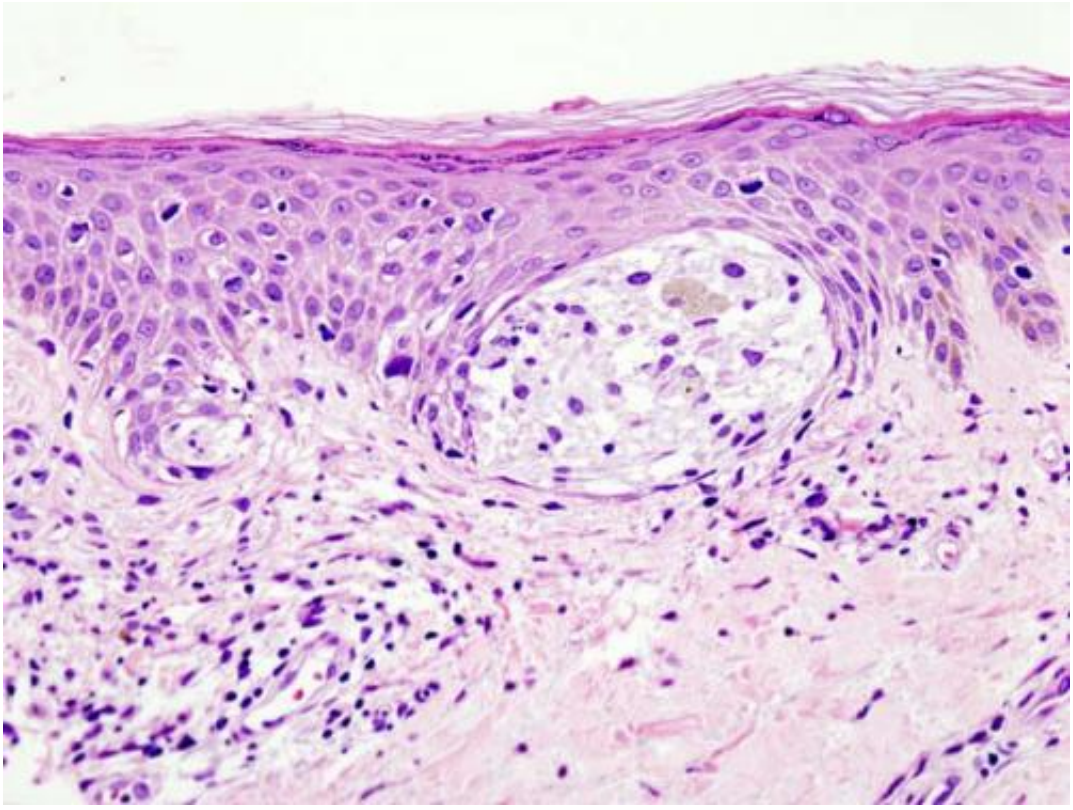
New nanosystem enhances treatment for melanoma in animal models

September 8 2020



Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Researchers at Tel Aviv University, led by Prof. Ronit Satchi-Fainaro of TAU's Department of Physiology and Pharmacology at the Sackler School of Medicine, have developed an innovative nanotechnological drug delivery system that significantly enhances the effectiveness of

treatment for the aggressive skin cancer melanoma.

The nanocarrier is a biocompatible and biodegradable polymer, which comprises repeating units of glutamic acids. It packages together two drugs belonging to different families with proven efficacy for the treatment of melanoma: BRAF inhibitors (Dabrafenib) and MEK inhibitors (Selumetinib, approved for use in children with neurofibromatosis type I).

The research group included Ph.D. students Evgeni Pisarevsky, Dr. Rachel Blau, and Yana Epshtein from Prof. Satchi-Fainaro's research laboratory at the Sackler School. The paper was published on August 10, 2020, in *Advanced Therapeutics*.

"One of the major obstacles of the biological treatments is that, after a while, the cancer cells develop resistance to the drugs," Prof. Satchi-Fainaro says. "We assume that by precise delivery of two or more targeted drugs that will attack the cancer cells forcefully and simultaneously from different directions, we can delay or even prevent the acquisition of this drug resistance.

"In this project, we looked for a solution to a problem often associated with drug cocktails," Prof. Satchi-Fainaro continues. "Most oncological treatments today are administered in the form of cocktails of several medications. But even though the drugs are administered simultaneously, they do not reach the tumor at the same time, due to differences in basic parameters, like how long they survive in the bloodstream and the time it takes each drug to reach the tumor tissue. Thus, in most cases, the medications do not work concurrently, which prevents them from attaining optimal synergistic activity."

Responding to these challenges, the researchers developed an innovative, efficient, and biodegradable drug delivery system. Two drugs known to

be effective for the treatment of melanoma, Dabrafenib and Selumetinib, were chosen, with the intention of delivering them jointly to the tumor using a nanocarrier. The drug nanocarrier chosen for the task was PGA, a polymer of glutamic acid, one of nature's most common amino acids. Developed in Prof. Satchi-Fainaro's lab several years ago, the nanocarrier has already been tested successfully for treating pancreatic, breast, and ovarian cancer in animal models.

The researchers first determined the optimal ratio between the two medications based on levels and types of toxicity, as well as the resistance mechanism developed by cancer cells for each medication. This would ultimately ensure maximum effectiveness, minimal toxicity, and optimal synergistic activity. Another important advantage of joint delivery is reduced dosage: a much lower dose is required compared to each drug when administered independently.

The next step was using chemical modifications to enable bonding between the polymeric carrier and the chosen drugs. This combined system can travel through the body with total safety, inflicting no damage to healthy tissues. Upon reaching the cancer cells, the nanocarrier encounters proteins of the cathepsins enzyme family, which are highly activated in malignant tumors. The proteins degrade the polymer, releasing the drugs which become active and join forces to attack the tumor. "It's like several passengers riding in one cab and getting off together at the same address," Prof. Satchi-Fainaro explains. "They all arrive at the same destination, right at the same time."

Tested on a mouse model of melanoma, the new treatment showed promising results. The nanocarrier delivered the two drugs to the tumor and released them there simultaneously in quantities about 20 times greater than those that reach the tumor when similar doses of the same medications are administered independently. In addition, the therapeutic effect achieved by the drugs delivered by the nanocarrier lasted twice to

three times longer compared to a control group and a group treated with free medications.

According to the researchers, this means that the new platform enables much lower dosages—about one-third of the dose required in regular drug cocktails. The treatment as a whole is also both safer and more effective. If necessary, the new approach allows for dosages that are much higher than the maximum dosage permissible in current methods, thereby enhancing the effectiveness of the treatment even further.

"In this project, we developed an innovative drug delivery system for treating melanoma, delivering two proven medications and releasing them simultaneously at the tumor site," Prof. Satchi-Fainaro summarizes. "The treatment proved both safer and more effective than the same medications administered as a cocktail. Moreover, our new platform is highly modular and can be used for delivering a vast range of medications. We believe that its potential for enhancing therapeutics for different diseases is practically endless."

More information: Evgeni Pisarevsky et al, Melanoma: Rational Design of Polyglutamic Acid Delivering an Optimized Combination of Drugs Targeting Mutated BRAF and MEK in Melanoma (Adv. Therap. 8/2020), *Advanced Therapeutics* (2020). DOI: 10.1002/adtp.202070017

Provided by Tel Aviv University