Novel RNA delivery system may treat incurable blood cancers

January 5 2016

With a median survival rate of just five to seven years, Mantle Cell Lymphoma (MCL) is considered the most aggressive known blood cancer—and available therapies are scarce. Three thousand Americans are diagnosed with MCL every year, and despite progress in personalized therapies to treat metastases elsewhere in the body, systemic therapeutic drug delivery to cancerous blood cells continues to challenge the world of cancer research.

A new study by Tel Aviv University researchers offers tangible hope of curing the currently incurable blood cancer—and others like it. The revolutionary system was found to successfully halt the proliferation of a

cancer-related protein in white blood cells in both animal models and samples taken from MCL patients.

The research was led by Prof. Dan Peer of TAU's Department of Cell Research and Immunology and conducted by TAU PhD students Shiri Weinstein and Itai Toker, in collaboration with Prof. Pia Raanani of Rabin Medical Center and Prof. Arnon Nagler of Sheba Medical Center. The study was published in the early edition of the *Proceedings of the National Academy of Sciences*(*PNAS*).

A "Zip code identifier" system for cancer drug delivery

"MCL has a genetic hallmark," said Dr. Peer. "In 85 percent of cases, the characteristic that defines this aggressive and prototypic B-cell lymphoma is the heightened activity of the gene CCND1, which leads to the extreme overexpression—a 3,000- to 15,000-fold increase—of Cyclin D1, a protein that controls the proliferation of cells. Downregulation of Cyclin D1 using siRNAs is a potential therapeutic approach to this malignancy."

The research validates a novel strategy developed two years ago in Dr. Peer's lab that involved small interfering RNAs (siRNAs). The radical new delivery system harnesses nanoparticles coated with "GPS" antibodies that navigate toward the location of the cancerous cells, where they then offload Cyclin D1-blockers in the form of siRNAs.

For the purpose of the research, the scientists designed lipid-based nanoparticles (LNPs) coated with anti-CD38 monoclonal antibodies that were taken up by human MCL cells in the bone marrow of affected mice. When loaded with siRNAs against Cyclin D1, the targeting LNPs induced gene silencing in MCL cells and prolonged the survival of tumor-

bearing mice with no observed adverse effects.

"In MCL, Cyclin D1 is the exclusive cause of the over-production of B Lymphocytes, the cells responsible for generating antibodies," said Dr. Peer. "This makes the protein a perfect target for RNA therapy by siRNAs. Normal, healthy cells don't express the gene, so therapies that destroy the gene will only attack cancer cells. The RNA interference we have developed targets the faulty Cyclin D1 within the cancerous cells. And when the cells are inhibited from proliferating, they sense they are being targeted and begin to die off."

The new research highlights the therapeutic potential of Cyclin D1 therapy in MCL and presents a novel RNA delivery system that opens new therapeutic opportunities for treating MCL and other similar B-cell malignancies.

Making cancer personal

"This research makes a definite contribution to the revolution of personalized medicine, whereby you tailor the drug based on the genetic profile of patient," said Dr. Peer. "In this case, MCL is a disease with a specific genetic hallmark, so you can sequence the patient to identify the mutation(s), and design RNA blockers to be placed inside a nanovehicle.

"While the targeting antibodies—the 'GPS'—can be used to target many different B-cell malignancies, the drug itself is designed to silence this specific disease. However, the delivery system can be used to accommodate any disease with a genetic profile. This could be the future. We are seeing it happen before our very eyes."

Provided by Tel Aviv University