available, and these cancer cells are being selectively killed by this drug. So then we decided to pursue it further."

The further study yielded an understanding of the mechanism-of-action by which the drugs work against PEL. And that knowledge led Gopalakrishnan and Chaudhary to discover that IMiDs display synergistic anti-PEL effects when combined with another new class of drugs, called BRD4 inhibitors.

"There were already five clinical trials going on for BRD4 inhibitors related to other cancers," Gopalakrishnan said in explaining the decision process in the USC research. "So, when we combined the drugs, we knew how they could be toxic to this other situation with PEL."

"Not only have we figured out that the drug works," Chaudhary

explained, "but Ram has also figured out what the underlying molecular mechanism is. And that has allowed us to combine this drug with other drugs in a more intelligent way. "

Chaudhary, the Bloom Family Chair in Lymphoma Research at the Keck School, is senior author of the study. His lab has done previous work on cancers that are found in patients with human immunodeficiency virus (HIV) infection, including cancers such as PEL that are caused by infection with Kaposi's sarcoma associated herpesvirus, also known as Human Herpesvirus-8.

"Primary effusion lymphoma is very aggressive. Median survival with current therapy is just three to six months," Chaudhary noted. "And the current treatment is also very toxic and requires medications that have other side effects, and that need to be given intravenously. This becomes an issue for countries with limited resources, for example in Africa where this disease is prevalent."

The study results are promising, but Chaudhary cautioned that the USC research is based on in vitro and animal model studies that involved putting human lymphoma cells into immunodeficient mice.

"We are not suggesting that the patients begin taking these drugs," Chaudhary said, "but the results do provide a very strong rationale for the clinical testing of these drugs."

Because the medicines are all FDA-approved, a clinical trial could occur quickly, the researchers believe.

"But it all depends on getting enough investigators excited about this," Chaudhary said. "The disease itself is not very common, so it's not feasible for a single center to conduct the clinical trail. You would have to work as a consortium."

Such a consortium already exists for physicians who have patients with both cancer and AIDS.

"So once they see our study, hopefully it will create enough excitement and enough interest that they will say, 'Let's put this study through our consortium. Let's conduct a proper clinical trial,'" Chaudhary said.

Breakthroughs like this one related to less-prevalent diseases are now possible because of evolving attitudes in the medical research community.

"In the old days, we were mainly interested in drugs that effect millions or thousands of patients," Chaudhary noted. "The paradigm has changed at the NIH level and at the highest levels of medicine, and rare disease research has also become a priority now."

Provided by University of Southern California