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Researchers identify potential immunotherapy drug combination

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Studies Reveal the Combination’s Ability to Ramp Up the Destruction of Cancers in Mice. Credit: Mayo Clinic

A drug combination designed to enhance the immune system's ability to zero in and attack cancer cells has shown a pronounced therapeutic

effect against advanced and metastatic cancers in mice, according to a Mayo Clinic study, published in the July 12 edition of the online journal *Oncotarget*.

"Cancers can remain inconspicuous in the body for months to years before causing major problems, leading the immune system to coexist rather than to attack cancers," explains Mayo Clinic cancer immunotherapist Peter Cohen, M.D., who co-led the study with Mayo Clinic immunologist Sandra Gendler, Ph.D., and postdoctoral fellow Soraya Zorro Manrique, Ph.D.

"We tested Toll-like receptor (TLR) agonists—drugs that mimic invasive bacteria—as a strategy to trick the immune system into attacking cancer as if it were a life-threatening infection. Since chemotherapy can enhance immunotherapy, we also screened the pairing of TLR agonists with over 10 different chemotherapy agents," says Dr. Cohen, adding that the Mayo Clinic team targeted mouse models that included highly aggressive forms of breast cancer (known as 4T1) as well as pancreatic cancer (known as Panc02).

The investigative team observed that when the chemotherapy agent cyclophosphamide was combined with TLR agonists, advanced 4T1 and Panc02 cancers largely regressed within two cycles of treatment and did not recur if the mice completed five additional cycles of consolidating treatment. Only the combination of the TLR agonist and cyclophosphamide resulted in permanent cancer eradication, and no other tested chemotherapy came close to working as well as cyclophosphamide. The Mayo Clinic team also reported that the combined treatment was very well tolerated and actually less toxic than either TLR agonists or cyclophosphamide given individually.

Studies revealed that, even before treatment, the cancer-bearing mice had T-lymphocyte immune responses against their tumors, requiring only

weekly injections of the TLR agonist and cyclophosphamide to become therapeutically effective. Importantly, the treatment agents did not need to be injected directly into tumors, and were fully effective against widespread metastases as well as the primary tumor sites.

The drug combination also revealed an additional benefit—it activated monocytes (a type of white blood cell) to participate in the killing of cancer cells. Explains Dr. Gendler, "It appears very likely that each round of treatment stimulates the bone marrow to churn out freshly activated monocytes, which distribute throughout the body, spare normal cells, and find and kill cancer cells."

Dr. Cohen adds, "We were also able to identify TLR agonists that can similarly activate human monocytes to seek out and kill tumors."

Mayo Clinic is continuing its research, now studying within an FDA-approved clinical trial whether patients with advanced cancers, including pancreas, breast, colorectal, melanoma and others, respond similarly to mice when cyclophosphamide treatment is paired with the TLR agonist motolimod.

Provided by Mayo Clinic