A biological approach to precision medicine targets endless number of diseases

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Credit: Tel Aviv University

The biological complexity of cancer and other diseases demands a more formidable arsenal of therapies than currently available. Most therapeutic approaches ignore the dynamic molecular network of genes, targeting instead only very few selected disease-related genes.

A new Tel Aviv University study published in *Nature Nanotechnology* proposes a novel approach to manipulate genes using a self-assembling platform that delivers nucleic acids, such as small interfering RNAs (siRNAs), to distinct cell subsets. While current practices of precision medicine target a single cellular receptor, the new modular platform offers a robust biological approach—and may hold the key to the future

of personalized medicine.

"The siRNA delivery targeted carriers constructed today hone in on specific cells and require chemical conjugation of the targeting agent," says Prof. Dan Peer of the Laboratory of Precision Nanomedicine at TAU's School of Molecular Cell Biology and Biotechnology, who led the research. "The new platform is based on biological affinity, a self-assembling approach that can be translated to target an endless number of diseases and conditions."

Research for the study was conducted by first co-authors Dr. Ranit Kedmi and Nuphar Veiga and colleagues at Prof. Peer's TAU Laboratory, in collaboration with Prof. Itai Benhar of TAU's School of Molecular Cell Biology and Biotechnology, Dr. Michael Harlev of TAU's Veterinary Service Center, Dr. Mark Belkhe of Integrated DNA Technologies (IDT) and Prof. Judy Lieberman of Boston Chidren's Hospital and Harvard Medical School.

Locating the "linker"

According to Prof. Peer, the new platform "removes many of the hurdles" plaguing precision medicine today. At the heart of the delivery platform is the "linker," a lipoprotein that binds to the antibody constant region. Since all antibodies of the same family share a common region, a simple alteration of the antibody results in a novel delivery carrier that adjusts to the target receptor of choice.

"Because its construction relies on affinity interactions, there's no need to introduce chemical conjugation optimizations for the method to function," says Prof. Peer. "Linkers are stuck in the nanoparticle membrane and bind to a fixed region of any antibody of the same isotype. This affords safe passage to a theoretically unlimited selection of carriers targeting distinct cell surface receptors."

"We believe this modular delivery platform serves as a milestone that renders precision medicine truly feasible," says Ms. Veiga. "The challenge has been how to direct certain therapies designed to manipulate genes of interest in specific cells without developing a specific drug carrier for each specific cell type. It would be very costly and impractical to develop millions of different drugs to treat every specific cell type and specific gene. Rather, the focus should be on developing a nucleic acid-based tool to manipulate gene expression through a simple, constant exchange."

Fast results

For the research, the scientists used the platform to target colon macrophages in order to reduce inflammatory symptoms caused by Inflammatory Bowel Disease (IBD) in mouse models. "One can easily obtain fast results using these targeted carriers," says Prof. Peer. "The mice exhibited far less inflammation, which suggests the possibility of promising new IBD therapeutic opportunities."

The researchers also affected mouse models with Mantle Cell Lymphoma, using the new platform to target cancer cells, induce cell death and dramatically improve overall survival.

"Our research supports the development of targeted nucleic acid delivery platforms for therapeutics for autoimmune diseases and cancer," says Prof. Peer. "Our delivery platform can be adjusted for each patient to target a potentially endless number of receptors.

"It's flexible enough to be easily customized to target any cell subset and to knock down any gene of choice. We think it has tremendous research and therapeutic potential."

The researchers are currently interested in advancing a proof-of-concept

in humans.

More information: Ranit Kedmi et al, A modular platform for targeted RNAi therapeutics, *Nature Nanotechnology* (2018). DOI: 10.1038/s41565-017-0043-5

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