RNA-based therapy brings new hope for an incurable blood cancer

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Three thousand new cases of Mantle Cell Lymphoma (MCL), a form of blood cancer, appear in the United States each year. With a median survival span of only five to seven years, according to the Leukemia and Lymphoma Society, this disease is devastating, and new therapies are sorely needed.

One of the characteristics that defines MCL is heightened activity in the gene CCND1, which leads to the aggressive over-production of Cyclin D1, a protein that controls the proliferation of cells, explains Prof. Dan Peer of Tel Aviv University's Department of Cell Research and Immunology. In this disease, Cyclin D1 production spins out of control,

producing a 3,000 to 5,000 fold increase.

Now, in an international collaboration between academia and industry, Prof. Peer has developed a new class of drugs based on RNA interference, which can repair or destroy faulty proteins and reprogram cells to act in normal ways. The drugs have the ability to kill off the mutated protein and stop the over-proliferation of cells. Their method, proven in experiments with human cells and published in the journal PLoS One, was generously supported by the Lewis Trust and the Israeli Science Foundation.

Academia and industry work for a cure

In the past, scientists have attempted and failed to knock out this protein in the quest to develop a cure for MCL. But despite the prevalent belief that Cyclin D1 is not an effective target for therapies, Prof. Peer and his fellow researchers, including his PhD student Shiri Weinstein and Dr. Rafi Emmanuel and the Sheba Medical Center's Prof. Arnon Nagler and Dr. Avigdor Abraham, knew there was cause for hope.

To prove their theory that Cyclin D1 was indeed an appropriate target for the treatment of MCL, the researchers turned to two companies considered world-experts in RNA, Alnylam Pharmaceuticals in Cambridge, Massachusetts and Integrated DNA Technologies in Iowa, both of which donated their time and resources to the project. Working in parallel, they were able to design potent RNA interference sequences to stop the production of Cyclin D1.

In MCL, Cyclin D1 is the exclusive cause of the over-production of B Lymphocytes, cells responsible for generating antibodies, explains Prof. Peer. This makes the protein a perfect target for RNA interference – because normal, healthy cells don't express the gene, therapies that destroy the gene will only attack cancer cells. The RNA interference that

the researchers 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 "commit suicide," he says.

In the lab, the researchers have successfully used their RNA interference in human cells, a crucial step towards proving that Cyclin D1 can be targeted through the right interventions. "Ultimately, we want to be able to cure this disease, and I think we are on the way," says Prof. Peer. He hopes that their results might cause scientists to reconsider previous and unproductive results on the effectiveness of treating MCL by addressing aberrations of this protein.

Pairing with nano-delivery methods

The researchers are working to develop a mouse population with MCL to test their newly-developed therapies in vivo. Typically, new therapies for any disease are tested on human cells as well as mouse models in the lab before being taken to clinical trials in humans. But there has never before been a test using mice with this disease, says Prof. Peer, a deficiency that has limited the quality of research. The animal test will allow researchers to conduct a more cautious and in-depth investigation of this new class of drugs before moving to the clinical stage.

As for strategies for delivering the new therapy into the body, the researchers will make use of Prof. Peer's extensive work with nano-sized medical "submarines" which are designed to travel to the source of disease or disorder in the human body, and offload drugs inside specific cells or proteins as needed.

Provided by Tel Aviv University